34 Years of Documentation of Maternal-Child Transmission of Lyme Disease and Congenital Lyme Borreliosis - A Review - by Sue Faber, RN, BScN

Transplacental transmission, adverse outcomes and reports of congenital infection of Borrelia burgdorferi have been clearly documented over the last 34 years (1985 to 2019) by multiple international physicians, pioneering researchers and scientists including Dr. Willy Burgdorfer (after whom Borrelia burgdorferi was named), Dr. Alan Steere (one of the primary investigators of Lyme disease in Lyme Connecticut), Dr. Alan MacDonald (pathologist who meticulously documented Borrelia burgdorferi in tissues of fetal autopsies) and Dr. Tessa Gardner (Pediatric Infectious Disease Specialist).

Most recently in 2018:

- *In the US, The Tick-Borne Disease Working Group 2018 Report to Congress* ***acknowledges transplacental transmission*** *of Borrelia burgdorferi in the human fetus.*[5]
- *In France, The High Council of Public Health* [4] ***acknowledges that maternal-fetal infection of Borrelia burgdorferi*** *is possible.*
- *In Canada, a Systematic Review* [3] *written by Public Health Agency of Canada scientists* ***acknowledges transplacental transmission of Borrelia burgdorferi*** *and also identifies in their meta-analysis, a strikingly high rate* ***(50%) of adverse outcomes in mothers with untreated Lyme disease****.*

This alternate mode of transmission has been clearly documented by the CDC [143,147] *World Health Organization* [145] *and Canadian Public Health authorities* [3, 127, 130] *and published in top-tier peer-reviewed medical and scientific journals. The March of Dimes*[7] *and National Institutes of Health*[50, 97] *(NIH) have also highlighted infection can be transferred in-utero and possible adverse outcomes in pregnancy if mothers are untreated for Lyme disease. The Maine USA Government website currently acknowledges transplacental transmission as an alternate mode of transmission of Lyme disease.* [6]

There have been several animal studies of horses, cows, dogs, mice, rats and coyotes where in-utero transmission of Borrelia burgdorferi including cases of spirochetemia has been identified in offspring, often resulting in adverse outcomes. As clearly articulated by Gustafson, Burgess et al, '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'.[1] [2] [3] [4] [5] [6]

Transplacental transmission has been definitively documented and proven with spirochetes identified as Borrelia burgdorferi in tissues and organs of deceased babies using culture, immunohistochemistry, PCR, indirect immunofluorescence and staining techniques. These individual case-reports and further primary research gave important clues that this disease is complex, protean and multi-systemic, resulting in the possibility of a heterogeneous range of adverse outcomes in babies and children alike including spontaneous

[1] 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.
[2] 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.
[3] 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.
[4] 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.
[5] 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.
[6] Altaie SS, Mookherjee S, Assian E, Al-Taie F, Nakeeb SM, Siddiqui SY. Transmission of Borrelia burgdorferi from Experimentally Infected Mating Pairs to Offsprings in a Murine Model. Abstract #1-17. 1996 FDA Science Forum.

abortion, miscarriage, stillbirth, preterm delivery, hyperbilirubinemia, sepsis, syndactyly, cortical blindness, developmental delay, rash of the newborn, congenital heart abnormalities and urologic abnormalities [7].

According to Dr. Alan MacDonald, pathologist, 'the complex spectrum of clinical manifestations of Lyme borreliosis in the mother is complementary to an equally complex array of signs and symptoms of prenatal borreliosis in the fetus and infant.' [8]

Multiple clinician experts in obstetrics/gynecology have documented Lyme disease as etiologic for stillbirth and furthermore, one study histologically identified spirochetes in brain sections of 2 cases of SIDS. 36,39,53, 96, 123, 135,141. The Royal Society of Obstetricians and Gynecologists acknowledges transplacental transmission of Lyme disease as being etiologic for stillbirth.[9]

In each of its last three editions since 2001, a leading medical reference textbook on the subject matter of infectious diseases of the fetus and newborn infant (Remington and Klein eds), has included Lyme disease in their list of in-utero/congenital infections by recommending expansion of the well-known medical acronym for microorganisms that cause congenital infections, 'TORCH' to 'TORCHES-CLAP' with 'L' representing Lyme disease[10]. This same chapter has listed Lyme disease as causing congenital disease. A 2004 paper titled 'Update on TORCH Infections in the Newborn Infant', 2004, also highlighted Remington and Klein's recommendation that that Borrelia burgdorferi, the agent of Lyme disease should be added to list of infectious organisms which can cross the placenta and infect the child.[11]

Our careful review of the published medical literature points to unequivocal, clear documentation of this alternate mode of transmission which was agreed upon by physicians, researchers and scientists, in affirmative language which was far from undecided, inconclusive or ambiguous. We have included direct quotes from these publications in this paper, so readers who may not have access to the full publications can read for themselves - what has been clearly documented.

It is important to learn from other infectious diseases which can be transmitted in-utero to better understand the broad spectrum of manifestations in an infant infected with Borrelia burgdorferi. Dr. J.A. Dudgeon from the Department of Microbiology at the Hospital for Sick Children, London, England, authored an introduction to a symposium on Intrauterine Infections and stated '..we have been obsessed for 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 those children who may have been at risk during pregnancy'.[12]

It is well established that a chronic, persistent and often asymptomatic infection in a mother may result in 'clinically silent' vertical transmission to an infant who has no established symptoms at birth but develops symptomatic infection months or years later. Such cases have been reported in, for example, syphilis, toxoplasmosis, Chagas' disease (Trypanosoma cruzi) and HIV [1].

Lyme disease has been well-documented in the peer reviewed medical literature to have the ability to cause chronic, persistent infection [13] and thus a clinical investigator would be remiss not to consider the hypothesis that asymptomatic (and sometimes seronegative) mothers infected with B. burgdorferi could indeed transfer

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[7] 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

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

[9] Late Intrauterine Fetal Death and Stillbirth. Royal College of Obstetricians and Gynecologists. Green-top Guideline No. 55, October 2010. https://www.rcog.org.uk/globalassets/documents/guidelines/gtg_55.pdf

[10] 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, 2016.

[11] 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.

[12] Dudgeon, J.A. Introduction. Intrauterine Infections. Editors Elliot K, Knight J. Ciba Foundation, 1973.

[13] Phillips S.E. Active Infection: Clinical Definitions and Evidence of Persistence in Lyme Disease - Contesting the Underlying Basis for Treatment Limitations for Early and Late Lyme Disease, and Post-Lyme Syndrome. April 16, 2009.

the bacteria in-utero to the fetus. In a 1989 publication in Current Clinical Topics of Infectious Diseases, authors Dattwyler and Luft acknowledged that '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'[117] Pathologist, Dr. Alan MacDonald, answered this question in his study of fetuses whereby he identified borrelia spirochetes in fetal tissues by immunohistochemistry with monoclonal antibodies[14], indirect immunofluorescence, silver staining and culture, and in most cases the mother was asymptomatic with no recollection of a tick-bite and seronegative by standard tests for B. burgdorferi.[15]

Dr. Horst (German physician) highlighted a 3-day old infant diagnosed with neonatal sepsis who had positive IgG and IgM borrelia antibody titres in blood and cerebral-spinal fluid and whose mother was asymptomatic with no recollection of tick-bite.[16] The author highlights concern, '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'.

A 1986 case-report from Slovenia highlighted an asymptomatic mother with no recollection of tick-bite who delivered a 34-week stillborn female infant. Upon autopsy, darkfield examination of lung, liver and brain tissue specimens revealed spirochetes. The mother tested positive for Lyme disease using IFA testing and negative for syphilis.[17]

In another case-report authored by Lavoie and colleagues[18], an initially healthy newborn was re-admitted at 8 days with lethargy, unresponsiveness, peripheral cyanosis, systemic hypertension, myocardial dysfunction and abdominal aortic thrombosis and died. Upon autopsy, Borrelia burgdorferi (Bb) was cultured from a frontal cerebral cortex inoculation and also identified in the heart and brain by silver staining. The mother was seronegative with no recollection of a tick-bite or EM rash and had non-specific symptoms.

Dattwyler and colleagues[19] reported a case of neonatal Lyme disease in which the baby was born with neonatal neurologic dysfunction and B. burgdorferi infection was confirmed by serological evidence of antibodies specific to borrelia in the CSF. The mother had been infected with Bb in the second trimester and <u>had been treated</u> with antibiotics. She was asymptomatic and seronegative at time of parturition.

A review of TORCH infections highlights that systemic infection in a baby <u>may not be obvious at birth</u> and absence of clinical symptomology in the infant at birth may be misleading if the infant is assumed 'healthy' without longitudinal observation and follow-up.[1] In-utero infection may lead to late-onset disease and may not manifest with signs and symptoms until weeks, months or years later[1]. Infants with congenital HIV are often asymptomatic at birth and only 30% of infants are PCR positive at birth.[1] Furthermore the median age of onset for signs of congenital HIV infection is approximately 3 years.[1]

*In congenital syphilis, authors report that a majority of congenitally infected infants are **<u>asymptomatic at birth</u>**.[20] Syphilitic babies may be seronegative at birth, born to seronegative mothers, and only later develop signs and symptoms.[12] Mothers with primary, secondary, early latent or late syphilis should have all their*

[14] Barbour A, Tessier S, Todd, W. Lyme Disease Spirochetes and Ixodid Tick Spirochetes Share a Common Surface Antigenic Determinant Defined by a Monoclonal Antibody. Infection and Immunity, Vol 41. No. 2. Aug. 1983. pp. 795-804.
[15] Macdonald, AB. Gestational Lyme borreliosis. Implications for the fetus. Rheum Dis Clin North Am. 1989;15(4):657-77.
[16] 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.
[17] Maraspin V, Cimperman J, Lotric-Furlan, S et al. Erythema migrans in pregnancy. Wein Klin Wochenschr (1999) 111/22-23:933-940.
[18] Lavoie PE, Lattner BP, Duray P. H et al. Culture positive, seronegative, transplacental Lyme borreliosis infant mortality. Arthritis Rheum; 1987. p. S50.
[19] Dattwyler R, Volkman D and Luft B. Immunologic aspects of Lyme borreliosis. Review of Infectious Diseases Vol 11(6) 1989.
[20] Wicher V, Wicher K. Pathogenesis of Maternal-Fetal Syphilis Revisited. CID 2001:33 (1 August), pg. 354-363.

young children evaluated for signs of congenital syphilis[21]. Congenital toxoplasmosis has a wide range of clinical symptomology but is subclinical in approximately 75% of infected newborns. [22]

There are case reports whereby congenital B. burgdorferi infection manifested weeks to years later after birth. [23] [24] There are several cases highlighted by an Infectious Disease physician Dr. Tessa Gardner, whereby the infants were seronegative by standard serology measuring an antibody response[25] and yet diagnosed with congenital Lyme borreliosis by measuring a T-cell immune response (lymphocyte proliferation assay) which also has been used to diagnose Lyme borreliosis in seronegative adults[26] [27].

In congenital Chagas' disease, the severity of disease varies from asymptomatic to fatal infection and the reported prevalence of asymptomatic congenital infection ranges from 40-100%. If left untreated, these babies may develop chronic, late disease.[28] Clustering of cases within families has been reported and all children born to seropositive mothers should be tested. [29]

A review of the literature on Gestational Lyme and Congenital Lyme borreliosis reveals:

- *Scientists, researchers and physicians unequivocally agreeing with documentation of transplacental transmission of Bb in humans.*
- *Asymptomatic and sometimes seronegative mothers without recollection of a tick-bite, EM rash or 'typical' Lyme symptoms giving birth to babies infected with Borrelia burgdorferi*
- *Seronegative, asymptomatic mothers with stillbirths/miscarriages and Borrelia burgdorferi identified in fetal tissues and placentas upon autopsy*
- *Standard serologic testing may not be an appropriate diagnostic tool to determine if the baby has been exposed/infected with B. burgdorferi and reliance on infant serology alone can lead to misdiagnosis of congenitally infected infants.*
- *Borrelia burgdorferi and borrelia cysts identified in placenta by electron microscopy and or PCR in women treated for Lyme disease*
- *Mothers treated with antibiotics for Lyme disease and still transmitting Borrelia burgdorferi to baby.*
- *Heterogeneous range of multi-systemic adverse outcomes in babies born to mothers with untreated Lyme disease including some babies who were asymptomatic at birth*

For Lyme disease to be passed from mother to child in pregnancy drastically challenges and deconstructs the status quo - from a purely zoonotic disease - to a disease which can be transferred from human to human; mother to baby. It only makes rational sense that this infectious bacterial micro-organism would be transferred in-utero and follow similar patterns to other well-established TORCH infections. Acknowledging and confronting this reality head-on, opens up Pandora's box which will undoubtedly result in upheaval, rethinking,

[21] 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.
[22] McAuley J. Congenital Toxoplasmosis. Journal of Pediatric Infectious Diseases Society, Vol 3, suppl 1, ppS30-S35.
[23] Trevison G, Stinco G, Cinco M. Neonatal skin lesions due to a spirochetal infection: a case of congenital Lyme borreliosis? Journal of Dermatology, 1997, 36, 677.
[24] Lazebnik T, Zal'tsman P. A Case of Congenital Neuroborreliosis. St Petersburg Medical Academy of Postgraduate Education, St. Petersburg, Russia, 2005.
[25] 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
[26] Dattwyler R, Volkman D, Luft B et al. Seronegative Lyme Disease. The New England Journal of Medicine. Vol 319, No 22. 1988. pp1441-1446.
[27] Dressler F, Yoshinari H, Steere A. The T-Cell Proliferative Assay in the Diagnosis of Lyme Disease. Annals of Internal Medicine. 1991;115:533-539.
[28] Carlier Y, Torrico F, Sosa-Estani S et al. Congenital Chagas Disease: Recommendations for Diagnosis, Treatment and Control of Newborns, Siblings and Pregnant women. Plos Neglected Tropical Diseases, Oct 2011, Vol 5, Issue 10.
[29] Cevallos AM, Hernandes R. Chagas' Disease: Pregnancy and Congenital Transmission. BioMed Research International, Volume 2014, Article ID 401864.

reordering, reinvestigating and re-prioritizing. However, we have no choice but to act with the highest integrity, impartiality and honesty.

The historical and current documentation is now compounded and amplified by the lived suffering of entire families in Canada and abroad who are sick with Lyme disease - many concerned and rightfully so, that the infection was passed through pregnancy and furthermore, concerns of inter-generational infection. The alarm-bells are ringing, ***for good reason****.*

As entire families worldwide are affected by Lyme borreliosis often resulting in serious debilitating illness and complex multi-systemic chronic infection, we must take this alternate mode of transmission - from mother to child in pregnancy, seriously. We must listen, engage and learn from those that suffer - mothers describing all their children sick with Lyme disease, families pleading for acknowledgement of the truth which they must confront daily, often alone, criticized and misunderstood.

It is clear that research and urgent investigation of transplacental transmission of Lyme disease is needed and requires an all-hands-on-deck, streamlined, multi-disciplinary approach – with a Patient First, Evidence-Based integrative model of bringing together patients with lived experience, front-line clinicians, clinical researchers and scientists – to examine the issues and dig broader and deeper together. A process which is firmly anchored in transparency, integrity and scientific rigor with patients as valued partners. A meaningful process whereby patients must be respected and involved in decision-making at all steps in the research process.[30]

We have no choice but to move forward, to constructively engage, discuss and determine solutions. In doing so, we will be a light for those who suffer, a beacon of Hope and healing. We need to prevent more miscarriages, stillbirths and babies from being born with Lyme and tick-borne illnesses – potentially leading to chronic pervasive, persistent and often disabling illness. Are we willing to engage, problem-solve and collaborate with our very best thinking?

Sue Faber, RN, BScN. Co-Founder and Director LymeHope

[30] Patrick, K. Editorial: Realizing the vision of patient-relevant clinical research. CMAJ. Oct. 3, 2016

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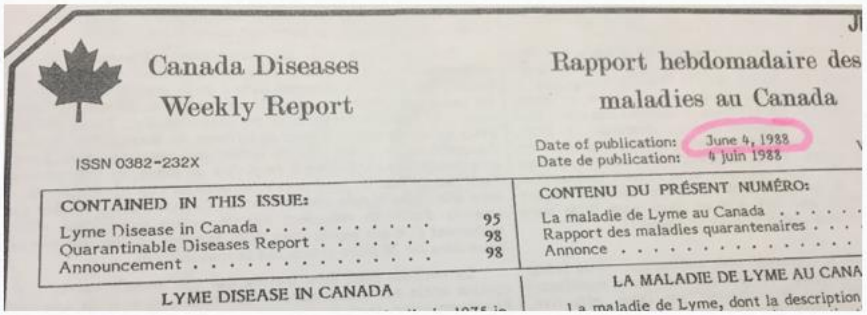
What Canadian Federal Health Authorities Reported in 1988



Canada Diseases Weekly Report

Rapport hebdomadaire des maladies au Canada

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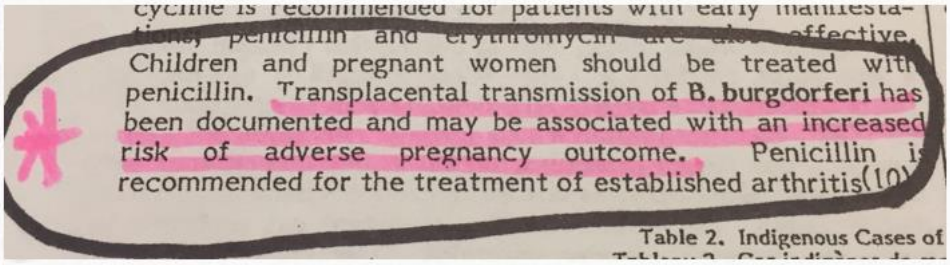
Rapport des maladies quarantenaires . . . .
Annonce . . . . . .

LYME DISEASE IN CANADA

LA MALADIE DE LYME AU CANA
La maladie de Lyme, dont la description

Health and Welfare Canada

Canada Diseases Weekly Report, June 4, 1988



cycline is recommended for patients with early manifesta-
tions, penicillin and erythromycin are also effective.
Children and pregnant women should be treated with
penicillin. Transplacental transmission of B. burgdorferi has
been documented and may be associated with an increased
risk of adverse pregnancy outcome. Penicillin is
recommended for the treatment of established arthritis(10)

Table 2. Indigenous Cases of

This same report was published in the Canadian Medical Association Journal August 1988. Vol 139. August 1, 1988.

RESEARCH ARTICLE

A systematic review on the impact of gestational Lyme disease in humans on the fetus and newborn

Lisa A. Waddell, Judy Greig, L. Robbin Lindsay, Alison F. Hinckley, Nicholas H. Ogden

Published: November 12, 2018 • https://doi.org/10.1371/journal.pone.0207067

Article | Authors | Metrics | Comments | Media Coverage

Waddell LA, Grieg J, Lindsay LR et al. A systematic review on the impact of gestational Lyme disease in humans on the fetus and newborn. Plos One, Nov 12, 2018. https://doi.org/10.1371/journal.pone.0207067

In-utero Transmission of Borrelia burgdorferi

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.**"

'Thus, the data suggest there is some evidence that **adverse birth outcomes may occur more frequently if gestational LD is not treated.**'

"Across cases, **evidence that transplacental transmission of *B. burgdorferi* can occur** was shown by testing the placenta (n = 11) and deceased fetal/newborn tissue (n = 18)"

'There **are examples among the 59 case reports included in this SR that suggested transplacental transmission occurs** including 4 cases of infection in the fetus or newborn determined using relatively reliable laboratory diagnostic methods.'

"This SR summarizes evidence from case studies that **provide some limited evidence for transplacental transmission of *B. burgdorferi*.**"

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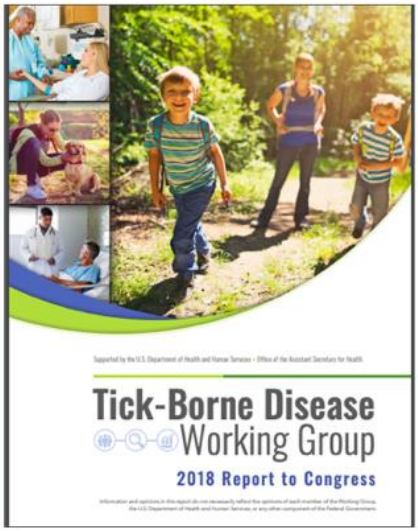
Department of Health and Human Services Tick-Borne Disease Working Group Report to Congress, 2018.



https://www.hhs.gov/sites/default/files/tbdwg-report-to-congress-2018.pdf

- **Pregnancy:** Transplacental infection of the human fetus has been recognized for relapsing fever borreliosis, as well as Lyme disease, babesiosis, and certain arthropod-borne flaviviruses. Pregnancy poses particular challenges for treatment because few antimicrobials have been approved and are safe to use during pregnancy. Additional research into appropriate treatment options are needed.

Transplacental transmission of the human fetus has been recognized for relapsing fever **as well as Lyme disease..**

Pregnant Women

Gestational tick-borne disease can be transmitted to unborn children *in utero* and has the potential to cause premature labor and fetal death. One priority research area involves the risks of maternal-fetal transmission for various tick-borne diseases, as well as how to treat this population if exposed during pregnancy and needing treatment while pregnant.

Gestational tick-borne disease can be transmitted to un-born children in-utero and has the potential to cause premature labor and fetal death.

cases, reliance on currently available serological tests may not be appropriate. Moreover, hormonal changes during pregnancy can lead to changes in immune function that may affect the detection of clinical or laboratory findings.

Hormonal changes during pregnancy can lead to changes in immune function that may affect detection of clinical or laboratory findings.

NATIONAL ASSEMBLY

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Since January 2017, the Ministry of Health has put in place a plan to fight against Lyme disease and other pathogens transmitted by ticks. The goals of this plan are to strengthen prevention, improve and standardize patient care by updating recommendations, and to organize specialized consultations for patients with tick-borne diseases. The High Health Authority has already published recommendations of good clinical practice allowing all doctors to take care, in a harmonized manner on the national territory, the different forms of the disease. The Directorate-General for Health (DGS) works, in conjunction with the regional health agencies, setting up specialized centers for the care of patients; Practitioners from these centers will participate in the initial and ongoing training of health professionals. The High Council of Public Health (HCSP), seized by the DGS, has already decided on the risks of transmission of the dis ase: in general, no transmission thr ugh breast milk, sexually or via products blood and transplantation is currently documented man . Maternal-fetal infection is possible, nd HCSP recommends antibiotic treatment for pregnant women with a diagnosis of Lyme borr iosis. Su veillance of the geographical distribut n of the disease continues, with the epidemiological work of the National Public Health Agency (ANSP) and the internet reporting application open to individuals. The ANSP notes an increase in 2016 in the early cutaneous forms of the disease (erythema migrans), with no increase or other forms or hospitalizations.

Question publiée au JO le : **06/03/2018** page : 1852
Réponse publiée au JO le : **24/07/2018** page : 6689

Response from the High Council of Public Health, France, July 2018.

'**Maternal-fetal infection is possible**, and HCSP recommends antibiotic treatment for pregnant women with a diagnosis of Lyme borreliosis.'

Retrieved from: http://www2.assemblee-nationale.fr/questions/detail/15/QE/6138

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Royal College of Obstetricians & Gynaecologists

https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg55/

Late Intrauterine Fetal Death and Stillbirth

Green–top Guideline No. 55
October 2010

UK Royal College of Obstetricians and Gynecologists, **October 2010**.

'Transplacental infections associated with late intrauterine fetal death include: Lyme Disease.'

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

AJOG REVIEWS

The infectious origins of stillbirth

Robert L. Goldenberg, MD, and Cortney Thompson, BS
Birmingham, Ala

OBJECTIVE: Our objective was to determine the relationship between various types of perinatal infections and stillbirths.
STUDY DESIGN: By use of various textbooks on perinatal infections, multiple MEDLINE searches, and the reference list of all appropriate manuscripts, the appropriate English language literature was reviewed to define the relationship between various perinatal infections and stillbirths.
RESULTS: Infection may cause stillbirth by a number of mechanisms, including direct infection, placental damage, and severe maternal illness. A large variety of organisms have been associated with stillbirth, including many bacteria, viruses, and protozoa. In developed countries, between 10% and 25% of stillbirths may be caused by an infection, whereas in developing countries, which often have much higher stillbirth rates, the contribution of infection is much greater. Ascending bacterial infection, both before and after membrane rupture, with organisms such as *Escherichia coli*, group B streptococci, and *Ureaplasma urealyticum* is usually the most common infectious cause of stillbirth. However, in areas where syphilis is very prevalent, up to half of all stillbirths may be caused by this infection alone. Malaria may be an important cause of stillbirth in women infected for the first time in pregnancy. The two most important viral causes of stillbirth are parvovirus and Coxsackie virus, although a number of other viral infections appear to be causal. *Toxoplasma gondii*, leptospirosis, *Listeria monocytogenes*, and the organisms that cause leptospirosis, Q fever, and Lyme disease have all been implicated as etiologic for stillbirth.
CONCLUSION: Because infection-related stillbirth is relatively rare in developed countries, and those that do occur are caused by a wide variety of organisms, reducing this etiologic component of stillbirth much further will be difficult. However, in certain developing countries, the stillbirth rate is so high and the infection-related component so great that achieving a substantial reduction in stillbirth should be possible simply by reducing maternal infections. (Am J Obstet Gynecol 2003;189:861-73.)

Key words: Stillbirth, infection, chorioamnionitis

'In recent years, Lyme disease, a systemic illness caused by the tick-borne spirochete Borrelia burgdorferi also has been shown to cause stillbirth.'

Goldenberg R, Thompson C. The infectious origins of stillbirth. American Journal Obstet gynecol, Sept 2003.

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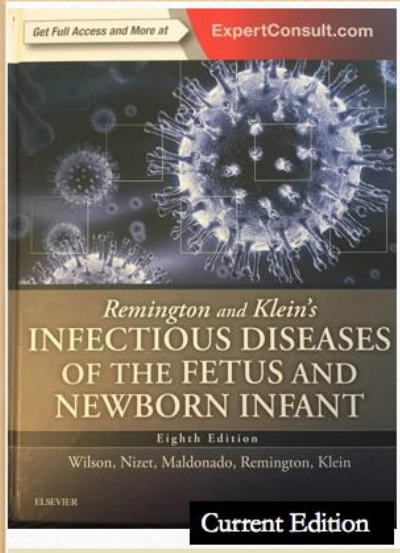

Current Edition

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., 2016.

'TORCHES CLAP'

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

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

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.

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

Despite these limitations, *B. burgdorferi* can cross the placenta, presumably during a period of spirochetemia. The frequency and clinical significance of transplacental transmission of *B. burgdorferi* are unclear. Although a temporal relationship between Lyme disease during pregnancy and adverse outcomes has been documented, a causal relationship has not been established. Claims for the existence of

Once again, in-utero transmission of Borrelia burgdorferi recognized.

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

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

man immunodeficiency virus; *HSV*, herpes simplex virus; *LCV*, lymphocytic choriomeningitis virus; *VZV*,

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.

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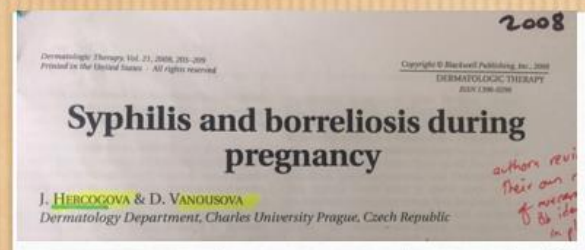

2008

DERMATOLOGIC THERAPY

Syphilis and borreliosis during pregnancy

J. HERCOGOVA & D. VANOUSOVA

Dermatology Department, Charles University Prague, Czech Republic

in 1989 (15). The present authors could observe one abortion in a pregnant woman with disseminated lyme borreliosis insufficiently treated with oral penicillin for 5 days when Borreliae were demonstrated by electron microscopy (using monoclonal antibodies against flagellin) in the placenta specimen. Recently, the present authors were able to observe in three placentas of women treated for lyme borreliosis during pregnancy both Borreliae and *Borrelia* cysts by electron microscopy and/or PCR (unpublished observation).

Some epidemiologic studies of lyme disease during

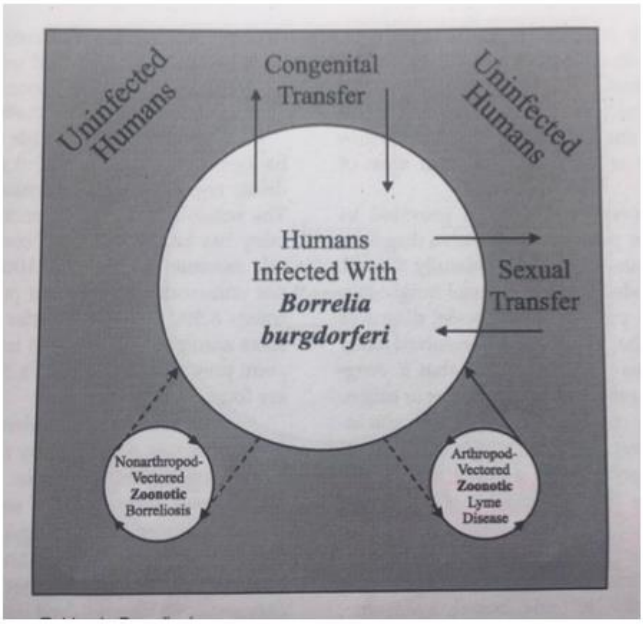
2008: Hercogova J, Vanousova D. Syphilis and borreliosis during pregnancy. Dermatologic Therapy, Vol. 21, 2008, 205-209.

Authors report an abortion in a pregnant woman with disseminated Lyme borreliosis insufficiently treated with oral penicillin for 5 days. **Borrelia demonstrated by electron microscopy and identified by monoclonal antibodies.**

Authors observe **three placentas of women treated** for Lyme borreliosis during pregnancy and both **borrelia and borrelia cysts by electron microscopy/PCR were identified.**

'The present authors believe that taxonomical relationship of T. pallidum and B. burgdorferi is responsible **for a similar clinical course of syphilis and lyme borreliosis including congenital infections**.'

Lyme disease': ancient engine of an unrecognized borreliosis pandemic? 2003



Hypothesis of two distinct but connected forms of B. burgdorferi infection.

Zoonotic transfer:
(from tick-bites)

Congenital transfer:
Congenital transfer (mother to baby)

Sexual transfer?

Currently 'Lyme Disease' only refers to the zoonosis arm and is a limited conceptualization and case definition.

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

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Transplacental Transmission of Borrelia burgdorferi in animals

Intrauterine transmission of *Borrelia burgdorferi* in dogs

John M. Gustafson, DVM, MS; Elizabeth C. Burgess, DVM, PhD; Michael D. Wachal, BS; Howard Steinberg, VMD, PhD

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.

Study results include:

'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.'

'Intrauterine infection by B burgdorferi does occur in dogs and is a potential means by which the spirochete can be transmitted in a breeding population in the absence of a tick vector.'

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Evidence for in utero Transmission of *Borrelia burgdorferi* from Naturally Infected Cows

Mira M. Leibstein, BS, Mazhar I. Khan, DVM, PhD, and Sandra L. Bushmich, MS, DVM

'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.'

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.

Journal of Wildlife Diseases, 25(1), 1989, pp. 47–51

BORRELIA SP. INFECTION IN COYOTES, BLACK-TAILED JACK RABBITS AND DESERT COTTONTAILS IN SOUTHERN TEXAS

Elizabeth C. Burgess[1] and Lamar A. Windberg[2]
[1] Department of Medical Sciences, School of Veterinary Medicine, and Research Animal Resources Center, University of Wisconsin, Madison, Wisconsin 53706, USA
[2] Denver Wildlife Research Center, Animal Plant Health Inspection Service, United States Department of Agriculture, 319 Stowe Street, Laredo, Texas 78041, USA

ABSTRACT: Coyotes (*Canis latrans*) from southern Texas were sampled for antibodies to *Borrelia burgdorferi* from 1980 to 1986; black-tailed jack rabbits (*Lepus californicus*) and desert cottontails (*Sylvilagus audubonii*) were sampled in 1986. Coyote fetuses, adult coyote kidneys, and black-tailed jack rabbit and desert cottontail kidneys were cultured for *B. burgdorferi* in 1986. Results of indirect immunofluorescent antibody (IFA) tests for *B. burgdorferi* in coyotes were as follows (number positive at a dilution of ≥1:128/number tested): 1980 (0 of 30), 1981 (0 of 21), 1982 (0 of 53), 1983 (0 of 78), 1984 (47 of 97), 1985 (20 of 88), and 1986 (42 of 80). Eight of 26 black-tailed jack rabbits and two of seven desert cottontails tested in 1986 had IFA titers to *B. burgdorferi* of ≥1:128. *Borrelia burgdorferi* was isolated from one of five coyote fetuses, three of 31 adult coyote kidneys, and two of 10 black-tailed jack rabbit kidneys in 1986. These results indicate that *B. burgdorferi* infection has been present in coyotes in Texas, at least since 1984 and that transplacental transmission occurs.

Key words: *Borrelia burgdorferi*, coyote, *Canis latrans*, black-tailed jack rabbit, *Lepus californicus*, desert cottontails, *Sylvilagus audubonii*, transplacental transmission, Lyme disease, survey.

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.

The case of an antibody negative coyote have a B. burgdorferi 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." (Bb was cultured from kidney of coyote fetus)

"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."

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Foal Mortality Associated with Natural Infection of Pregnant Mares with *Borrelia burgdorferi*

Elizabeth C. Burgess, Annette Gendron-Fitzpatrick, and Mark Mattison

"This study shows that B. burgdorferi can cause in utero infections in horses and can be associated with foal mortality. The kidney lesions in the foals that died soon after birth and in the yearling contributed to the deaths of the animals. The lesions were attributed to B. burgdorferi infection as B. burgdorferi was isolated from the kidneys of three of the four animals and spirochetes were identified in the kidneys of histologic sections."

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.

From the 1996 FDA Science Forum

Abstract # I-17

Transmission of *Borrelia burgdorferi* from Experimentally Infected Mating Pairs to Offsprings in a Murine Model. S.S. Altaie[1,3], S. Mookherjee[2] E. Assian[2], F. Al-Taie[2], S.M. Nakeeb[3], and S.Y. Siddiqui[3].
[1]CDER, FDA, Rockville, MD, [2]CHOB, Buffalo, NY, [3]State University of New York at Buffalo, NY

In an effort to develop a murine model for studying other modes of transmission of *B. burgdorferi* (Bb), we started with the well studied C_3H/HeJ mouse. Splenectomized 6-8 week-old mice were divided into 4 groups. Groups A, B, and C had 23, 24, and 26 mating pairs respectively. Prior to mating, in group A ♀, in group B ♂, and in group C both ♀ & ♂ were infected subcutaneously with 10^6-10^7 (Bb) in 250 ml SKB II media. The control group D had 12 mating pairs in which both ♂ & ♀ received sterile media. Resulting pups were sacrificed at 1, 7, 14, and 21 days of age. Milk content of the stomach, sections from ear, skin, heart, liver, spleen, brain, bladder, and kidney of the 1, 7, and 14 day-old pups were cultured for Bb. The above mentioned tissues except milk were also cultured from sacrificed 21 day-old weanlings. Transmission to offsprings was indicated when Bb was isolated from any tissue from a given pup. From the experimentally infected ♀ in which the milk was cultured, 2 (8%) transmitted Bb to their pups on day one via their milk. 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. These results indicate that Bb can transmit by other modes than the tick bite. The described mouse model with further modifications may provide a tool for studying such transmission modes and treatment strategies.

'Among 49 infected from groups A and C, 5 (10.2 %) transmitted Bb to their pups either in-utero or intrapartum. 4 of the litters from the mating pairs in Group B had infected pups.'

'<u>These results indicate that Bb can transmit by other modes than the tick bite</u>.'

Altaie SS, Mookherjee S, Assian E, Al-Taie F, Nakeeb SM, Siddiqui SY. Transmission of Borrelia burgdorferi from Experimentally Infected Mating Pairs to Offsprings in a Murine Model. Abstract #1-17. 1996 FDA Science Forum. (Mouse model)

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Preliminary investigation on reservoir hosts of *borrelia burgdorferi* in China

Wan Kanglin, Zhang Zhefu, Wang Hongying, Hou Xuexia, et al.
Institute of Epidemiology and Microbiology, Chinese Academy of Proventive Medicine, Beijing 102206, China

From 1987 to 1997, the reservoir hosts of *Borrelia burdorferi* (*B. b.*) were investigated in 16 provinces, municipalities and autonomous regions of China. Seroepidemiological findings indicated that cattle, sheep, dogs and rats from forest areas had a high antibody titer for *B. b.* (B_{31}) with positive rates of 18.18%~32.61%, 17.12%~61.21%, 38.50%~60.00% and 41.18%~86.05% respectively. Using BSK medium, 20 strains of *B. b.* were isolated from *Apodemus agrarius*, *Clethrionomys rufocanus*, *Eutamias sibiricus*, *Rattus coxingi*, *Rattus norvegicus*, *Rattus edwardsi*, *Rattus confucianus*, *Rattus fulvescens* and *Caprolagus sinensis*. These spirochetal strains were identified as *B. b.* by indirect immunofluorescence assay using species and genus specific monoclonal antibodies. Vertical transmission of *B. b.* was confirmed with *B. b.* isolated from foetuses of *Apodemus agrarius* and *Rattus edwardsi*. The results showed that lyme disease spirochetes, *B. b.*, might be naturally maintained in an enzootic cycle by transplacental transmission. *Apodemus agrarius* and *Clethrionomys rufocanus* might serve as major reservoir hosts for *B. b.* in China.

Key words: lyme disease, *borrelia burgdorferi*, reservoir host, *apodemus agrarius*, *clethrionomys rufocanus*

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.

'Vertical transmission of B.b was confirmed with B.b isolated from fetuses of apodemus agrarius (field mice) and Rattus edwardsi – Edwards rat. The results showed that the Lyme disease spirochetes Bb might be naturally maintained in an enzootic cycle by transplacental transmission.'

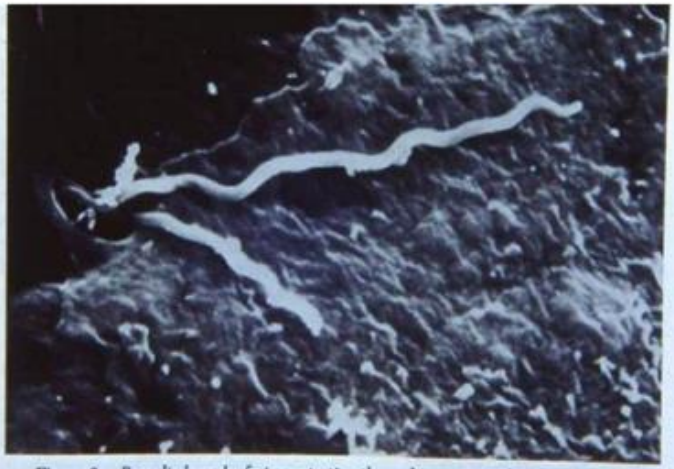

Figure 2. *Borrelia burgdorferi* penetrating through an opening between human umbilical cord endothelial cells grown on human amniotic membrane. Photo courtesy of Dr. Andrew Szczepanski, Department of Pathology, State University of New York at Stony Brook, New York (×16,400)

Can Borrelia burgdorferi be transmitted in the womb causing congenital disease and adverse outcomes?

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Vertical Transmission in Humans – a review of the evidence.

Maternal-Fetal Transmission of the Lyme Disease Spirochete, *Borrelia burgdorferi*

PETER A. SCHLESINGER, M.D.; PAUL H. DURAY, M.D.; BARBARA A. BURKE, M.D.; ALLEN C. STEERE, M.D.; and M. THOMAS STILLMAN, M.D.

Hennepin County Medical Center and the University of Minnesota Medical School, Minneapolis, Minnesota; Yale University School of Medicine, New Haven, Connecticut.

LYME DISEASE usually begins with a characteristic skin lesion, erythema chronicum migrans, accompanied by "influenza-like" or "meningitis-like" symptoms (1). Some patients later develop cardiac abnormalities such as atrioventricular heart block or myopericarditis, neurologic complications, or intermittent attacks of arthritis (1). The causative agent, the Lyme disease spirochete *Borrelia burgdorferi* (2), is transmitted by *Ixodes dammini* or related ixodid ticks (3). Antibiotic treatment with tetracycline or penicillin is usually curative (4).

We report the case of a woman who developed Lyme disease during the first trimester of pregnancy. She did not receive antibiotic therapy. Her infant, born at 35 weeks gestational age, died of congenital heart disease during the first week of life. Histologic examination of autopsy material showed the Lyme disease spirochete in the spleen, kidneys, and bone marrow.

Maternal Fetal Transmission of the Lyme Disease Spirochete Borrelia burgdorferi, 1985.

Schlesinger PA, Duray PH, Burke BA, Steere AC, Stillman MT. Maternal-fetal transmission of the Lyme disease spirochete, Borrelia Burgdorferi. (1985). Ann Internal Med, 103, 67-8

- EM rash and other symptoms first trimester
- **NO** antibiotic therapy
- Infant born at 35 weeks with respiratory distress
- **died after 39 hours**
- **Autopsy = widespread** cardiac abnormalities
- **Lyme disease Spirochetes** (Bb) were identified in **spleen, renal tubules/kidney** and **bone marrow.**
- **No evidence of inflammation** in tissues/organs
- Maternal Lyme serology positive postpartum
- Dr Alan Macdonald later demonstrated Bb in the
- myocardium by IHC - immunohistochemical technique.

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Centers for Diseases Control and Prevention
MMWR
Morbidity and Mortality Weekly Report

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

June 28, 1985

Update: Lyme Disease and Cases Occurring during Pregnancy — United States

Since transplacental transmission of *B. burgdorferi* has been documented, it will be important to determine whether maternal infection with *B. burgdorferi* is associated with an increased risk of adverse pregnancy outcome. Cases of Lyme disease during pregnancy should be reported to state health departments and CDC (telephone [404] 329-3687) before delivery so the types and approximate frequency of any adverse outcome can be determined and appropriate diagnostic tests obtained.

References

1. Schlesinger PA, Duray PH, Burke BA, et al. Maternal-fetal transmission of the Lyme disease spirochete, *Borrelia burgdorferi*. Ann Intern Med 1985 (in press).

The World Health Organization. (WHO) reported on transplacental transmission of Lyme disease in their 26 September, 1986 Weekly Epidemiological Record. This was based on the first case report from 1985 by Schlesinger etal.

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5 SEPTEMBER 1986 — 61ST YEAR – 61e ANNÉE

LYME DISEASE
Cases occurring during pregnancy

UNITED STATES OF AMERICA. – Lyme disease is a tickborne illness caused by a spirochete, *Borrelia burgdorferi*. The number of cases reported to the Centers for Disease Control (CDC) has increased over the past 2 years so that Lyme disease is now the most commonly reported tickborne illness in the United States. Although it is reportable in only a few states, informal national surveillance was initiated by CDC in 1980 and has been compiled annually since 1982. In 1980, 1982 and 1983, 226, 491, and 599 cases, respectively, were reported in the United States. In 1984, a provisional total of 1 498 cases was reported.[1] For Lyme disease patients for whom 1983 and 1984 surveillance data are available, ages ranged from 1 year to 81 years (median 34 years). Fifty-four per cent of cases occurred among males. Eighty per cent of cases occurred during the 4-month period May-August, with the peak incidence in July.

Since 1980, reported cases of Lyme disease have been reported in an increasing number of states. Lyme disease occurred in 11 states in 1980 and 1982, 18 states in 1983, and 21 states in 1984. However, in all reporting years, over 90% of all cases occurred in only 7 states: Connecticut, Massachusetts, Minnesota, New Jersey, New York, Rhode Island, and Wisconsin.

The possible association between Lyme disease during pregnancy and adverse outcome has recently received attention. Transplacental transmission of *B. burgdorferi* has been documented in a pregnant woman with Lyme disease who did not receive antimicrobial therapy. She delivered an infant with a congenital heart defect. The relationship between the intrauterine infection and congenital heart defect has not been established. In an effort to assess the risk of Lyme disease during pregnancy, the state and territorial epidemiologists and CDC have established a registry to enrol cases of Lyme disease in pregnant women before the outcome of pregnancy is known. Of the 19 pregnancies evaluated to date, none resulted in a child with a congenital heart defect. However, other adverse outcomes were found, including intrauterine fetal death in the second trimester, prematurity, and developmental delay with cortical blindness. None of the adverse outcomes have been documented to be caused by Lyme disease.

[1] See No 17, 1986, pp 129-130

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1986 – Human Fetal Borreliosis – Dr. Alan MacDonald

Zbl. Bakt. Hyg. A 263, 189–200 (1986)

Human Fetal Borreliosis, Toxemia of Pregnancy, and Fetal Death

ALAN B. MACDONALD

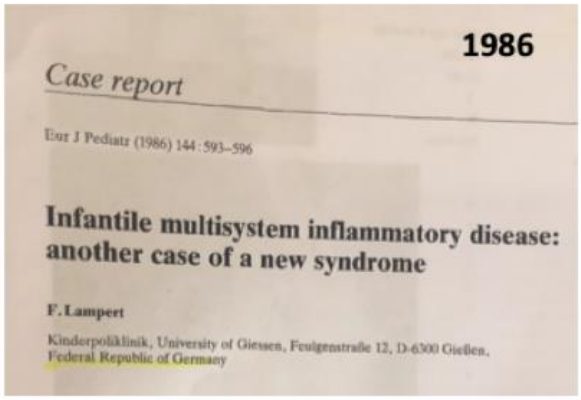
Southampton Hospital, Long Island, New York, U.S.A.

Introduction

The potential for transplacental infection of the human fetus is recognized for syphilis, leptospirosis, and relapsing fever borreliosis. A case of maternal – fetal transmission of the Lyme disease spirochete, *Borrelia burgdorferi*, has recently been reported (1). This report describes four cases of fetal borreliosis which were encountered in a prospective study of abortuses.

'Spirochetes were cultured from fetal liver in four stillborn human fetuses, three of whom demonstrated congenital malformations of the heart or great vessels.' Using culture and immunohistochemistry techniques.

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



1986

Case report

Eur J Pediatr (1986) 144 : 593–596

Infantile multisystem inflammatory disease: another case of a new syndrome

F. Lampert

Kinderpoliklinik, University of Giessen, Feulgenstraße 12, D-6300 Giessen, Federal Republic of Germany

'The neonatal onset suggests a prenatal infection'

Baby girl delivered 37 weeks and admitted to hospital with neonatal onset of:

- Maculopapular skin rash
- Hepatosplenomegaly
- Hypertrophy of heart
- C Reactive Protein elevated
- Chromosome analysis normal
- Negative testing for Treponema pallida
- **Elevated antibody titres against I. ric. Borrelia burgdoferi antigen found in serum**
- Anemia
- Fever accompanied by recurrent infections (enteritis, bronchitis, rhinitis, cystopyelitis)
- Further course was characterized by retarded growth and development, head enlargement with wide open fontanel, protruding eye balls, conjunctivitis, blepharitis, massive enlargement of cervical, axillary and inguinal lymph nodes, bilateral arthritis of knees, itching maculopapular rash aggravated in sun and heat.

Elevated IgG titres (480, 370, 330 units) were found repeatedly in patients serum. The titres dropped after 3 weeks (150, 160, 185) of 9 Mega Pen G daily i.v. Titres in CSF not elevated.

The mother (asymptomatic) also had positive titres (ELISA: 290;330 units). Father was negative.

'Thus it cannot be ruled out that our patient developed this specific syndrome as a self propagating inflammatory host response after an intrauterine infection with Lyme disease spirochetes.

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

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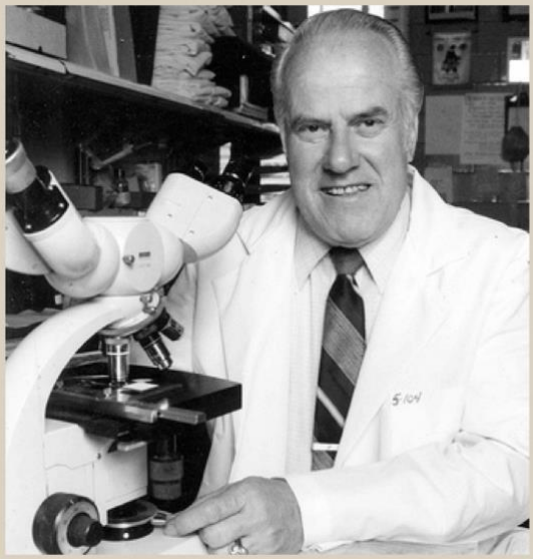

The Enlarging Spectrum of Tick-Borne Spirochetoses: R. R. Parker Memorial Address

... 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 ;

— Dr. Willy Burgdorfer

REVIEWS OF INFECTIOUS DISEASES • VOL. 8, NO.6· NOVEMBER-DECEMBER 1986

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

LYME DISEASE IN MATERNAL INFECTIONS

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

28. SCHLESINGER, P. A., P. H. DURAY, B. A. BURKE, A. C. STEERE & M. T. STILLMAN. 1985. Maternal fetal transmission of the Lyme disease spirochete, *Borrelia burgdorferi*. Ann. Intern. Med. **103:** 67–68.
29. MACDONALD, A. 1986. Human fetal borreliosis, toxemia of pregnancy, and fetal death. Zbl. Bakt. Hyg. A **263:** 189–200.

1. It is clear that Bb can be transmitted in the blood of infected pregnant women across the placenta into the fetus
2. Transmission resulted in congenital infections and fetal demise
3. Spirochetes were recovered from infant's tissues including brain, spleen and kidney
4. Cardiac abnormalities seen
5. Inflammation changes not pronounced but possibly due to immature immune system.

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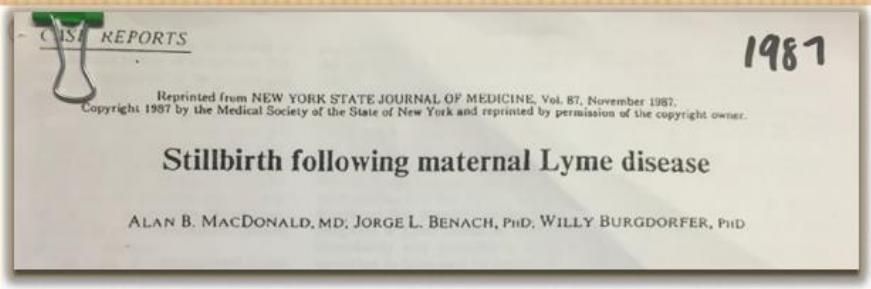
CASE REPORTS

1987

Reprinted from NEW YORK STATE JOURNAL OF MEDICINE, Vol. 87, November 1987.
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Stillbirth following maternal Lyme disease

ALAN B. MACDONALD, MD; JORGE L. BENACH, PHD; WILLY BURGDORFER, PHD

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

- Mother had EM rash first trimester
- Did not seek medical help and no antibiotic therapy
- **Stillborn** delivered at term and **Autopsy** revealed heart defect
- **'Overwhelming spirochetosis** in the fetus'
- **Spirochetes cultured** from **fetal liver and confirmed as Borrelia burgdorferi using H5332 monoclonal IgG antibody provided by Dr Alan Barbour**
- **Spirochetes** also identified by immunofluorescence in **heart, adrenal gland, placenta and mid brain** using histological techniques
- **Silver stains** disclosed spirochetes in myocardium, placenta, liver and brain
- No significant inflammation in tissue
- Lyme serology (IFA/ELISA) on postpartum maternal blood was positive at 2 of 3 laboratories

Maraspin, Cimperman etal – Erythema Migrans in Pregnancy, Slovenia

Case #1 - 1986

33 year old woman delivered **stillborn infant at 34 weeks**

- did **not remember tick bite**
- asymptomatic
- no medications taken
- Maternal testing for syphilis was negative
- Maternal testing for **Borrelia burgdorferi IgG antibody titers positive**

Autopsy revealed: fluidothorax, ascites, hepatosplenomegaly

Spirochetes seen by dark-field examination of lung, liver, and brain tissue specimens

Case #2

26 year old woman developed EM rash after tick bite in first trimester

- treated with penicillin for 10 days,
- at the end of second trimester develops vertigo
- **Maternal Serologic tests for B. burgdorferi positive**
- retreated with penicillin for 14 days,
- **32 weeks** delivered a female infant who **died within a few hours of birth**

Autopsy revealed: hydrocephalus, fluidothorax, ascites

Spirochetes seen by dark-field examination of lung, liver tissue

Two case reports from 1986 describe infants who died at 34 weeks and 32 weeks gestation. In both cases upon autopsy, spirochetes were seen infant organs and tissues.

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

No attempt to culture spirochetes from fetal autopsy tissues.

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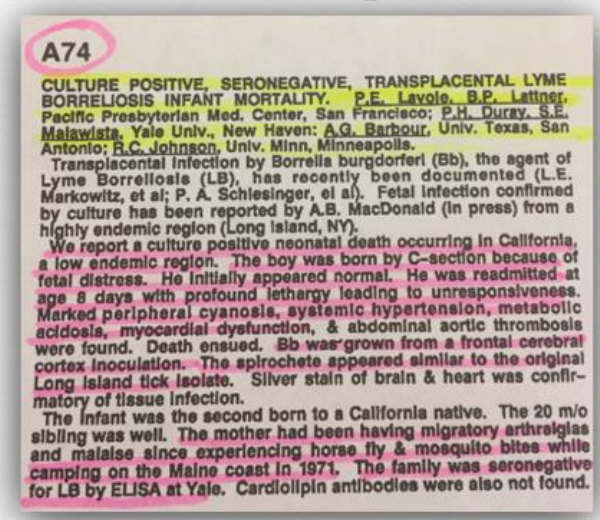
Case Report Culture Positive, Seronegative Transplacental Lyme Borreliosis 1987.



A74

CULTURE POSITIVE, SERONEGATIVE, TRANSPLACENTAL LYME BORRELIOSIS INFANT MORTALITY. P.E. Lavoie, B.P. Lattner, Pacific Presbyterian Med. Center, San Francisco; P.H. Duray, S.E. Malawista, Yale Univ., New Haven; A.G. Barbour, Univ. Texas, San Antonio; H.C. Johnson, Univ. Minn, Minneapolis.

Transplacental infection by Borrelia burgdorferi (Bb), the agent of Lyme Borreliosis (LB), has recently been documented (L.E. Markowitz, et al; P. A. Schlesinger, el al). Fetal infection confirmed by culture has been reported by A.B. MacDonald (in press) from a highly endemic region (Long Island, NY).

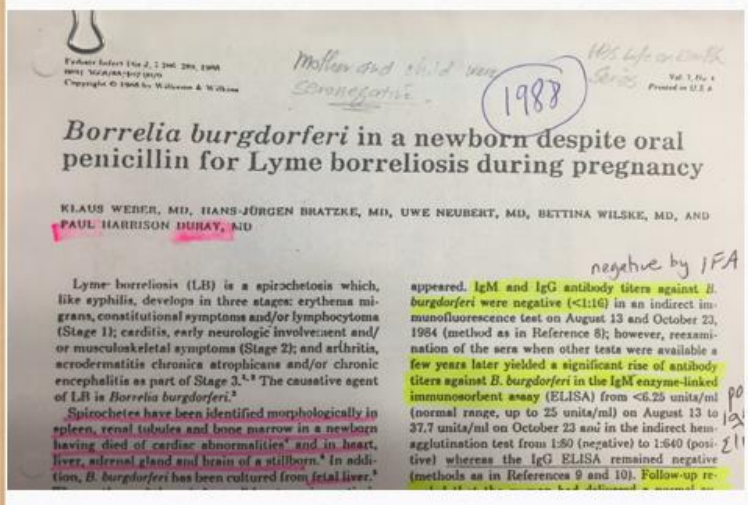
We report a culture positive neonatal death occurring in California, a low endemic region. The boy was born by C-section because of fetal distress. He initially appeared normal. He was readmitted at age 8 days with profound lethargy leading to unresponsiveness. Marked peripheral cyanosis, systemic hypertension, metabolic acidosis, myocardial dysfunction, & abdominal aortic thrombosis were found. Death ensued. Bb was grown from a frontal cerebral cortex inoculation. The spirochete appeared similar to the original Long Island tick isolate. Silver stain of brain & heart was confirmatory of tissue infection.

The infant was the second born to a California native. The 20 m/o sibling was well. The mother had been having migratory arthralgias and malaise since experiencing horse fly & mosquito bites while camping on the Maine coast in 1971. The family was seronegative for LB by ELISA at Yale. Cardiolipin antibodies were also not found.

- Mother from California (low-endemic region)
- Mother had migratory arthralgias and pain after horsefly and mosquito bites after camping in Maine
- **No** antibiotic therapy, no clear onset for Lyme
- Neonatal distress born by C-section
- Infant **initially appeared healthy** and discharged
- Readmitted at 8 days with profound lethargy and progressive multisystem failure, died.
- Upon autopsy Borrelia Burgdorferi was cultured from a frontal cerebral cortex.
- Silver stain of brain and heart confirmatory of tissue infection.
- Mother and infant were **seronegative** for LB by ELISA at Yale

Lavoie PE, Lattner BP, Duray PH, Barbour AG, Johnson HC. Culture positive seronegative transplacental Lyme Borreliosis infant mortality (1987) Arthritis Rheum, 30(4), 3(suppl):S50

Case Report Borrelia Burgdorferi in Newborn despite oral antibiotics for Lyme in Pregnancy – 1988, Germany



1988

Borrelia burgdorferi in a newborn despite oral penicillin for Lyme borreliosis during pregnancy

KLAUS WEBER, MD, HANS-JÜRGEN BRATZKE, MD, UWE NEUBERT, MD, BETTINA WILSKE, MD, AND PAUL HARRISON DURAY, MD

negative by IFA

Lyme borreliosis (LB) is a spirochetosis which, like syphilis, develops in three stages: erythema migrans, constitutional symptoms and/or lymphocytoma (Stage 1); carditis, early neurologic involvement and/or musculoskeletal symptoms (Stage 2); and arthritis, acrodermatitis chronica atrophicans and/or chronic encephalitis as part of Stage 3.[1-3] The causative agent of LB is *Borrelia burgdorferi*.[3]

Spirochetes have been identified morphologically in spleen, renal tubules and bone marrow in a newborn having died of cardiac abnormalities[4] and in heart, liver, adrenal gland and brain of a stillborn.[5] In addition, *B. burgdorferi* has been cultured from fetal liver.[5]

appeared. IgM and IgG antibody titers against *B. burgdorferi* were negative (<1:16) in an indirect immunofluorescence test on August 13 and October 23, 1984 (method as in Reference 8); however, reexamination of the sera when other tests were available a few years later yielded a significant rise of antibody titers against *B. burgdorferi* in the IgM enzyme-linked immunosorbent assay (ELISA) from <6.25 units/ml (normal range, up to 25 units/ml) on August 13 to 37.7 units/ml on October 23 and in the indirect hemagglutination test from 1:80 (negative) to 1:640 (positive) whereas the IgG ELISA remained negative (methods as in References 9 and 10). Follow-up re-

- 37 year old woman bitten by ticks in Germany in 1984 first trimester of pregnancy, - late July developed EM
- Treated with a 7 day course of oral penicillin
- **Negative serology IgG and IgM antibody by IFA** for mother – first in August and repeated in October.
- Delivered a **healthy baby** after **healthy pregnancy**.
- 23 hours after birth the child had **respiratory distress** and **died**
- **Bb found in the brain and liver** of deceased neonate.
- Bb identified in brain **using monoclonal antibody H5332** provided by Dr. Alan Barbour.
- **No inflammation** seen in any organ examined including heart, liver brain and kidney

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

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Gestational Lyme Borreliosis

Implications for the Fetus

1989

*Alan B. MacDonald, MD**

* Attending Pathologist, Southampton Hospital, Southampton, New York

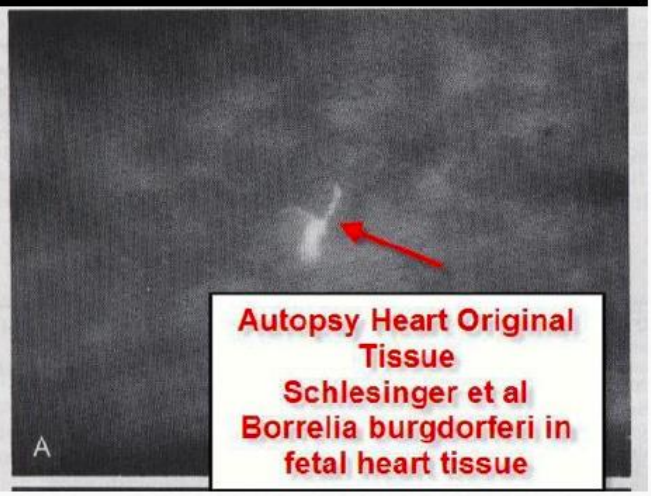
Rheumatic Disease Clinics of North America—Vol. 15, No. 4, November 1989

- Comprehensive review of **14 cases of adverse fetal and neonatal outcomes** of gestational borreliosis
- **Autopsy and clinical studies have *associated* gestational Lyme borreliosis** with various medical problems including:
- Whether any or all of these associations are coincidentally or causally related remains to be clarified by further investigation.
- 'It is my expectation that the spectrum of gestational Lyme borreliosis **will expand into many of the clinical domains** of prenatal syphilis.'

- fetal death
- hydrocephalus
- cardiovascular anomalies
- neonatal respiratory distress
- hyperbilirubinemia
- intrauterine growth restriction,
- cortical blindness
- sudden infant death syndrome
- maternal toxemia of pregnancy.

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

Observations from cases of Fetal Borreliosis



1: Tissue **inflammation is absent** in fetuses with transplacentally acquired Bb infection

2: Gestational Lyme Borreliosis **may be associated** with fetal death in utero, fetal death at term, or infant death after birth

3: **Maternal blood is seronegative** for specific antibodies against Bb **in cases where the spirochete can be demonstrated** in the fetus or placenta

4:**Clinical diagnosis** of probable Lyme must be the 'gold standard of diagnosis' because Lyme serologic studies may be non-diagnostic.'

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

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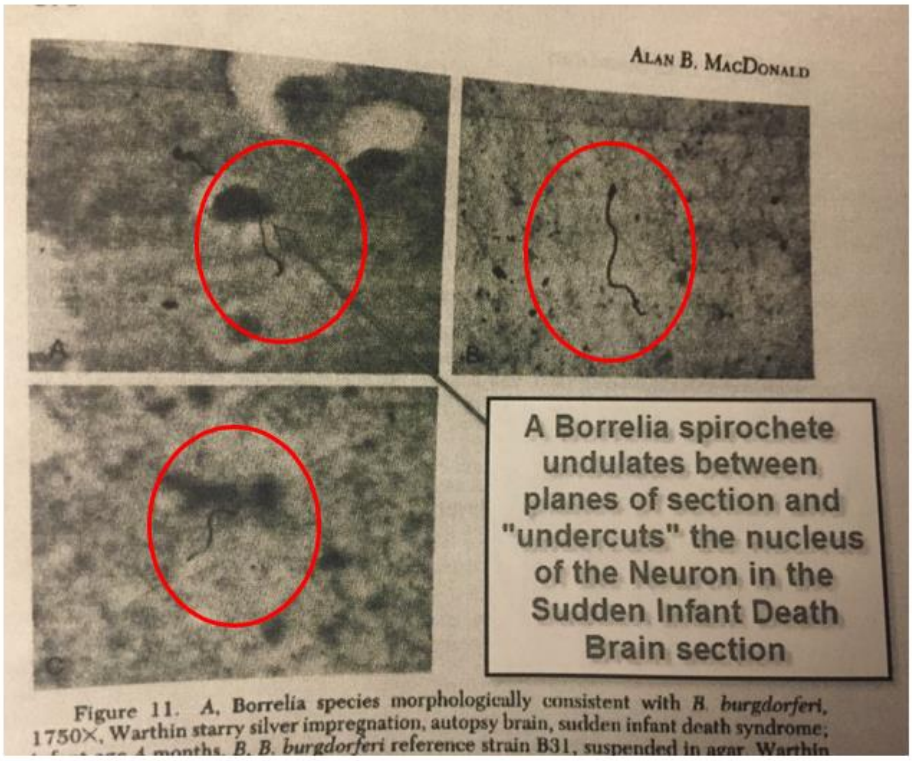

Figure 11. A, Borrelia species morphologically consistent with *B. burgdorferi*, 1750×, Warthin starry silver impregnation, autopsy brain, sudden infant death syndrome; [illegible] months. B, *B. burgdorferi* reference strain B31, suspended in agar, Warthin

Borrelia spirochetes found in autopsy of infant brain age 4 months
Sudden Infant Death Syndrome (SIDS)

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

Neonatal Lyme Disease

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

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

This little case certainly has **important teaching points and big implications**:

1: The mom **was asymptomatic** but followed by researchers because she was infected (presumably with a tick bite) in her second trimester
2: Mom was **TREATED with oral antibiotics**
3: At time of giving birth - **Mom is SERONEGATIVE** by standard testing - meaning she would not be positive on standard Lyme tests.
4: **Baby is born with neonatal neurologic dysfunction**
5: A **spinal tap on neonate reveals serological evidence of antibodies specific to borrelia** in cerebral spinal fluid. (no other details given)
6: **This is a congenitally infected baby.** Borrelia burgdorferi has been transmitted from asymptomatic mom who was inadequately treated and seronegative - to her baby!
7: Authors go on to **EMPHASIZE the importance of effective therapy to eradicate borreliae on both maternal and fetal side of the placenta** - as **PERSISTENT infection** may be difficult to be diagnosed after the initial course of antibiotics .
8: Authors one-line recommendation based on this case has huge potential ramifications for management of pregnant moms infected with Lyme and their infants.

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Infusionstherapie 16: 248–251 (6/1989)

Prevalence of Erythema migrans Borreliosis in Blood Donors

R. Schmidt[a], E. Gollmer[a], R. Zunser[a], J. Krüger[b], R. Ackermann[c]

[a]Department of Neurology, and
[b]Department of Transfusion Medicine of the University Hospital of Cologne
[c]Institute of Laboratory Medicine, Cologne, FRG

Summary and Key Words

European Erythema migrans Borreliosis and North American Lyme disease are closely related to syphilis. This implicates a potential risk of infection for blood recipients. Eighty-six of 3,157 blood donors tested showed IgG-antibodies against Borrelia Burgdorferi. From among 47 persons of this group who could be examined, clinical signs of diseased skin, joints or nervous system, not diagnosed before, were found or could be suspected in 13 cases. Since intrauterine transmission of Borrelia infection has been described, the inevitable question of whether this disease can also be transmitted as a result of blood transfusion becomes a major concern. As the pathogen can persist even in the presence of serum antibodies, it seems advisable to examine blood donors serologically, whenever Erythema migrans Borreliosis is suspected. Though further research is required to document a transfusion-transmitted Borrelia infection, infected persons should be treated to avoid serious or late manifestations.

Zusammenfassung und Schlüsselwörter

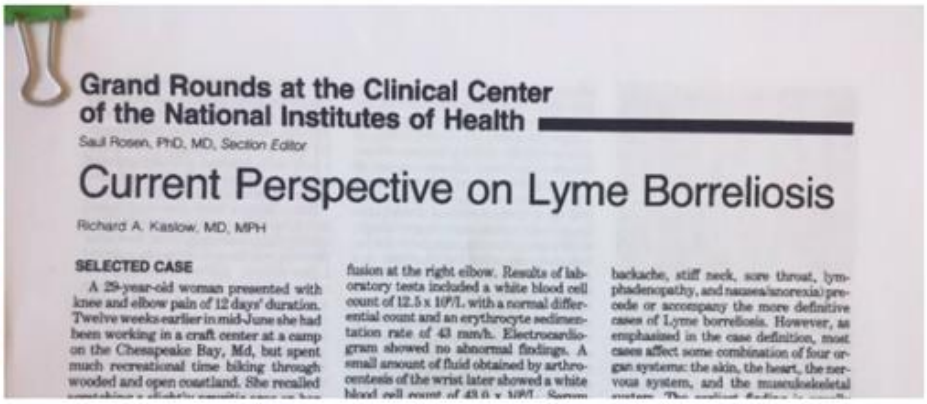
Die europäische Erythema-migrans-Borreliose und die nordamerikanische Lyme-Krankheit sind der Syphilis nahe verwandt. Interessant ist, inwieweit die Borrelien-Infektion eines Spenders in Analogie zur Transfusions-Syphilis ein Risiko für den Empfänger einer Blutkonserve darstellt. Es wiesen 86 von 3157 unausgewählten, serologisch überprüften Blutspendern IgG-Antikörper gegen Borrelia Burgdorferi auf. Unter 47 dieser Spender, die klinisch untersucht werden konnten, waren 13, bei denen sich bis dahin übersehene Symptome der Erkrankung an Haut, Gelenken und Nervensystem aktuell nachweisen oder rückblickend wahrscheinlich machen ließen. Da intrauterine Übertragungen inzwischen beschrieben wurden, sind weitere Untersuchungen zur Klärung des Transfusionsrisikos erforderlich. Es ist zu berücksichtigen, daß die Antikörper-Titer insbesondere zu Beginn der Erkrankung trotz eindeutiger klinischer Symptome negativ sein können und daß der Erreger auch in Anwesenheit von Serum-Antikörpern im Organismus persistieren kann. Derzeit sollten Spender bei Verdacht einer Erythema-migrans-Borreliose klinisch und

'Since intrauterine transmission of Borrelia infection has been described, the inevitable question of whether this disease can be transmitted as a result of blood transfusion becomes a major concern.'

Schmidt R. et al. Prevalence of erythema migrans borreliosis in blood donors. Infusionsterapie 1989;16(6): 248-251.

...sequelae occasionally noted late in the course of infection. Chronic dementia, encephalopathy, and demyelination[14,15] appear to occur only rarely. If such sequelae should prove more common, by analogy to the late degenerative features of tertiary syphilis, they would have profound implications for the intensity with which infection must be sought and treated. Instances of severe illness in infants following transmission from untreated mothers[16] has already lowered the threshold for more aggressive treatment of pregnant women.

Second, the new locations at which the disease has been observed, and to some



Grand Rounds at the Clinical Center of the National Institutes of Health

Saul Rosen, PhD, MD, *Section Editor*

Current Perspective on Lyme Borreliosis

Richard A. Kaslow, MD, MPH

SELECTED CASE

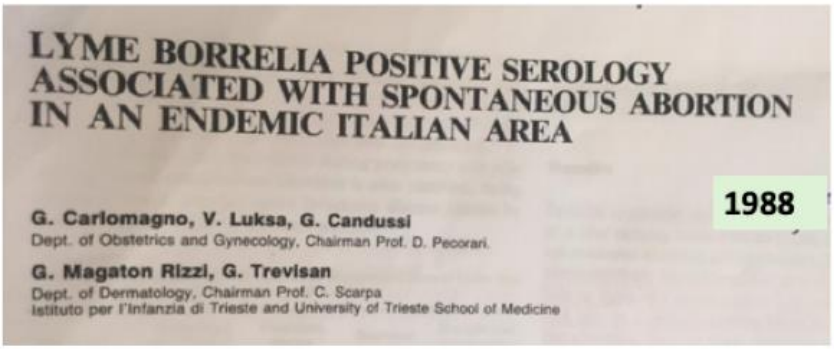
A 29-year-old woman presented with knee and elbow pain of 12 days' duration. Twelve weeks earlier in mid-June she had been working in a craft center at a camp on the Chesapeake Bay, Md, but spent much recreational time biking through wooded and open coastland. She recalled

fusion at the right elbow. Results of laboratory tests included a white blood cell count of 12.5 x 10⁹/L with a normal differential count and an erythrocyte sedimentation rate of 43 mm/h. Electrocardiogram showed no abnormal findings. A small amount of fluid obtained by arthrocentesis of the wrist later showed a white

backache, stiff neck, sore throat, lymphadenopathy, and nausea/anorexia) precede or accompany the more definitive cases of Lyme borreliosis. However, as emphasized in the case definition, most cases affect some combination of four organ systems: the skin, the heart, the nervous system, and the musculoskeletal

'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.



LYME BORRELIA POSITIVE SEROLOGY ASSOCIATED WITH SPONTANEOUS ABORTION IN AN ENDEMIC ITALIAN AREA

1988

G. Carlomagno, V. Luksa, G. Candussi
Dept. of Obstetrics and Gynecology, Chairman Prof. D. Pecorari.
G. Magaton Rizzi, G. Trevisan
Dept. of Dermatology, Chairman Prof. C. Scarpa
Istituto per l'Infanzia di Trieste and University of Trieste School of Medicine

"Necessity for routine serological screening of pregnant patients living in an endemic area 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."

"Paraffin 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 trans placental transmission."

Carlomagno V, Luksa V, Candussi G et al. Lyme Borrelia Positive Serology associated with spontaneous abortion in an endemic Italian Area. Acta Europaea Fertilitatis, Vol 19, n.5, 1988.

Blood samples from a series of 49 cases of spontaneous abortion and a series of 49 cases of normal term pregnancy tested for specific antibodies to Borrelia burgdorferi.

Specific antibodies were detectable in 6 (12.2%) of the spontaneous abortion group patients.

4 of 6 seropositive patients from spontaneous abortion group reported a tick bite ranging from 6 months to 36 months prior to the abortion.

3 sera (6%) from the 49 term pregnancy were positive – none of these patients remembered a tick bite or EM rash and all had healthy infants.

Although Bb could not be directly implicated directly as cause of abortion, seropositive women were more frequently detected (12.2%) than among term pregnancy group (6.12%)

1996

Gynecologic and Obstetric Investigation

Original Paper

Gynecol Obstet Invest 1996;41:240–243

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

Reinaldo Figueroa[a]
Luis A. Bracero[a]
María Agüero-Rosenfeld[b]
Debra Beneck[b]
John Coleman[c]
Ira Schwartz[c]

Departments of [a] Obstetrics and Gynecology, [b] Pathology, and [c] Biochemistry and Molecular Biology, New York Medical College, Westchester County Medical Center, Valhalla N.Y., USA

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.

Researchers studied placentas of asymptomatic women with reactive (ELISA positive or equivocal serology for Lyme antibodies). The study identified spirochetes in 3 of 60 placentas.

- The three women **were asymptomatic**, **no known history of a tick bite**
- **2 of three women had negative Western Blot** and one woman had indeterminate WB. This means that 2/3 of these women would be considered seronegative by current two tier process .
- Authors stated that presence of **Bb spirochetes in placenta implies fetal transmission**
- Cord blood serology IgG and IgM was done in all 3 infants and **negative** (this sero-negativity despite infection had previously been found by Dr. Macdonald and later found by Dr. Gardner).
- A normal perinatal outcome was observed in all cases – but no mention of follow-up (to compare to another spirochetal disease syphilis - we know from congenital syphilis that 2/3 of infected infants are asymptomatic at birth and only develop symptoms later on)
- 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 (this has never been done).

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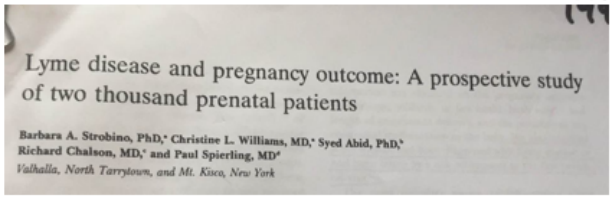
EPIDEMIOLOGICAL STUDY Lyme Disease and Pregnancy Outcomes – CORD BLOOD SEROSURVEY, 1993
Prospective Cohort Study


Lyme disease and pregnancy outcome: A prospective study of two thousand prenatal patients

Barbara A. Strobino, PhD,* Christine L. Williams, MD,* Syed Abid, PhD,† Richard Chalson, MD,‡ and Paul Spierling, MD‡
Valhalla, North Tarrytown, and Mt. Kisco, New York

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.

2014 women completed questionnaires and had serum tested for antibody to Borrelia burgdorferi at prenatal visit and delivery. 11 women (0.7%) were seropositive at first prenatal visit. Investigators only included women with a positive IgM serology (current infection) not IgG. Enrollment in the study would have missed miscarriages that occurred before that visit.

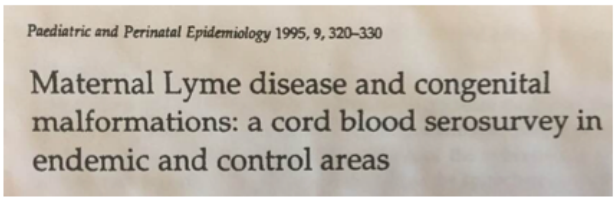
All 11 women had live births
Three congenital defects noted:
1. Metatarsus adductus
2. stomach reflux
3. Multiple major anomalies of Vater (vertebral defects, imperforate anus, radial and renal dysplasia
4. Babies cord blood tested with IgM and all negative

*Investigators only looking for congenital defects at 6 month maternal follow-up - No longitudinal follow-up or serial serology, no direct detection methods/histology of placentas or culture of cord blood.

- There was a statistically significant association between past miscarriages and a history of a tick bite.
- **Authors noted that the incidence of cardiac defects was two times higher born to mothers in high versus low endemic areas.**
- There was a significant association between having had a tick bite within 3 years of conception and congenital defects.

Their sample size was limited and **cannot draw conclusions** about risk of adverse outcomes

EPIDEMIOLOGICAL STUDY – CORD BLOOD SEROSURVEY, 1995


Paediatric and Perinatal Epidemiology 1995, 9, 320–330

Maternal Lyme disease and congenital malformations: a cord blood serosurvey in endemic and control areas

Williams etal (published in 1995): NY cord blood serosurvey – (1986-1988) – 5000 infants enrolled (2500 from endemic, 2500 from non-endemic areas)

Authors conclude:

- Maternal Bb exposure was 5-10 times higher in mothers from endemic versus non-endemic area and infants in endemic area had a significant higher (13%) incidence of congenital cardiac defects and murmors compared with 5% in non-endemic areas. (Gardner, T. Lyme Disease. Chapter 11. Infect Dis Fetus and Newborn Infant. 5th edition Saunders, 2001. pg. 576)
- The authors note that **late developmental sequalae would not be detected by this study** due to absence of long term follow-up.
- Study was funded in part by the March of Dimes. And **March of Dimes** website currently reports possible adverse outcomes in pregnancy associated with Lyme disease.
- Authors state: 'Little is known about persistence of the spirochete throughout the course of the disease." "Cases can go untreated, or although treated, **can recur** anyway." (Authors are acknowledging the possibility of persistence/chronicity of infection)

1995: 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

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Case report – Austria, 1994

A Most Unusual Case of a Whole Family Suffering from Late Lyme Borreliosis for Over 20 Years

R. Gasser, M.D., Ph.D., F.A.C.A., MNYAS
J. Dusleag, M.D.
E. Reisinger, M.D.
R. Stauber, M.D.
M. Grisold, M.D.
S. Pongratz, M.D.
C. Furian, M.D.
B. Feigl, M.D.
and
W. Klein, M.D., F.A.C.C.

1994 GRAZ, AUSTRIA

Glasser, R, Dusleag, J, Reisinger, E et al. A most unusual case of a whole family suffering from late lyme borreliosis for over 20 years. 1994. Angiology, 45(1), 85-86.

Wife acquired tickbite in **1968** resulting in early EM rash and later chronic symptoms including meningitis, depression, chronic arthritis.

Her husband had **no memory of primary infection** but remembers recurrent flu like symptoms a year after infection of his wife, he developed **progressive symptoms** including ventricular arrhythmias.

In 1969 a son was born **suffered from multiple symptoms** including weakness, recurrent fevers and irritability and depression.

All three patients **tested positive for Bb by immunoblotting** (WB) at clinic for Bb associated disorders.

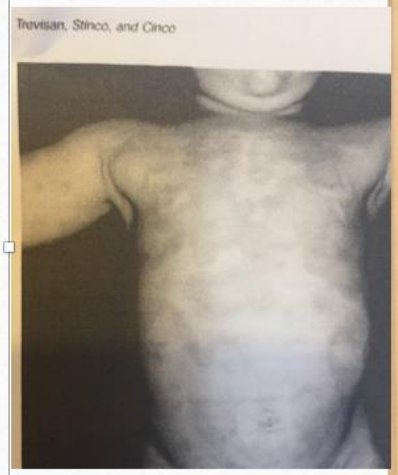
Case report represents the only report in literature of a **whole family infected and ill** with Lyme disease for a long period of time.

Raises questions of **sexual and transplacental** transmission.

Neonatal skin lesions due to a spirochetal infection: a case of congenital Lyme borreliosis? Case Report

- Infant presents to Pediatric Dermatology with **multiple annular erythematous patches**, **fever** and **lymphadenopathy** which had started at 3 weeks of age and were relapsing/remitting. **No history of tick bite**.
- 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. Postpartum **serum antibody to Bb was elevated – indicative of maternal exposure to LB**
- Initial infant serology 9 months **negative**. 13 month **seroconversion** by WB – IgG.
- B. burgdorferi was **isolated and detected by PCR** from skin biopsy samples
- Despite repeated courses of **oral antibiotic therapy**, lesions **recurred multiple 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**

Trevison et al - 1997



Trevisan, G, Stinco G, Cinco M. Neonatal skin lesions due to a spirochetal infection: a case of congenital Lyme borreliosis? Int J. Dermatol. 1997. 09;36(9);677-680

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abstract no W/TH-P-20 — In Abstracts (book 2) of the 4th International Conference on Lyme borreliosis, Stockholm, Sweden 1990

W/TH-P-20

56

Incidence of Lyme-Borreliosis in Middle-Europe
Hans Horst
State Public Health Laboratory, (MUA) Lüneburg, FRG

Objective To obtain epidemiological data which might be representative for Middle-Europe.

Results. Within one year (1987-1988) 1 600 cases of Lyme-borreliosis were registerd, with the following disease manifestations:

		% of total
Erythema chronicum migrans	1 191	74,3
Lymphadenosis benigna cutis	41	2,6
Acrodermatitis chronica atrophicans	29	1,8
Morphea	1	0,1
Neurological	167	10,4
Lyme-Arthritis	160	10,0
Myo-Pericarditis	4	0,3
Uveo-Chorioretinitis, Neuritis N.opt.	3	0,2
Gestational Borreliosis	1	0,1
Miscellaneous	3	0,2

Dr. Horst identified a case of Gestational Lyme Borreliosis in his abstract presented at the 4th International Conference on Lyme Borreliosis, Stockholm, Sweden.
Abstract no W/TH-P-20

2003: 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

3 day old newborn with septic disease – treated with antibiotics

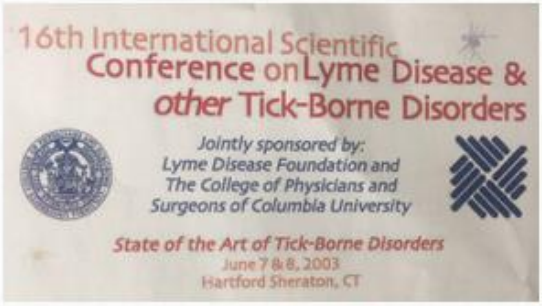
Infant: increased IgM and IgG Borrelia antibody titres in blood and CSF

No history of clinical disease in the mother - asymptomatic

Mother: significantly increased Borrelia antibody IgM titre and slightly elevated IgG titres

Syphilis and mononucleosis testing negative in mother and baby

'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' – Dr. Hans Horst



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.

37 year old female had a 4 month history of migratory joint pains and a positive IgG Western Blot.

She was treated with one month of doxycycline (100mg BID) but relapsed after stopping treatment.

Was retreated by author with multiple antibiotics and after four months was symptom free and completed therapy.

Became pregnant the month after stopping antibiotic therapy, had a normal Ob/Gyn Exam.

Miscarried at 18 weeks gestation

PCR testing was done on the fetus and placenta through Medical Diagnostic Laboratory in NJ and returned positive for Borrelia burgdorferi.

This case report raises concerns about persistence of Bb infection and transmission to fetus despite prior antibiotic therapy.

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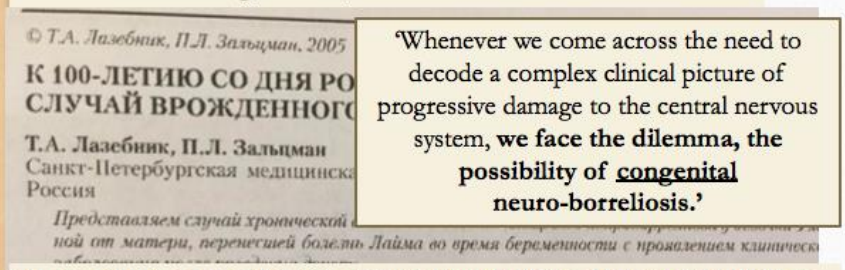
A case of Congenital Neuroborreliosis, 2005
St Petersburg, Russia, Dr. Lazebnik and Zal'tsman


© Т.А. Лазебник, П.Л. Зальцман, 2005

К 100-ЛЕТИЮ СО ДНЯ РО
СЛУЧАЙ ВРОЖДЕННОГ

Т.А. Лазебник, П.Л. Зальцман
Санкт-Петербургская медицинск
Россия

Представляем случай хронический
ной от матери, перенесшей болезнь Лайма во время беременности с проявлением клинич

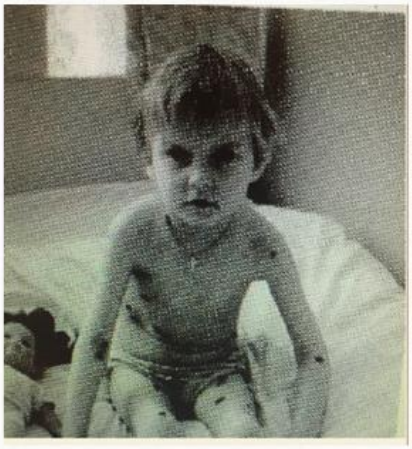
'Whenever we come across the need to decode a complex clinical picture of progressive damage to the central nervous system, **we face the dilemma, the possibility of congenital neuro-borreliosis.'**

'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'.

First trimester mother was bitten by a tick, no medical treatment
At 15-16 weeks pregnancy mother developed high fever presumed flu
Two months after giving birth mother develops weakness, diagnosed with tetraparesis and she is **diagnosed with neuroborreliosis and ALS**

Her daughter 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 through PCR.**
Significant improvement noted with treatment



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

Borrelia Burgdorferi identified in Placentas:

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

Spirochetes identified by silver stain on term stillbirth baby.

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

Case 1: Spirochetes in placenta with silver stain –term stillbirth

Case 4: mother seronegative, 15 weeks miscarriage, spirochetes in placenta by immunofluorescence.

Case 11: Live-birth, neonatal sepsis, respiratory distress, IV antx, spirochetes in placenta by immunofluorescence.

Case 13: Mom dx w Bb second trimester, treated 15 days PCN. Seronegative mom and baby (cord blood) IFA and EIA. Culture of placenta in BSK = motile spirochetes. Silver stain = spirochetes – mother baby treated.

1996: 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.

3 women equivocal ELISA,
2 neg WB, 1 indeterminate IgG by CDC criteria. Negative syphilis.

No history of tick-bites, asymptomatic

3 placentas silver stained positive – ' a few organisms in villi and intervillous space.

PCR confirmed Bb in 2 of 3 placentas – in separate tissue samples.

3rd placenta NOT evaluated by PCR.

Cord blood serology neg by IgG and IgM WB, normal perinatal outcome.

'No relationship between placental spirochetes and results of ELISA or WB'

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

Mother insufficiently treated for Lyme, Bb in placenta by electron microscopy using monoclonal antibodies to flagellin

3 women treated for Bb both borreliae and borrelia cysts by electron microscopy/PCR

2009: 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 .

Case 9: 29 week stillbirth placenta PCR positive for Borrelia garinni.
Case 12: Healthy twins (one twin had IgG and IgM antibodies to Bb). PCR positive for Borellia garinni

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Maternal Lyme Borreliosis and Pregnancy Outcome – Lakos, A, Solymosi, N. Maternal Lyme borreliosis and pregnancy outcome. International Journal of Infectious Diseases 2010 06;14(6):e494-e498

Table 1
Adverse outcomes in 20 pregnancies

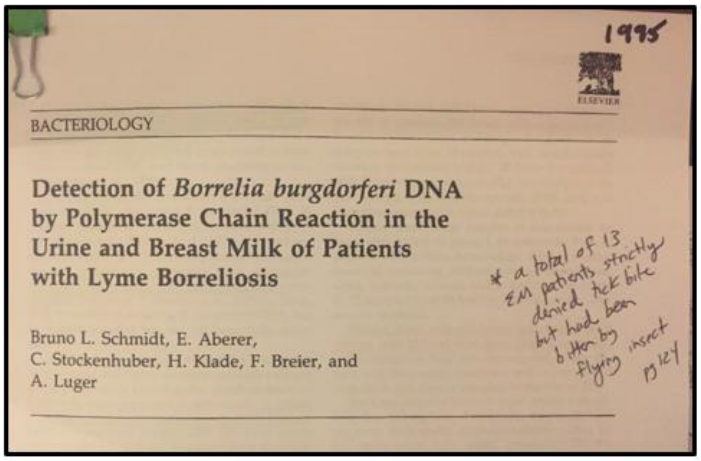
Adverse outcome	No. of cases
Spontaneous abortion	6
Stillbirth	1
Premature birth	1
Small for dates	1
Cavernous hemangioma	4
Neonatal jaundice requiring exchange transfusion	2[a]
Dysplasia coxae	2
Pyloric stenosis	1[b]
Papulovesicular eruption at birth	1
Cerebral bleeding	1
Muscular hypotonicity	1
Hypospadias	1[c]
Skeletal anomaly	1

This study acknowledged a **statistically significant association** between untreated Lyme disease and adverse outcomes

*"We found some of the **symptoms mentioned in other papers such as hyperbilirubinemia, cerebral bleeding, generalized rash and congenital urologic malformations.**"*

*"We **were unable to examine the placenta or fetus for direct Borrelia invasion** in the cases of pregnancy loss, therefore the causal relationship remains undecided in spite of the statistical association."*

Detection of Borrelia Burgdorferi in breastmilk


1995

BACTERIOLOGY

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

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

* a total of 13 EM patients strictly denied tick bite but had been bitten by flying insect

1995 Schmidt, B. et al. 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;21:121-128.

Breast milk from two untreated lactating women with EM rash was tested and **Bb DNA found by PCR**. In one of these patients Bb was also cultured from a skin biopsy.

No reports of Bb transmission via breastmilk in humans. – however one might consider the **Precautionary Principle** – when there isn't proof beyond reasonable doubt and yet reason and rationale come into play.

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Gestational Lyme Studies

Gestational Lyme Disease Case Studies of 102 Live Births

by Charles Ray Jones, M.D., Harold Smith, M.D., Edina Gibb, and Lorraine Johnson, JD, MBA

- Comprehensive case history studies were performed on 102 pediatric or adolescent patients diagnosed with gestational Lyme disease.
- **Majority of mothers diagnosed prior** to the child's diagnosis
- Children were typically diagnosed between 1 and 5 years of age.
- The diagnosis was clinical
- Progression of symptoms - many initial symptoms were present in infants but overlooked until progression in frequency and severity.
- 66% of mothers had **difficult pregnancy** – false labor, nausea, vomiting, fevers, severe fatigue, history of miscarriage, inability to function

37% culture positive
25% positive ELISA
58% positive Western Blot

Highlights inadequacies of currently accepted diagnostic standards for serologic diagnosis using the ELISA and WB

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

Multi-system Symptomology in Children born with Lyme (congenital transmission)

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% - GERD
23% - night sweats
23% - nausea
23% - cardiac manifestations – palpitations, PVC, Mitral VP, heart murmur
23% - generalized muscle pain or spasms
23% - anger and rage
21% - anxiety
21% - speech delay
19% - reading and writing delay
18% - developmental delays
14% - tic disorders
13% - auditory/visual processing problems
13% - aggression or violence
13% - depression
12% - word selection problems
14% - tic disorders
11% - OCD
11% - seizure disorder
9% - involuntary movements
9% - motion sickness
9% - autism
8% - dyslexia
7% - suicidal thoughts
7% - hypotonia at birth (floppy, poor muscle tone)

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

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Congenital Syphilis Associated With Negative Results of Maternal Serologic Tests at Delivery

delivery when results of serologic tests may be negative.[3-10] We describe three infants born to mothers with peripartum syphilis that was not diagnosed by routine serologic screening at delivery. Two mothers were seronegative at delivery, but their infants later developed evidence of congenital syphilis. The third infant was born to a seronegative mother with primary syphilis diagnosed post partum; this infant was asymptomatic and received prophylactic antimicrobial therapy after delivery. These cases underscore the limitations of current prenatal screening methods.

1991

'We describe three infants born to mothers with peripartum syphilis that were not diagnosed with routine serologic screening at delivery.

Two mothers were seronegative at delivery but their infants later developed congenital syphilis.

The third infant was born to a seronegative mother and was asymptomatic and received prophylactic antimicrobial therapy after delivery.

'Limitations on the usefulness and reliability of screening tests exist. **Serologic tests are poor diagnostic tools**.'

Comment.—Routine serologic testing of mothers during pregnancy and at delivery is essential to prevent congenital syphilis.[2] However, limitations on the usefulness and reliability of such screening tests exist. Serologic tests are poor diagnostic tools

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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IgM serology not recommended to diagnose congenital syphilis – why Lyme?

Congenital Syphilis: 'No commercially available immunoglobulin (IgM) test can be recommended.'

CDC https://www.cdc.gov/std/tg2015/congenital.htm

Why is IgM serology considered the standard for testing babies exposed to Lyme disease?

NICE guidelines state: 'Start treatment for Lyme disease under specialist care for babies of women treated for Lyme disease during pregnancy **if the baby has IgM antibodies specific for Lyme disease** or there is any suspicion the baby may be infected.'

https://www.nice.org.uk/guidance/ng95/chapter/Recommendations#management-for-women-with-lyme-disease-during-pregnancy-and-their-babies

Current Testing Approaches of other known Congenital Infections:

Zika: Recommended laboratory testing for possible congenital Zika virus infection includes evaluation for **Zika virus RNA** in infant **serum** and **urine** and Zika virus IgM antibodies in serum. https://www.cdc.gov/pregnancy/zika/testing-follow-up/evaluation-testing.html

HIV: Virologic assays (i.e., **HIV RNA and HIV DNA nucleic acid tests** [NATs]) that directly detect HIV must be used to diagnose HIV in infants and children aged <18 months with perinatal and postnatal HIV exposure; **HIV antibody tests should not be used** .
https://aidsinfo.nih.gov/guidelines/html/2/pediatric-arv/55/diagnosis-of-hiv-infection-in-infants-and-children

Cytomeglovirus: Congenital CMV infection is diagnosed by **detection of CMV DNA in the urine, saliva** (preferred specimens), or blood, within three weeks after birth. Infection cannot be diagnosed using tests that detect antibodies to CMV.
https://www.cdc.gov/cmv/clinical/congenital-cmv.html

Syphilis: All neonates born to mothers who have reactive nontreponemal and treponemal test results should be evaluated with a quantitative nontreponemal serologic test (RPR or VDRL) performed on the neonate's serum.
Darkfield microscopic examination or PCR testing of suspicious lesions or body fluids (e.g., bullous rash and nasal discharge) also should be performed. In addition to these tests, for stillborn infants, skeletal survey demonstrating typical osseous lesions might aid in the diagnosis of congenital syphilis. Pathologic examination of the placenta or umbilical cord using specific staining (e.g., silver) or a *T. pallidum* PCR test using a CLIA-validated test should be considered **No commercially available immunoglobulin (IgM) test can be recommended.** https://www.cdc.gov/std/tg2015/congenital.htm

Chagas' Disease: Infant diagnosis relies on detection of the parasite after birth by microscopic examination of **blood smears and/or PCR testing** for *Trypanosoma cruzi* DNA in blood. https://www.cdc.gov/parasites/chagas/health_professionals/congenital_chagas.html

Toxoplasmosis: *Toxoplasma* PCR assay results from amniotic fluid, peripheral blood, cerebrospinal fluid (CSF), urine, or other body fluids. persistence of positive *Toxoplasma* IgG antibodies beyond 12 months of age (gold standard). positive *Toxoplasma* IgG antibodies and positive *Toxoplasma* IgM antibodies and/or positive *Toxoplasma* IgA antibodies.
https://pediatrics.aappublications.org/content/139/2/e20163860

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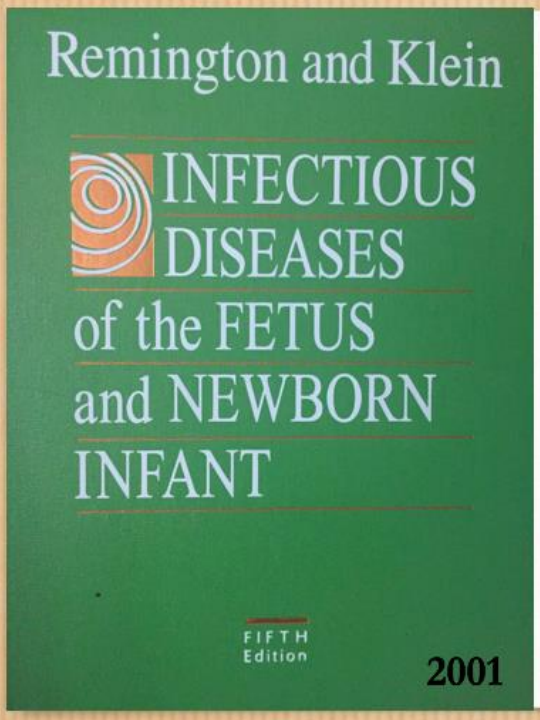

- Review of 263 cases of Gestational Lyme Borreliosis and 66 cases represent adverse outcomes
- 888 citations
- Most comprehensive, extensive and thoughtful review of Congenital Lyme Borreliosis in the Fetus and Newborn Infant

Tessa Gardner, M.D.
Division of Pediatric Infectious Diseases, St. John's Mercy Medical Center; Assistant Professor of Clinical Pediatrics, Washington University School of Medicine, St. Louis, Missouri
Lyme Disease

Clinical Manifestations of Congenital Lyme Borreliosis

CONGENITAL AND GESTATIONAL LYME BORRELIOSIS

A review of the congenital and gestational Lyme borreliosis literature yielded 259 reported cases for which the outcome of the individual episode of gestational Lyme borreliosis was noted,* and addition of four of the author's cases brought the total to 263 cases. A total of 66 cases of the 263 were found that the author considers to represent an adverse event at least associated with an episode of gestational Lyme borreliosis,[25, 26, 28–48] including miscarriage, stillbirth, perinatal death, congenital anomalies, systemic illness, early-onset fulminant sepsis, and later-onset chronic progressive infection (Tables 11–8, 11–13, and 11–14). These 66 cases have been

Gardner, T. Lyme Disease. Chapter 11. Infect Dis Fetus and Newborn Infant. 5th edition Saunders, 2001.

Table. Signs and Symptoms of Congenital Lyme Borreliosis

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

'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'

- Miscarriage during the first 20 weeks gestation
- High frequency of fetal cardiac abnormality, stillbirth, perinatal death
- **Severe early congenital infection** with neonatal sepsis and meningioencephalitis and high frequency of cardiac abnormality
- **Mild early congenital infection** with growth retardation and mild cardiac abnormality
- **Later onset chronic progressive infection**
- **Late congenital infection** with

  growth retardation, developmental delay, neurologic, cutaneous, dental and skeletal involvement.
- Although relatively few cases of congenital Lyme borreliosis have been studied pathologically, comparisons with congenital syphilis may be appropriate

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

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Dr. Tessa Gardner Observations:

'Serology does not appear to be a sensitive method of diagnosis and reliance on seropositivity leads to misdiagnosis of the majority of congenitally infected infants.'

Tetrogenicity: 'It is uncertain whether Bb is teratogenic, although there is an indication that there may be an increased risk of congenital cardiac malformations after first and early second trimester gestational Lyme borreliosis'.

Adverse events: 'It **is possible** that Bb gestational infection with transplacental dissemination **could cause fetal pathology** simply by causing Lyme borreliosis **with the same manifestations** (cutaneous, musculoskeletal, neurologic, neuropsychiatric, neurocognitive and urologic) **that it produces in children and adult patients** which would explain some of the adverse events reported.'

Gardner, T. Lyme Disease. Chapter 11. Infect Dis Fetus and Newborn Infant. 5th edition Saunders, 2001.

Dr. Tessa Gardner – Harvard Trained Pediatric Infectious Disease MD

'The lack of inflammatory findings even when spirochetes were present has been remarkable and could be related to the immunopathogenetic features of B. Burgdorferi infection in which the spirochete is able to spread and persist in tissues without eliciting a prominent host immune response.' pg 555.

'Because of bound host derived enzymes, the spirochete is **invisible to, and able to evade the host immune response,** in a mechanism refereed to as **stealth pathogenesis.** This **may explain the paradox of the ability of B Burgdorferi to persist in skin and other tissues for long periods of time** with **only minimal mononuclear cell infiltration** despite eliciting a strong immune response that, in vitro, is capable of killing it.' p. 553

'.in order for infants with congenital Lyme borreliosis and therefore initiation of prompt antibiotic therapy of the congenitally infected infant **usually depend on suspicion or confirmation of Lyme borreliosis in the mother.** In order for infants with congenital Lyme borreliosis to be recognized/ diagnosed, **it is essential for clinicians** caring for newborns and infants **to become familiar with the various manifestations of Lyme borreliosis in the adult**, as well as in the congenitally infected infant.' p564

Gardner, T. Lyme Disease. Chapter 11. Infect Dis Fetus and Newborn Infant. 5th edition Saunders, 2001.

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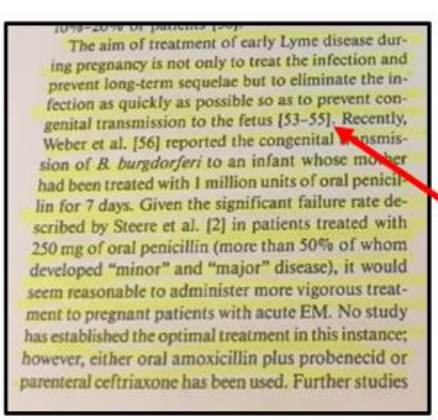
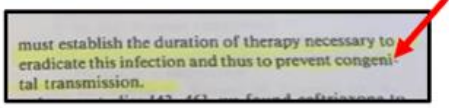
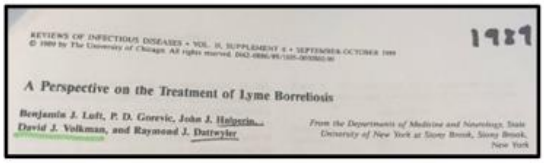


The aim of treatment of early Lyme disease during pregnancy is not only to treat the infection and prevent long-term sequelae but to eliminate the infection as quickly as possible so as to prevent congenital transmission to the fetus [53–55]. Recently, Weber et al. [56] reported the congenital transmission 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.



1989

A Perspective on the Treatment of Lyme Borreliosis

Benjamin J. Luft, P. D. Gorevic, John J. Halperin, David J. Volkman, and Raymond J. Dattwyler

From the Departments of Medicine and Neurology, State University of New York at Stony Brook, Stony Brook, New York

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**.

'Further studies must establish the duration of therapy necessary to eradicate this infection and thus prevent congenital transmission.'

Luft B, Gorevic P, Halperin J, Volkman D, Dattwyler R. A Perspective on the Treatment of Lyme Borreliosis. Review of Infectious Diseases Vol 11(6), 1989.

Intrauterine Infections
Editors: KATHERINE ELLIOTT and JULIE KNIGHT

Introduction

J. A. DUDGEON

Department of Microbiology, The Hospital for Sick Children, London & Institute of Child Health, London

Dudgeon, J.A.
Introduction.
Intrauterine Infections.
Editors Elliot K, Knight J.
Ciba Foundation, 1973.

but will show up as development proceeds and the possibility of neurotropic manifestations at a later date must be kept in mind'. I feel that, having been associated with this type of research for a number of years, we have been obsessed for 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 those children who may have been at risk during pregnancy.

The final problem, which I hope we shall discuss in some detail, is to try to

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HEALTH INFO

Lyme Disease

THE FACTS THE CHALLENGE

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

National Institute of Allergy and Infectious Diseases

National Institute of Arthritis and Musculoskeletal and Skin Diseases

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

Lyme Disease Prevention

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

NIH - '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. 05-7045, May 2005.

SMGroup 2017

Infection with *Borrelia*: Implications for Pregnancy

Dr. James O'Brien – Ob/Gyn
Division of Maternal Fetal Medicine, Pennsylvania College of Medicine.

'Transmission of Borrelia infections occurs via zoonotic vectors and other humans."

"Congenital transfer is an established fact"

O'Brien J, Hamidi O. Lyme Disease (www.smgebooks.com). Infection with Borrelia: Implications for Pregnancy, Nov. 2017.

- Transplacental transmission has been **clearly documented** from case reports of infected fetuses.
- Regardless of the presence or absence of adverse fetal outcomes, it is generally recommended that **every pregnancy associated with infection with Borrelia** include **pathologic examination of the placenta** in order to **detect evidence of spirochetes** within **placental tissue** and within **umbilical cord blood**.
- Final pathology of the placenta, **cultures, immunohistochemistry** and **indirect immunofluorescence** may be **additionally useful in confirming Borrelia infection.**
- **Negative serology in the infant does not necessarily rule out the risk of congenital infection**, since the majority of infants will indeed screen negative.
- Given the **potential for adverse pregnancy outcomes**, any time acute infection with Borrelia is suspected during pregnancy, women should undergo antibiotic treatment. **Treatment should not be delayed or withheld while awaiting serological studies**, which can often be inaccurate.
- **Maternal-fetal transfer of Borrelia can furthermore be clinically silent or unrecognized** and **if not successfully treated**, infection can be life long and latency, late activation and reactivation can occur.

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Testing possibilities for infants

Negative serology (ELISA and WB IgM) does not indicate lack of infection in the infant.

Most diagnoses on fetal/neonatal deaths were made on histology samples.

Blood/Serum

Culture / PCR on the cord or infant blood

Elispot – cellular response in T cells or I-spot

Placentas/cord tissue

PCR testing placentas, foreskin remnants from circumcised male infants

Placenta/fetal tissue examined for histologic abnormalities/spirochetes

16rRNA PCR and sequencing

Urine

Culture and PCR testing newborn urine

urinary OSP A test

Questionnaire

Prenatal screening tool/Questionnaire (Horowitz Questionnaire) can to be used by OB and midwives and Fam MD's

Dr Tessa Gardner – Research needed

Gardner, T. Lyme Disease. Chapter 11. Infect Dis Fetus and Newborn Infant. 5th edition Saunders, 2001. pg 577

Large-scale prospective studies of sufficient numbers of patients with gestational Lyme borreliosis, with follow-up to determine the **pregnancy outcome of each enrolled patient**; **B. burgdorferi specific evaluation** of any fetal or neonatal demise; and **long-term follow-up of each infant** born to determine the occurrence of possible early and late sequalae are needed.

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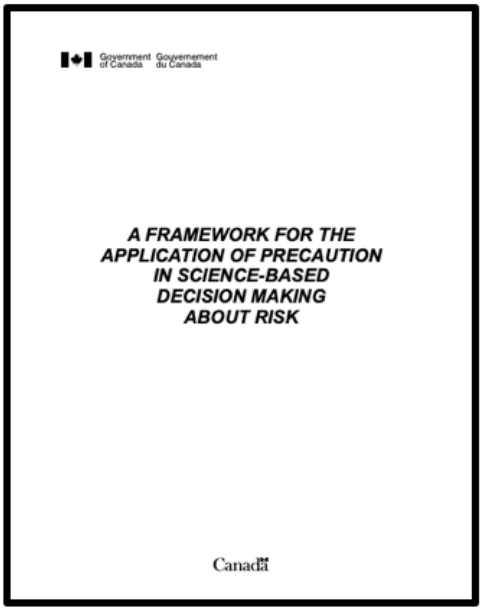
Precautionary Principle:


Government of Canada / Gouvernement du Canada

A FRAMEWORK FOR THE APPLICATION OF PRECAUTION IN SCIENCE-BASED DECISION MAKING ABOUT RISK

Canada

The principle implies that there is a social responsibility to protect the public from exposure to harm, when scientific investigation has **found a plausible risk**. These protections can be relaxed only if further scientific findings emerge that provide sound evidence that no harm will result. -https://en.wikipedia.org/wiki/Precautionary_principle

The application of "precaution", "the precautionary principle" or "the precautionary approach" recognizes that the absence of full scientific certainty **shall not be used as a reason for postponing decisions** where there is a **risk of serious or irreversible harm**.

The application of precaution is distinctive within science-based risk management and is characterized by three basic tenets: the need for a decision, a risk of serious or irreversible harm and a lack of full scientific certainty.
http://publications.gc.ca/site/eng/246284/publication.html


HEALTH July 5, 2017 12:45 pm

The CDC is urging moms to stop taking placenta pills after baby contracts deadly infection

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Health Canada Notice regarding products that contain human placenta

https://globalnews.ca/news/3576512/the-cdc-is-urging-moms-to-stop-taking-placenta-pills-after-baby-contracts-deadly-infection/

July 2017

https://www.canada.ca/en/health-canada/services/drugs-health-products/biologics-radiopharmaceuticals-genetic-therapies/applications-submissions/guidance-documents/human-placenta-products.html

November 2018

In November 2018, Health Canada issues bulletin through National newswire to alert Public and Healthcare professionals to the risk of consuming encapsulated placenta – this was based on **one case-report** from the CDC where baby contracted group B strep infection which was thought to be somehow linked to mother ingestion of dehydrated placenta pills.

Why has Health Canada **NOT alerted** all Public and Healthcare professionals to the **risk of in-utero transmission of Lyme Disease ?** There are several case-reports of confirmed in-utero Bb transmission. The **Precautionary Principle** must be applied.

LymeHope
Beacon of Hope. Anchored in Integrity.

NEXT STEPS – Research, Study and Solutions

- **Retrospective questionnaires/surveys**
- **Evaluate short and long-term outcomes (infants, stillbirth, miscarriages) of pregnancies complicated by Lyme disease.**
- **Large-scale long-term prospective follow-up study of mother-baby pairs to determine maternal cofactors related to maternal-infant transmission; early diagnostic methods to identify Borrelia-infected infants; and maternal and infant outcomes, including occurrence of possible early and late sequelae of congenital Lyme borreliosis**
- **B. Burgdorferi specific evaluation of any fetal or neo-natal demise**
- **Breast-milk and placenta studies**
- **Animal models**

'The fact is that most of the biggest catastrophes that we've witnessed rarely come from information that is secret or hidden.

It comes from information that is freely available and out there, but that we are willfully blind to, because we can't handle, don't want to handle, the conflict that it provokes.

But when we **dare to break that silence**, or when we **dare to see,** and we create conflict, we enable ourselves and the people around us to do our very best thinking.'

Margaret Heffernan – TED Talks

Break the Silence..

This personal letter was shared with LymeHope with permission to share publicly. For privacy purposes names and identifiers have been removed. This is but one heartfelt story from a Canadian mother worried about her baby and unable to access appropriate care. There are many more stories, we need to listen, pay attention and act.

To Whom it may concern, ***October 10, 2018***

Five years ago, I was bitten by a tick; and like many people in Canada with Lyme, my journey back to living a normal life has been a struggle. But I am not writing to you today to talk to you just about my experience. This past March my husband and I were blessed with our first child. It is his story that has concerned and the reason I am writing.

I thought that my battle to get help was hard but the struggle to get answers about my son's health has been even more so. It's been confusing, frustrating and extremely exhausting. Knowing there is a chance that I may have passed this disease onto him is an overwhelming feeling. I have guilt, and not just the typical mom guilt that new mothers' get, but actual guilt that I may have ruined my child's life forever. But I could live with this guilt. I really could. All that it would take is to have some answers or even someone from the medical community willing to help.

*We have a **positive PCR cord-blood test** from a private lab but because the tests we had done in Canada came back negative we have been told he does not have Lyme. We have been politely told by an Infectious Disease Pediatrician that Congenital Lyme does not exist. And when we met with him he dodged answering my questions and instead would tell me how perfect my son was. Well, my son is far from perfect.*

Each and every day I look at my son, instead of seeing and celebrating all the amazing new things he is learning and doing, I look at him and worry. I worry when I see a slight tremble of his hands. I worry that the heart issues he had at birth are because of Lyme. I worry about his immune system because he hasn't been able to shake this reoccurring eye infection for months now. And if he can't beat an eye infection how is he going to be able to shake a cold or flu. I worry when he wakes up in the middle of the night screaming, not crying, but actual screaming.

My son is special and although he could crawl and got his first tooth all before he was 6 months old he does not have a voice. He cannot tell me if something is hurting or if something is wrong.

Yes, there may be a chance that my son does not have Lyme. But let's say he does. Why do I have to wait until he becomes really sick before someone will start doing something about it? Why do we have to go to another country to get help with testing or treatment? And why does it cost a small fortune to get help?

I do not think I am not asking for much. I am asking that when I come to an appointment with questions that they get answered and not dodged. I am asking that when you request details about a lab test that these results do not take 5 phone calls and two months to get.

I am asking for compassionate doctors; ones who listen to their patients and do not have their mind made up before they even walk through the door and hear the whole story. I am asking for doctors to read the troubled look on my face and offer retesting and a follow up appointment. I am asking for help.

I am simply asking for someone to take this seriously and not minimalize what I have to say.

Thank you for your time,
A concerned and worried mother in Canada

This personal letter was shared with LymeHope with permission to share publicly. For privacy purposes names and identifiers have been removed. This is but one heartfelt story from a Canadian mother worried about herself, her husband and her children, unable to access appropriate care in Canada, unable to afford care outside of Canada. There are many more stories, we need to listen, pay attention and act.

To Whom it May Concern, ***October 14, 2018***

This letter is going to be very emotional for me to write. I will begin by telling you, I don't know when I got bit, but it is very likely it was in Texas in the 90's, but the possibility of it being passed to me from my mom is still in question.

My mom and I lived in South Texas for 6 years. She worked as an RN out there and I went to high school and graduated with honors in 1997. I never thought anything about it and consider myself to have been a happy and healthy individual with loads of energy and spunk.

My mom however was getting worse for wear. She was in between fatigue and insomnia, dealing with mental health issues such as PTSD and trying to work shift work as an RN and then doing travel nursing for many years until she had a dermoid growth, had surgery and got REALLY sick. She had numbness in her legs, really bad brain fog and lots of pain. All UNEXPLAINABLE. She saw many specialists, GPs, and so on all boiling it down to being MS and being CRAZY!! With her nursing background, she knew something was wrong and with all tests coming back normal, she looked further. She talked with a Canadian Lyme specialist and Lyme matched exactly what was going on with her. She was tested in the United States and came back positive.

During this time, I was going to University of Alberta and working as a server evenings and weekends and thinking back, I was tired but that was completely explainable. In 2003 I met my husband who was in the Armed Forces and we got married in 2010.

Then in 2011 we had our first son. My pregnancy was hard. I was so sick and extremely tired for all of it!! I really do not feel I enjoyed any of the pregnancy except for feeling him move and be alive inside me!! Being a mom exhausted me, but just summed it all up to being a new mom! He was a colic baby. He always seemed irritated. He got really bad diaper rashes, which I took him in for constantly and the only thing that helped clear it was nystatin. It was blister like and would last for days – weeks. I ended up getting the nystatin on my own accord as a recommendation from my mom. These rashes were persistent!! He got sick a lot with colds and flu. He was tested for Lyme in the United States and this has come back indeterminate, but as of now he seems to have some anxiety but keeping an eye on it and managing. Other than those issues, he seems to be fine.

When my second son arrived, I just got worse. I was so tired all the time and just didn't have any energy. Every outing took me twice as long to accomplish and he was a very sick baby. He was very colicky baby. It all seemed to start when his umbilical cord stump got infected, then he got really red and patchy skin from head to toe, terrible diaper rashes, very sensitive to sound and light. His cries were very high pitched almost piercing, and it would take so much to calm him down. When his skin irritation went on for months I finally went to the local children's hospital. They didn't know what to do for him. They referred him to a dermatologist who recommended a rigorous treatment for psoriasis. We did this treatment and it did calm the inflammation down a lot and things seemed to be getting better. But, as soon as I skipped a week or so, it would come back just as bad. The doctor told me this is all normal to the condition and to keep on with the treatment. We were applying high steroid cream on him 1-2 times a week with a bleach bath. His skin was getting better but the other behavioral issues still remained.

I remember the last day he was alive, we needed to go grocery shopping and my first son went down for a nap so I put my little one down too. I was so tired I had to have a nap before we left. I knew he was teething, so I gave him some Tylenol and put him down. He was crying so I turned the monitor volume down and just let him cry for an hour while I just closed my eyes. I remember being so aggravated that he wouldn't just calm down and go to sleep and I was so tired. We went grocery

shopping and he was still very aggravated, so I gave him another dose and he just wouldn't take it and I got frustrated and put them in the car and we went home, had supper then gave them a bath. I remember feeling so relieved they both just went to bed! I remember thinking how tired he must be for crying all day and how that could be normal for him to cry all day??? By then it was too late. Sometime between the time I put him to bed to the time I went to wake him up, he died. The official cause of death for my youngest son was "no cause of death". He was only a year old.

About 2 months later we found out we were pregnant again. With everything that happened and my mom finding out everything she did about Lyme disease, my mom wanted us all to get tested. My husband, my first son and myself send out for testing from the US. My husband and my first son came back indeterminate and mine came back positive.

Since I was pregnant, we reached out to a US pediatric Lyme specialist who gave us specific instructions to pass on to my doctor. My next appointment my mom came with me to ensure the instructions were followed. It was with great hesitation, but we received a prescription for antibiotics. I was transferred from that clinic to a high-risk clinic. Nothing was done differently at the high-risk clinic than any other time I was pregnant. This time though I did not have gestational diabetes and I actually felt good for most of my pregnancy while on the antibiotics. This was the first time I had received treatment and I noticed a big difference.

When it came time to give birth, I had made it very clear that I wanted a kit to be completed that would test my new baby daughter's cord blood and test the placenta. I had the kit and made sure the forms were filled out by my doctor.

*We received the test back and the **cord blood came back PCR positive**. I was referred to a pediatric infectious disease specialist that the numbers were so low that I should not be concerned about it. I did not receive any further treatment for myself and no further questions were asked about the test results for my daughter.*

I sought out the advice of the same American pediatric specialist and was told to just be aware of any signs or symptoms in her before I get too worried about bringing her all the way to see him. That according to her test, she does in fact have Lyme and even that little amount is something to be aware of and can have an impact on her in the future. As long as she is developing well, I should not worry too much. My main concern to him was what am I supposed to do when there is nobody to see her in Canada and I cannot afford to get us to him?!

I was able to get myself referred to Lyme specialist who also agreed with the American pediatrician that my daughter does have Lyme, but that there just isn't anyone who treats children with Lyme in Canada and that it would be at my own expense to get her to the states for proper treatments. I haven't been able to carry out the treatment recommended for myself by the specialist because the testing he needs me to do is at my own cost and I currently have been unable to afford it.

In this whole letter has been about trauma brought on by a disease that has been ignored and minimized. My mom has Lyme and is still affected by it. I have Lyme and continue to be affected by it. My first son and husband show signs of having Lyme. My daughter was born with it and my second son may have died from it. So much pain and suffering for one family out of the countless others who are affected by it.

There is research already done that needs to be recognized and testing needs to be made available to Canadians. Doctors need to be educated on this disease. We need to expand the theories of how this disease is spread. It could be the answer to a lot of the childhood diseases and behavioral issues we are seeing on the rise today. The ignorance needs to stop.

Please help my family,
A worried mother in Canada

34 Years of Documentation of Maternal-Child Transmission of Lyme Disease and Congenital Lyme Borreliosis - A Review - by Sue Faber, RN, BScN

2019: Mothers on a mission to prove Lyme disease can be passed to unborn child. **CTV National News**. Published Sunday January 20, 2019. https://www.ctvnews.ca/health/mothers-on-a-mission-to-prove-lyme-disease-can-be-passed-to-unborn-child-1.4261403 (1)

'LymeHope is pushing for the screening of Lyme disease in pregnant women, research into better testing, and for the use of preventative antibiotics if there are concerns. They say mothers can be asymptomatic and still pass on the disease. And the infant can appear healthy at birth, but display symptoms months or even years later.'

'It has been known for quite some time in both humans and animals that some types of the bacteria that cause Lyme disease can be transmitted from mother to the baby in utero but we really don't know anything else about it," said Vett Lloyd, the biology professor leading the research at Mount Allison. "We don't know how often it occurs. We don't know under what circumstances it occurs. We don't know which types of the Lyme bacteria do it the most. So there is this huge black box.'

2019: These mothers say they transferred Lyme disease to their children in the womb. CTV Your Morning Interview Monday January 20, 2019. https://www.theloop.ca/these-mothers-say-they-transferred-lyme-disease-to-their-children-in-the-womb/ (2)

'Two Ontario women want to put a new aspect of Lyme disease into the public eye. They say there's a clear possibility it can be transmitted from mother to unborn child and their goal is to have more women tested for Lyme disease during pregnancy.'

2018: 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. https://doi.org/10.1371/journal.pne.0207067 (3)

*'Across cases, **evidence that transplacental transmission of B. burgdorferi can occur** was shown by testing the placenta (n = 11) and deceased fetal/newborn tissue (n = 18), Table 3. Adverse birth outcomes occurred in 4/5 placenta positive cases (2 stillbirths and 2 cases of respiratory distress that recovered), in 2/6 placenta-negative cases (one premature birth and one case reported as relapsing LD beginning at 3 months of age, and spirochetes were identified in one or more fetal tissues in 15/18 autopsies (Table 2).'*

*'There are examples among the **59 case reports included in this SR that suggested transplacental transmission occurs** including 4 cases of infection in the fetus or newborn determined using relatively reliable laboratory diagnostic methods.'*

*'This SR **summarizes evidence from case studies that provide some limited evidence for transplacental transmission of B. burgdorferi**.'*

'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.'

*'Thus, the data suggest there is **some evidence that adverse birth outcomes may occur more frequently** if gestational LD is not treated.'*

2018: France National Assembly, High Council of Public Health. Response on July 24, 2018. Retrieved on October 10th from: http://www2.assemblee-nationale.fr/questions/detail/15/QE/6138
* translated from French. (4)

*The High Council of Public Health (HCSP), seized by the DGS, **has already decided on the risks of transmission of the disease**: in general, no transmission through breast milk, sexually or via products blood and transplantation is currently documented in humans. **Maternal-fetal infection is possible**, and HCSP recommends antibiotic treatment for pregnant women with a diagnosis of Lyme borreliosis.*

2018: Tick-Borne Disease Working Group 2018 Report to Congress. Supported by the U.S. Department of Health and Human Services. Office of the Assistant Secretary for Health. Recovered from: https://www.hhs.gov/sites/default/files/tbdwg-report-to-congress-2018.pdf (5)

*Pregnancy: **Transplacental infection of the human fetus has been recognized** for relapsing fever borreliosis, **as well as Lyme disease**, babesiosis, and certain arthropod-borne flaviviruses. Pregnancy poses particular challenges for treatment because few antimicrobials have been approved and are safe to use during pregnancy. Additional research into appropriate treatment options are needed. (pg 53).*

*Gestational tick-borne disease **can be transmitted to unborn children in utero and has the potential to cause premature labor and fetal death.** One priority research area involves the risks of maternal-fetal transmission for various tick-borne diseases, as well as how to treat this population if exposed during pregnancy and needing treatment while pregnant. (pg. 70).*

*Moreover, hormonal changes during pregnancy can lead to **changes in immune function that may affect the detection of clinical or laboratory findings**. (pg. 41).*

2018: Maine, USA Government Website: Retrieved from: https://www1.maine.gov/dhhs/mecdc/infectious-disease/epi/vector-borne/lyme/tick-attachment-and-tickborne-diseases (6)

***'There is evidence of transplacental transmission** of the Borrelia burgdorferi spirochete.[20]*

2018: March of Dimes. Lyme disease and Pregnancy
retrieved from: www.marchofdimes.org/complications/lyme-disease-and-pregnancy.aspx. (7)

"We don't know for sure about the effects of Lyme disease on pregnancy. Untreated Lyme may cause complications during pregnancy, including:

***An infection in the placenta**. The placenta grows in your uterus (womb) and supplies your baby with food and oxygen through the umbilical cord.*

***Stillbirth**.. This is when a baby dies in the womb after 20 weeks of pregnancy.*

***Congenital heart defects**. These are heart conditions that are present at birth. They can affect the heart's shape or how it works, or both.*

***Urinary tract defects**. The urinary tract is the system of organs (like the kidneys and bladder) that helps your body get rid of waste and extra fluids. Urinary tract defects can cause pain, urinary tract infections, kidney damage and kidney failure.*

*Problems with your baby's blood, like **hyperbilirubinemia**. This is when your baby's blood has too much bilirubin in it. Bilirubin is a yellow substance that forms as red blood cells break down. Too much bilirubin can cause your baby to have jaundice. This is when your baby's skin and the white parts of his eyes look yellow because his liver isn't fully developed or isn't working.*

*Untreated Lyme disease also **may cause your baby to have a rash** after he's born."*

2018: Bransfield R. Neuropsychiatric Lyme Borreliosis: An Overview with a Focus on a Speciality Psychiatrist's Clinical Practice. Healthcare 2018, 6(3), 104. retrieved from: http://www.mdpi.com/2227-9032/6/3/104 (8)

*"Congenital LB infections can contribute to developmental disorders and neuropsychiatric impairments [51,52,53]. Congenital transmission of Bartonella has also been documented [48,49,50,51,52,53,54]. Since 1985 there are over **60 references documenting congenital transmission** and associated pathological outcomes with LB/TBD [2,55].*

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 [56].

The study most relevant to neuropsychiatric symptoms was a retrospective chart review of 102 gestational LB cases which were diagnosed by clinical criteria, Lyme enzyme-linked immunosorbent assay testing, Lyme Western blot testing, Lyme urine antigen testing, culture, polymerase chain reaction (urine), polymerase chain reaction (blood), single-photon emission computed tomography and magnetic resonance imaging.

This study demonstrated 9% had been diagnosed with autism and 56% with attention deficit disorder in addition to a broad spectrum of multisystem symptoms. Other psychiatric symptoms included irritability or mood swings (54%), anger or rage (23%), anxiety (21%), depression (13%), emotional lability (13%), obsessive compulsive disorder (11%), suicidal thoughts (7%), developmental delays (18%), tic disorders (14%), seizure disorders (11%), involuntary athetoid movements (9%), photophobia (43%), auditory hyperacuity(36%),other sensory hypersensitivity (tactile, taste or smell) (23%), poor memory (39%), cognitive impairments (27%), speech delays (21%), reading/writing impairments (19%), articulation impairments (17%), auditory/visual processing impairments (13%), word selectivity impairments (12%),and dyslexia (18%). "

2018: Luche-Thayer J, Perronne C, Meseko C. Obstruction to Treatments Meeting International Standards for Lyme and Relapsing Fever Borreliosis Patients. World Academy of Science, Engineering and Technology International Journal of Law and Political Sciences. Vol 12, No: 6, 2018 (9)

"*Lyme borreliosis infection creates complex conditions, and many are potentially fatal. Hundreds of peer reviewed studies and publications describe a range of physical conditions caused by the infection. As with syphilis, the LB infection can affect every bodily system, **be congenitally transferred from mother to fetus** and persist as latent as well as seronegative infection."*

2018: Registered Nurses Association of Ontario (RNAO). Faber S, Kinsella C, Manankil-Rankin L. Resolution #1: Patient First Treatment for Ontarians with Lyme Disease. Submitted on behalf of Halton Chapter. Voted through April 2018 at Toronto AGM. Retrieved from: http://www.lymehope.ca/news-and-updates/registered-nurses-association-of-ontario-resolution-on-lyme-disease. (10)

*"**Canadian patients, advocates, nurses, treating physicians, scientists, and researchers agree that the Lyme Framework failed its mandate and is insufficient to drive meaningful patient-centered change in Canada** (HESA, 2017). **It neglects to acknowledge the vast body of peer reviewed literature which documents persistence of infection resulting in chronic Lyme disease** (International Lyme and Associated Diseases Society [ILADS], 2015) **as well as clear evidence of vertical transmission from mother to child in utero** (LymeHope, 2017)."*

***"WHEREAS** there is a lack of education and awareness regarding persistence of infection, **transplacental transmission**, co-infections, other possible modes of transmission (sexual, blood supply, needle sticks, organ donation and other insect vectors), symptoms (acute vs. chronic), surveillance of chronic cases, modes of testing, treatment, and the existence of up to date, evidence-based guidelines published by ILADS;"*

***"WHEREAS** these challenges along with the politicization of this disease has created fear and uncertainty amongst healthcare professionals thereby forcing patients with Lyme disease and/or co-infections to pay for out of Country testing and seek health care outside of Canada at their own expense; "*

***"THEREFORE** be it resolved that the Registered Nurses' Association of Ontario (RNAO) advocate, at all levels of government, for the rights of all patients with symptoms consistent with Lyme and/or co-infections to receive fair and proper treatment for both acute and multi-systemic chronic presentations of the disease in Canada; **emphasizing healthcare provider education that acknowledges alternate modes of transmission**, persistence of infection, and integration of a collaborative clinical model inclusive of ILADS guidelines in the treatment of this illness."*

2017: O'Brien J, Hamidi O. Lyme Disease (www.smgebooks.com). Infection with Borrelia: Implications for Pregnancy, Nov. 2017. (11)

*"Transmission of Borrelia infection occurs **via both zoonotic vectors and other humans**. **Congenital transfer is an established fact**. **Maternal to fetal transfer of Borrelia, can furthermore be clinically silent or unrecognized, and if not successfully treated, infection can be life long and latency, late activation and reactivation can occur**."*

"There are several points, which are evident from the review of the current literature: 1) lack of tissue inflammation seen in tissues with evidence of spirochetes, 2) significant discrepancy in maternal serology testing (serology often negative in mothers), 3) positive cultures of spirochetes from fetal organs, 4) effects of infection during the first trimester with cardiac organogenesis, 5) fetal growth restriction, 6) and mother's infected in 'non-endemic' areas for borrelia."

2017: Kucharska, M. Child with autism, Mother with Lyme - Congenital Borreliosis? - Presentation and Poster at the 18th Annual Scientific Conference, International Lyme and Associated Diseases Society (ILADS) Conference; Nov 9-12, 2017, Boston, Massachusetts. (12)

"In Neurodevelopmental clinic for children we examined 28 mothers of 31 children (1.5-13 years), 20 boys and 11 girls) with confirmed borreliosis and no evidence of tick bite in anamnesis, with aim to assess possible mother-to-child transmission. In all children except one, borreliosis was detected by elispot, in one case by Western Blot."

"27 children (20 boys, 11 girls) had autism, 1 girl was neurotypical sibling of autistic child, diagnosed with chronic gastrointestinal inflammation, 3 girls had neurodevelopmental problems other than autism. All mothers were bitten by tick in the past 15 years - 2 months before pregnancy."

"24 mothers developed symptoms possibly indicating borreliosis (chronic pain and swelling of joints, chronic fatigue), 20 never attributed these symptoms to Lyme, nor realized there is a connection between a tick bite and their condition. Four of them suffered chronic inflammation of joints and were treated with NSAID. None of them had been tested for Lyme after tick bite nor received antibiotic prophylaxis."

*"**Absence of tick bite in medical history of children infected with borreliosis and positive Lyme results in their mothers, who had history of tick bite, may indicate that Borrelia spirochete was transmitted to them in utero, or during delivery, or during breastfeeding**"*

2017: O'Brien J, Baum, J. Case Report. The Journal of Family Practice. Vol 66, No 8, Aug, 2017. (13)

"Pregnant women who are acutely infected with Borrelia burgdorferi (the primary cause of Lyme disease) and do not receive treatment have experienced multiple adverse pregnancy outcomes including preterm delivery, infants born with rash and stillbirth."

*"In obstetric patients acutely infected during the first trimester, a fetal echocardiogram is reasonable, **given the demonstrated high potential of fetal cardiac abnormalities**.'*

2017: CDC: Pregnancy and Lyme Disease retrieved from: www.cdc.gov/lyme/resources/toolkit/factsheets/10_508_Lyme-disease_PregnantWoman_FACTSheet.pdf (14)

*"If you get infected with Lyme during pregnancy, **it may cause problems for your baby**. We don't know for sure about the effects of Lyme disease on pregnancy. **Untreated Lyme disease can cause complications during pregnancy**."*

"Lyme disease acquired during pregnancy may lead to infection of the placenta and possible stillbirth; however, no negative effects on the fetus have been found when the mother receives appropriate antibiotic treatment."

2017: Scott JD, Clark KL, Anderson JF, Foley JE, young MR, et al. (2017) Lyme Disease Bacterium, Borrelia burgdorferi Sensu Lato, Detected in Multiple Tick Species at Kenora, Ontario, Canada. J Bacteriol Parasitol 8:304. (15)

*"**Neurological Lyme disease can be fatal in neonates and infants** [71,72]. A newborn whose mother had suffered from Lyme disease during early pregnancy died 23 hours after birth, and B. burgdorferi s.l. was demonstrated in the brain and liver by silver staining and immunochemistry [73]."*

2017: O'Brien J, Hamidi O. 'Borreliosis Infection during Pregnancy'. Ann Clin Cytol Pathol 3(8). Oct. 2017. (16)

"Intra-human transfer of Borrelia can be initially silent or unrecognized'

*'**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**."*

2017: *Parliamentary Testimony of Sue Faber, RN - Parliamentary Standing Committee of Health Study of the Federal Framework on Lyme Disease, June 6, 2017* (17)

*"**Many parents across Canada believe that their children contracted Lyme disease through pregnancy."***

*"Yesterday, Jennifer and I had the opportunity to speak with Dr. Njoo, deputy chief public health officer. **We asked Dr. Njoo why congenital Lyme transmission had not been mentioned in the federal framework, considering the available body of scientific literature and evidence, including pathology reports, case studies, and an entire chapter written and dedicated in a reference medical textbook, which I have brought with me today.** I also ask Dr. Njoo why the Public Health Agency has not mentioned the June 4, 1998 Canada Diseases Weekly Report, which is included in your brief. It states: **"Transplacental transmission of B. burgdorferi has been documented and may be associated with an increased risk of adverse pregnancy outcome**.'*

*'**Why has nothing been done in 29 years to address this concern?** There is no Canadian research, no further mention, nothing**. Our public health officials are fully aware of this information, yet they choose not to share it. In their silence, they are allowing more children to become infected.'***

*'Despite this failed framework, **I still have great hope that this isn't the end of the story, but rather a fresh beginning, a reawakening to the reality of the Lyme crisis, which continues to sweep across our nation**. Your decisions and actions on this issue will directly impact the fate of millions of Canadians.'*

Sue Faber's full testimony in front of the Parliamentary Standing Committee of Health (HESA) can be found here: ***https://youtu.be/-gByuqmZBNk*** *and here:*

https://www.ourcommons.ca/DocumentViewer/en/42-1/HESA/meeting-59/evidence#Int-9584379

2017: New Jersey Department of Health. Communicable Disease Service Manual. Lyme Disease, Borrelia burgdorferi**.** July, 2017. (18)

"Lyme disease acquired during pregnancy **may lead to infection of the placenta and possible stillbirth**; however, no negative effects on the fetus have been found when the mother receives appropriate antibiotic treatment."

2016: Utenkova EO. Lyme disease and Pregnancy. Kirov State Medical Academy, Kirov Russia. Journal of Infectology, Volume 8, Number 2, 2016. *translated from Russian (19)

*"**It was stated and proved transplacental transfer of borrelia**"*

*"We need **serious studies** among pregnant women and newborn children in endemic regions...and in the future **such patients should be monitored throughout pregnancy and after childbirth**. Children born to these women should be examined for tick-borne infections at least during the first two years of life."*

2016: 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. (20)

*"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."*

*"TORCHES CLAP is an inclusive acronym." (**L=Lyme Disease**)*

*"clinical evidence of intrauterine infections, resulting from tissue damage or secondary physiologic changes caused by invading organisms, **may be present at birth or may manifest soon thereafter or years later**."*

"Many infectious diseases with serious consequences for the fetus are difficult or impossible to diagnose in the mother solely on clinical grounds."

"Review of the maternal record provides important clues for the diagnosis of infection in the neonate."

"an agent capable of persisting in the mother as a chronic asymptomatic infection could infect the fetus long after the initial infection."

***"In utero infection and intrapartum infections may lead to late-onset disease. Such infections may not be apparent at birth but may manifest with signs and symptoms weeks, months or years later**."*

"the clinical diagnosis of systemic infection in the newborn can be difficult because the signs of infection may be subtle and non-specific."

*"absence of clinically apparent disease in the newborn may be misleading. **Careful observation of infected but healthy-appearing children over months or years often reveals defects that were not apparent at birth**."*

*"Not all infected infants have increased levels of serum IgM, however, and some infants who do have elevated concentrations of total IgM are apparently uninfected; **thus, increased levels of total IgM are neither sufficiently specific nor sensitive for clinical decision making**."*

2016: 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., 2016. (21)

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

2015: Jasik K, Okla H, Slodki J et al. Congenital Tick-Borne Diseases, is this an alternative route of transmission of tick-borne pathogens in mammals? Vector-Borne and Zoonotic Diseases, Volume 15, Number 11, 2015. (22)

*"Histological observations have **confirmed the presence of Bb in children with congenital Lyme**. It is interesting that spirochetes may exist in the spleen, kidney, bone marrow and nervous system."*

*"The problem of vertical transmission of pathogens presents a new challenge for medicine. **Transfer of pathogens through the placenta may lead not only to propagation of diseases in the population, but also constitute a direct health threat to health and fetal development**."*

"It is possible that Bb 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, symptoms are not homogeneous****."*

"The ability of long term survival of Bb sl in tissues and spreading of spirochetes in the body despite antibiotic treatment can contribute to intergenerational infection with Lyme disease."

2014: O'Brien JM, Martens MG. Lyme disease in Pregnancy, a New Jersey Medical Advisory. MD Advisor, 2014;7:24-27. (23)

"There is documentation of Borrelia Burgdorferi isolated from the heart and other organs, where were examined during autopsy in cases of perinatal death. Reported cases have shown Borrelia Burgdorferi to be found in fetal spleen, renal tubules and bone marrow."

"Many cases that demonstrated adverse effects on fetal development, unfortunately lacked the appropriate examination of the placenta in order to determine if spirochetes were indeed present."

"these ***documented cases strongly suggest that transplacental transfer occurred via identification of Borrelia Burgdorferi in fetal tissues by culture, immunohistochemistry or indirect immunofluorescence****."*

"the outcome of a pregnancy affected by Lyme disease remains relatively unknown and unstudied. However, it is still important to equip obstetrical patients with information that will help protect them against Lyme disease and provide treatment options if a suspected case of Lyme disease occurs during pregnancy."

2014: Hatchette TF, Davis I, Johnston BL. Lyme Disease: clinical diagnosis and treatment. Found in Vol 40-11, May 29, 2014: Clinical aspects of Lyme disease. Canada Communicable Disease Report Monthly (CCDR) (24)

"While there have been reports of Lyme disease in pregnant women ***and sporadic case reports of transplacental transmission of*** **B burgdorferi***, there is not a clear link between fetal infections and adverse outcomes."*

2013: Dotters-Katz S, Kuller J, Heine P. Arthropod-Borne Bacterial Diseases in Pregnancy. Obstetrical and Gynecological Survey, Vol 68(9). 2013. (25)

"Borrelia Burgdorferi ***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."*
"Adverse pregnancy outcomes are also more likely in women with untreated Lyme disease."

2013: Esposito S, Bosis S, Sabatini C, Tagliaferri L, Principi, N. Borrelia burgdorferi infection and Lyme disease in children. International Journal of Infectious Diseases 17 (2013) e153-e158. (26)

Vertical infection of the fetus:

"The transplacental passage of causative agents from the infected mother to the offspring resulting in an adverse outcome has been acknowledged in several spirochetal diseases such as syphilis, relapsing

fever, and leptospirosis.[44] The corresponding information for Lyme borreliosis is limited. ***Although the in-utero transmission of B. burgdorferi during pregnancy resulting in fetal involvement has been reported,[45, 46] the information is restricted to a description of single cases, in some of which the proof of borrelial infection is uncertain****."*

2012: Kuhn M, Grave S, Bransfield R, Harris S. Long term antibiotics therapy may be an effective treatment for children co-morbid with Lyme Disease and Autism Spectrum Disorder. Medical Hypothesis (2012) (27)

"The parents of the five children in the study could not pinpoint an exact date of infection, but their treating physician suggested that the Bb bacteria could have been transmitted congenitally since all five of their mothers were diagnosed with Lyme disease and ***Bb has been shown to be transmitted congenitally in infected mothers****. If the Bb bacteria were transmitted congenitally and this latency period presented itself in the infected children it could lead to an explanation of their late onset autistic symptomology."*

2012: Relic, M, Relic, G. Lyme borreliosis and pregnancy. Vojnosanit Pregl 2012; 69(1):994-998. *translated from Polish (28)

*"****The clinical picture of a fetus infected by B Burgdorferi is similar to that seen in the course of a syphilis infection****. Most frequently they are: premature birth, intrauterine foetus death and malformation "In the second stage of the illness,* ***B. Burgdorferi traverses the placental barrier. Apart from foetal death, the following occur most frequently: syndactyly, sight loss, premature birth, neonatal rash, heart, liver, kidney damage or damage to the central nervous system****."*

2011: Mylonas I. Borreliosis during pregnancy: a risk for the unborn child? Vector borne zoonotic dis. 2011;11(7):891-8. (29)

"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****."*

2011: 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 (30)

*"****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.****"*

2011: 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. (31)

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

2010: Lakos A, Solymosi N. Maternal Lyme borreliosis and pregnancy outcomes. Inf J Infect Dis 2010;14:e494-e498. (32)

*"**early publications suggested that, like syphilis, maternal Borrelia burgdorferi sl infection may seriously influence the outcome of pregnancy. Stillbirth and congenital heart malformations have been described**."*

*"our findings demonstrate **a statistically significant association between untreated Lyme borreliosis and adverse pregnancy outcome**."*

"..spontaneous abortion, stillbirth, and preterm birth have frequently been identified in other published studies and were also found in our series."

*"We found some of the **symptoms mentioned in other papers such as hyperbilirubinemia, cerebral bleeding, generalized rash and congenital urologic malformations**."*

*"We **were unable to examine the placenta or fetus for direct Borrelia invasion** in the cases of pregnancy loss; therefore the causal relationship remains undecided in spite of the statistical association."*

"Ideally, a prospective, multicenter study should be conducted, enrolling sufficient numbers of women, in order to adequately address these research questions.

2010: Late Intrauterine Fetal Death and Stillbirth. Royal College of Obstetricians and Gynecologists. Green-top Guideline No. 55, October 2010. https://www.rcog.org.uk/globalassets/documents/guidelines/gtg_55.pdf (33)

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**. Malaria parasitemia has also been associated with stillbirth (OR 2.3, 95% CI 1.3–4.1) (Evidence level 2++).*

2009: Maharaj, D. Complications of Infections in Pregnancy. In Infectious Pregnancy Complications. Nova Science Publishers, editor Richard N Canfield, 2009. (34)

Table 1. Causative agents, transmission, and effects on mother and neonate

Infecting agent	Transmission	Potential effects on mother	Potential effects on fetus/newborn
Borrelia burgdorferi (Lyme disease)	*Intrauterine*	*3 stages: early localized, early disseminated and late disease. Erythema migrans, rash, palsies of the cranial nerves, meningitis, conjunctivitis, carditis, arthritis, meningoradiculoneuritis, systemic symptoms such as arthralgia, myalgia, headache, fatigue*	*Hydrocephalus, intracranial calcification, chorioretinitis, jaundice, anemia, hepatosplenomegaly lymphadenopathy*

2009: 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. (35)

"Three women suffering from Erythema migrans in the first trimester had positive PCR for Ap and/or Borrelia in the blood and two of them, later, in the placenta.

"The woman no. 9 had a lot of anaplasma cells in PNL in the blood smears, positive IFA IgG titre to Ap and C6ELISA for Bbsl in all three examinations and also after the ***abortion in the 29th week of pregnancy*** *when* ***borrelia Garinii (strain 840) was isolated from the placenta****".*

"Another woman (no 12) had positive IgM and IgG to Ap and Bbsl in the blood after bearing twins from whom one had positive IgG and IgM antibodies against Bb."

2009: McClure E, Goldenberg R. Infection and stillbirth. Semin Fetal Neonatal Med. August; 2009 14(4): 182–189 (36)

"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****."*

"In other reports, after first-trimester infection and subsequent fetal death, ***spirochetes were found in fetal liver, spleen, kidney and brain****. Subsequently, small series of stillbirths after maternal Lyme disease have been described, with most deaths occurring in the mid-trimester."*

2009: Maraspin V, Strle F. How Do I manage tick bites and Lyme Borreliosis in Pregnant Women? Lipsker D, Jaulhac B(eds): Lyme Borreliosis. Curr Probl Dermatol. Basel, Karger, 2009, vol 37, pp183-190. (37)

"Information on the influence of borrelial infection on the fetus is also incomplete. In general, circumstances in which an infection of a pregnant woman may have detrimental influence on the fetus include: 1) severe illness of the mother, associated with circulatory instability and/or other harmful effects that subsequently damage her fetus, 2) induction of immunological mechanisms and or 3) production of toxins that damage the fetus directly or indirectly through impairment of the placenta, and/or 4) damage of the fetus by the microorganisms causing illness in the pregnant woman either directly or indirectly through damage of the placenta. ***The prerequisite for the latter outcome is (hematogenous) dissemination of the causative agent to the placenta and eventually to the fetus****."*

*"****In Lyme borreliosis, in utero transmission of B. burgdorferi sensu lato during pregnancy, resulting in fetal involvement has been reported in humans*** *and in animals such as cows, horses, dogs and mice."*

"We propose intravenous antibiotic therapy, preferably with ceftriaxone 2 G daily for 14 days, for all gestational Lyme borreliosis. This suggestion is offered because case reports, although rare, have suggested that Lyme borreliosis during pregnancy may be associated with adverse outcomes for the fetus and out of concern that neither the occurrence of transplacental dissemination nor the timing of such an occurrence during the acute infection can be accurately assessed."

2009: Bransfield, R. Preventable cases of autism: relationship between chronic infectious diseases and neurological outcome. Future Medicine, Pediatric Health, 3(2), 125-140. (38)

" **It is advisable to evaluate women who are planning on becoming pregnant for chronic, low-grade, relapsing infections, especially if they appear symptomatic with a systemic illness or infection or with persistent inflammatory symptoms, and to treat when indicated**. Adequate evaluations and treatments could help to prevent some cases of ASD and their associated human and financial costs."

"Four independent studies demonstrated significant reactivity of ASD patients for Lyme disease on western blot testing, another study ***demonstrated a high incidence of autism and hyperactivity in over 300 gestational Lyme disease patients with the mothers reporting difficult pregnancies and frequent miscarriages****, and similarities were noted between ASD and Lyme disease patients in regard to clinical symptoms, epidemiological findings, brain imaging studies and pathophysiology."*

*"*There are a number of reports and citations of maternal transmission of Lyme disease and associated adverse events. Gardner reviewed 263 cases of congenital and gestational Lyme borreliosis in the literature. A total of 66 of the 263 were associated with adverse outcomes and 15% of the 263 cases had neurological malformations."

"Jones et al. performed a comprehensive ***case history review*** on the charts of ***102 gestational cases of B. burgdorferi and other tick-borne disease infections***. Of these cases 9% had been diagnosed with autism and 56% with ADHD."

'"***Psychiatric symptoms*** included irritability or mood swings (54%), anger or rage (23%) anxiety (21%), depression (13%), emotional (13%), obsessive compulsive disorder (11%) and suicidal thoughts (7%).'

"***Neurological symptoms*** included headache (50%), vertigo (30%), developmental delays (18%), tic disorders (14%), seizure disorders (11%), involuntary athetoid movements (9%), and hypotonia (7%)."

*"****Sensory sensitivity symptoms*** *included photophobia (43%), hyperacuity (36%), motion sickness (9%) and other (tactile, taste or smell; 23%).*

*"****Cognitive symptoms*** *included poor memory (39%), cognitive impairments (27%), speech delays (21%), reading writing delays (19%), articulation (17%), auditory/visual processing (13%), word selectivity (12%) and dyslexia (18%).*

*"****Gastrointestinal symptoms*** *were common and included gastroesophageal reflux disease (27%), abdominal pain. (29%), diarrhea or constipation (32%) and nausea (23%)."*

2008: Theiler R, Rasmussen S, Treadwell T, Jamieson D. Emerging and Zoonotic Infections in Women. (39)

"During the 1970's, Borrelia burgdorferi was identified as the cause of a chronic, relapsing febrile illness named Lyme disease after the Connecticut town where it was discovered. The Lyme 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."*

2008: Burrascano, J. Advanced Topics in Lyme Disease. Diagnostic Hints and Treatment Guidelines for Lyme and other Tick-Borne Illnesses. 16th edition. October 2008. (40)

LYME DISEASE AND PREGNANCY

"**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 1980s. They found that ***if patients were maintained on adequate doses of antibiotic therapy*** during gestation, then no babies were born with Lyme."

"My own experience over the last twenty 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."

2008: *Dr Sarah Chissell, Consultant Obstetrician William Harvey Hospital, Kent. Presentation at 7th Tick-Borne Disease Conference, July 2008. Lyme Disease and Pregnancy. Presentation can be downloaded:* https://www.lymediseaseaction.org.uk/wp-content/uploads/2011/05/chissell.pdf (41)

"Congenital Lyme disease exists
Reinterpretation of literature needed in light of current knowledge
More studies needed in high risk areas
Offer screening questionnaire to pregnant women
Low threshold for treating women: risk versus benefit analysis"

2008: Hercogova J, Vanousova D. Syphilis and borreliosis during pregnancy. Dermatologic Therapy, Vol. 21, 2008, 205-209. (42)

"The present authors could observe ***one abortion in a pregnant woman with disseminated Lyme borreliosis insufficiently treated with oral penicillin for five days when Borreliae were demonstrated by electron microscopy*** *(using monoclonal antibodies against flagellin) in the placenta specimen."*

"Recently the present authors were able to observe in three placentas of women ***treated for Lyme*** *borreliosis during pregnancy both* ***borreliae and Borrelia cysts*** *by electron microscopy and/or PCR (unpublished observation)."*

*"****If Borreliae are proved by direct/and or indirect methods in the blood of a newborn, congenital infection should be considered****."*

*"****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 tetrogenic effect of B. burgdorferi in humans."*

2007: Bransfield R, Wulfman J, Harvey W, Usman A. The association between tick-borne infections, Lyme borreliosis and autism spectrum disorders. Medical Hypothesis, 2007, doi:10.1016/j.mehy.2007.09.06. (43)

*"Chronic infectious diseases including tick-borne infections such as **Borrelia burgdorferi may have direct effects, promote other infections and create a weakened, sensitized and immunologically vulnerable state during fetal development and infancy** leading to increased vulnerability for developing autism spectrum disorders."*

*"Support for this hypothesis includes **multiple cases of mothers with Lyme disease and children with autism spectrum disorders**; fetal neurological abnormalities associated with tick-borne diseases and autism spectrum disorder regarding symptoms, pathophysiology, immune reactivity, temporal lobe pathology and brain imaging data; positive reactivity in several studies with autistic spectrum disorder patients for Borrelia burgdorferi (22%, 26% and 20-30%) and 58% for mycoplasma; similar geographic distribution and improvement in autistic symptoms from antibiotic treatment."*

*"**Gestational transmission of the Bbsl and other tick-borne infections may be more common that previously recognized** and **may be an important mode of infection in the ASD population**."*

2006: Walsh C, Mayer E, and Baxi L. Lyme Disease in Pregnancy: Case report and review of the literature. Obstetrical and Gynecological Survey, Volume 62, 1, 2006. (44)

*"**Confirmed transplacental transmission of B Burgdorferi** has been documented in several cases."*

2006: Evison J, Aebi C, Francioli P, Pete O et al. Lyme Borreliosis 3 Parts: prevention, pregnancy, immunodeficiency states, syndrome Lyme post-borreliosis Rev Med Suisse 2006 ; 2 : 935-40
*translated from French (45)

*'**Transplacental infections of the fetus may be observed in all three trimesters**.'*

'Spontaneous abortion, cases of premature birth and perinatal mortality, urinary system malformations and cardiac malformations as well as cases of syndactyly have been documented. In many cases however, alternative explanations were possible.'

'Although no clinical studies have demonstrated a significant increase in cardiac malformations, these malformations in connection with an erythema migrans during the first trimester of pregnancy, makes a probable causal association'.

2006: Larsson C, Andersson M, Guo BP, et al. Complications of Pregnancy and Transplacental Transmission of Relapsing-Fever Borreliosis. The Journal of Infectious Diseases. 2006; 194:1367-74. (46)

"In Lyme disease during pregnancy, fetal death is determined by acute infection early during gestation."

*"We have shown that Relapsing Fever (RF) borrelia reside in placenta and infect the fetus with the transplacental transmission occurring at an incidence of 74%, **which is consistent with incidences of other spirochetal infections, Lyme disease and syphilis, which can also be transmitted congenitally**."*

2005: Jones, CR, Smith H, Gibb E, Johnson L. Gestational Lyme Disease Case Studies of 102 Live Births. Lyme Times. 2005(summer):36-38 (47)

'Gestational Lyme disease continues to be an often misunderstood and misdiagnosed condition. A significant number of past studies conducted on LD during pregnancy have repeatedly found pregnancies resulting in adverse fetal outcomes and cases that presented with clinical findings possibly caused by transmission of Lyme disease but the lack of positive diagnostic testing using ELISA, indirect fluorescent antibody (IFA), and Western blot has left researchers still questioning the cause of these findings as being Lyme disease.'

'Therefore, in light of a recent report by Dr. Steven Phillips, et al (2) ***showing the inadequacies of currently accepted standards for serologic diagnosis using the ELISA and Western blot, dismissal of Bb in maternal-fetal transmission based on this type of testing is not possible****.'*

"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."

"A ***retrospective analysis of the progression of symptoms revealed that oftentimes many initial symptoms were present in infants, were overlooked until they gradually progressed in frequency and severity****.'*

"Of 66 mothers with Lyme disease who were treated with antibiotics prior to conception and during the entire pregnancy, all gave birth to normal healthy infants. However, 8 pregnancies resulted in Borrelia burgdorferi and/or Bartonella hensalae positive placentas, umbilical cords and/or foreskin remnants. Those with positive PCRs were treated with 6 months of oral antibiotics and are without symptoms 3 months to 4 years later."

Multi-system symptomology in children with Gestational Lyme Borreliosis	
72% - fatigue lack of stamina	23% - anger and rage
69% - joint pain	21% - anxiety
59% - Low grade fevers	21% - speech delay
56% - hyperactivity, lack of concentration	19% - reading and writing delay
55% - jointed sensitivity	18% - developmental delays
54% - irritability and mood swings	14% - tic disorders
50% - headaches	13% - auditory/visual processing problems
43% - photophobia (sensitive to light)	13% - aggression or violence
42% - pale and sickly – dark eye circles	13% - depression
39% - poor memory	12% - word selection problems
36% - hyperacuity (sensitive to noise)	14% - tic disorders
30% - vertigo	11% - OCD
32% - diarrhea and constipation	11% - seizure disorder
29% - Abdominal pain	9% - involuntary movements
27% - GERD	9% - motion sickness
23% - night sweats	9% - autism
23% - nausea	8% - dyslexia
23% - cardiac manifestations – palpitations, PVC, Mitral VP, heart murmur	7% - suicidal thoughts
	7% - hypotonia at birth
23% - generalized muscle pain or spasms	

2005: Lazebnik T, Zal'tsman P. A Case of Congenital Neuroborreliosis. St Petersburg Medical Academy of Postgraduate Education, St. Petersburg, Russia. Translated from Russian. (48)

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

'The presence of motor-sensory polyneuropathy in both the mother and the daughter enabled us to view the clinical picture of the girl's disease as a chronic stage of neuroborreliosis.'

'We hope that this clinical case of congenital neuroborreliosis will stimulate discussion and exchange of opinions on the pages of this journal on the part of the specialists who examined and treated our patient and others like her, so that solutions may be found to the issues of prevention, vaccination, and the early preclinical treatment of newborns from mothers bitten by ticks in endemic regions and treated in connection with development of the neuroborreliosis infection in the first year of the child's life.'

2005: 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. (49)

"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."

"In this report a rare case of a girl surviving intrauterine Lyme disease, who subsequently developed triventricular hydrocephalus and aqua ductus cerebri stenosis was presented."

"The serologic evidence of Borrelia burgdorferi non-specific antibodies in a neonate with an MRI image of congenital hydrocephalus and maternal infection during pregnancy proved by Borrelia burgdorferi high-specific antibodies were crucial to diagnosing Lyme disease consisting of congenital hydrocephalus."

2005: U.S Department of Health and Human Services, National Institutes of Health. Lyme Disease: The Facts, the Challenge. NIH Publication No. 05-7045, May 2005. (50)

"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****.*

2004: Brzosek, T. Human Granulocytic Ehrlichiosis coincident with Lyme Borreliosis in Pregnant Woman - A Case Study. Epidemiological Review 2004; 58:289-94. (51)

*"**It is accepted that the Borrelia burgdorferi infection can be vertically transmitted** through the placenta, but it is extremely rare.'*

*"In the literature, **there is evidence of the presence of Borrelia burgdorferi spirochete in miscarried fetuses, or tissues of children with congenital disorders**; however, there is not enough evidence to claim that the infection causes the death of the fetus, preterm birth or birth defects."*

*"In our case study, the test performed on the child did not show specific antibodies. **In case of infection, most neonates don't produce specific antibodies, only a few of them can produce IgM antibodies**."*

2004: Boyer S, Boyer K. Update on TORCH infections in the newborn infant. Newborn and Infant Nursing Reviews. 2004;4(1). (52)

"TORCH, as an acronym, stands for Toxoplasmosis, Other (T. pallidum, Varicella Zoster Virus, Parvovirus), Rubella virus, Cytomeglavirus and Herpes Simplex (HSV). ***Klein and Remington have suggested this classification is too limiting*** *and that* ***several additional infectious agents should be considered*** *in the other category, such as enteroviruses,* ***Borrelia burgdorferi (the cause of Lyme disease),*** *and of course, human immunodeficiency virus (HIV)."*

"The usual way in which fetus is infected is by transplacental spread after maternal infection in which the organism circulates in the mother's blood. These infections, acquired in utero, can be severe enough to cause fetal loss or can result in intrauterine growth restriction, prematurity, or chronic postnatal infection."

*"**Clinical evidence of infection may be seen at birth, soon afterward, or not until years later**."*

2003: Goldenberg R, Thompson C. The infectious origins of stillbirth. American Journal Obstet gynecol, Sept 2003. (53)

"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."

2003: Harvey, W and Salvato, P. 'Lyme disease': ancient engine of an unrecognized borreliosis pandemic? Medical Hypothesis 60(5), 742-759, 2003. (54)

"The CDC position on intra-human Bbsl transmission is that 'Lyme disease are not transmitted from person-to-person.' ***Current human and veterinary data make this position indefensible****. Schlesinger and Macdonald reported the first human congenital cases of Bbsl."*

"Gardner provided the initial and now most exhaustive review of human gestational transfer cases. Her credible supporting studies utilized histological, PCR or culture identification of Bb in mother and newborn or aborted fetuses. She reviewed 263 Bbsl-infected cases and summarized the birth outcomes. ***If mothers are untreated, Gardner notes the high percentage of negative pregnancy outcomes along with symptomatic as well as seemingly asymptomatic neonates****."*

"In her (Gardner) table 11-8, ***72% of neonates with tissue verified borreliosis did not produce antibodies in sufficient quantity to be seropositive****."*

"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."*

"The general principles of neonate immune function, adult immune function, and transplacental transfer of pathogens provide further insight into the relationship between trans-placental agents and a new and developing immune system."

*"We conclude that **'Lyme Disease' currently acknowledged only its zoonosis arm and is a limited conceptualization of a far more pervasive and unrecognized infection state that must be considered a global epidemic**."*

2003: 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. (55)

"A 37-year-old female presented to our office with a 4-month history of migratory joint pains and a positive IgG Western Blot through Igenex laboratory. She was given 1 month of Doxycycline 100 mg po bid by her PMD, but relapsed upon stopping the medication, and came to our office for a consultation. She was placed on Amoxicillin and Probenecid, which promptly resolved her symptoms but caused hives, and was instead changed to Ceftin 1000 mg bid, Flagyl ER 750 mg q12hrs, and Zithromax 250 mg bid to address the cell wall, cystic, and intracellular forms of Bb.

*This medication regimen was tolerated well without side effects, and after 4 months, the patient reported feeling 100% back to normal (two months symptom free) with none of her mid cycle flares, and rare fleeting aches of unclear significance. The medication regimen was therefore stopped, and the patient subsequently became pregnant within the next month, with no change in her overall level of well-being. She had a normal OB/GYN exam, **but had a miscarriage at week 18**. **Polymerase Chain Reaction (PCR) testing was done on the placenta and fetus through Medical Diagnostic Laboratories in NJ, which both returned positive for Borrelia burgdorferi**.*

***Borrelia burgdorferi is known to be transmitted transplacentally**. Initial reports had revealed adverse outcomes including syndactyly, cortical blindness, and intrauterine fetal death, but these adverse outcomes occurred in cases with infections during each of the trimesters, **not in women previously treated for Lyme disease** (Steere et.al. Lyme Disease During Pregnancy. JAMA 1986; 255; 3394-3396).*

Spirochetes have been found by culture, silver stain, or B.burgdorferi specific IFA in autopsied organs (liver, spleen, bone marrow, heart, brain, kidney) of congenitally infected fetuses and neonates by Schesinger et. al. (Maternal-fetal transmission of the Lyme disease spirochete, Borrelia burgdorferi. Ann. Intern. Med. 103; 67, 1985) and MacDonald et.al. (Gestational Lyme borreliosis: Implications for the fetus. Rheum. Dis. Clin. North Am. 15; 657, 1989), but again the late stillbirths and perinatal deaths generally followed first trimester gestational Lyme disease.

Borrelia burgdorferi is known to survive in antibiotically treated patients with Lyme borreliosis (Preac-Mursic et.al. Infection 1989; 17: 355-359), but there are no adequate scientific studies available to guide physicians in treating women who have been successfully treated for Lyme disease without significant ongoing symptoms.

Until such studies are available, it would seem prudent based on this case report to advise any woman wishing to get pregnant who has a history of Lyme disease to have an open dialogue with her physician, and consider serial PCR testing (urine/blood) before and during pregnancy to determine if there is

evidence of persistent infection. ***<u>However since Bb may lie deep in tissues with long dormancy periods, an individual PCR may not be adequate to rule out ongoing infection.</u>***

Therefore, if PCR testing is negative, and the patient is completely asymptomatic for less than one year, or if any symptoms persist even minor in nature that can be attributed to Lyme disease (i.e. migratory joint and muscle pains, with symptoms coming and going, intermittent paresthesias, with hormonal flares around the menses), such a clinical situation should prompt a dialogue with the treating physician to discuss the risks and benefits of antibiotic treatment with Amoxicillin before and during pregnancy. Amoxicillin is known to be safe for the fetus and is therefore a reasonable choice for a woman wishing to get pregnant. Amoxicillin peak blood levels should be obtained however to ensure adequate dosing. Further scientific studies need to be performed to determine the optimum course of treatment for women wishing to become pregnant who have received successful treatment for clinical symptoms of the disease."

2003: 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 (56)

*"**In 1985, Schlesinger et al (21) for the first time showed evidence of Borrelia burgdorferi transmission from the mother to the fetus**. Cardiac malformations were found in the newborn born 39 hours after birth. Histologically, spirochetes in the spleen, kidney and bone marrow could also be detected in the myocardium in a supplementary examination by MacDonald. In the first trimester of pregnancy, the mother had undergone an erythema migrans that was not treated."*

"In 1986 and 1987 MacDonald published 4 cases of a retrospective study of stillbirths (15,17). ***Cardiac malformations were present in 3 cases, and proof of spirochete was obtained in numerous fetal organs as well as in placental tissue*** *(Figs. 1-4). There had been no signs of Lyme disease in the pregnant women during pregnancy, but twice in one pre-eclampsia".*

"In 1988, Weber et al (24) described the ***first case of congenital Lyme disease in Germany****. Although the woman who had erythema migrans in the second month of pregnancy was treated with penicillin, the child died shortly after birth.* ***Here, too, spirochetes are found in the brain and in the liver****. In the stillbirth described by Lavoie et al (13) in 1987, autopsy revealed aortic occlusion due to thrombosis;* ***Borrelia burgdorferi could be bred from the child's brain and histologically visualized in fetal tissue"****.*

"Furthermore, the results of a study by MacDonald for (16). The 192-bed Southampton Hospital, where he worked as a pathologist, is located in a high-density area in the United States not far from Lyme and has about 700 births annually. During the period 1985-1988 MacDonald prospectively recorded 9 cases of maternofetal infection."

"Strikingly, in all histologically confirmed cases of congenital Lyme disease the Borrelia burgdorferi infestation of the organs ***<u>was not</u>*** *accompanied by an inflammatory tissue reaction.* ***<u>It is also noteworthy that in almost all cases Borrelia serology was negative</u>****."*

*"**We ourselves have a case (12) that could be attributed to a congenital Lyme disease due to the serological findings: in a 3-day-old newborn with an antibiotic-treated septic disease, increased IgG and IgM Borrelia antibody titers could be detected in the blood and cerebrospinal fluid , The total IgM in the blood was greatly increased (217 mg / dl), which speaks for a congenital infection in general.** IgA was negative, which ruled out a "placental leak".*

"The subsequent blood test in the mother showed a significantly increased IgM and a slightly increased IgG Borrelia antibody titer. Also with her the total IgM was increased (329 mg / dl). The serological tests against a variety of pathogens, including syphilis and mononucleosis, were negative in mother and child. Placental tissue for histological examination was no longer available."

*"**Although the serological constellation made congenital Lyme borreliosis probable, there was no history of clinical disease for the mother**. According to the serological findings in mother and child, the infection should have taken place in the late phase of pregnancy. As far as it can be assessed after 4 years, the previous development of the child was unremarkable after the treatment. In the meantime, the mother has also had no symptoms of Lyme disease suspected disease. In both, the Borrelia antibody titers returned to normal after this time."*

*"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."*

2002:Tsai H, Lu C, Shih C, Chao L, Hu C. Lyme Disease during Pregnancy, A Case Report. Dermatol Sinica 20:147-151, 2002. (57)

*"**The maternal-fetal transmission of B burgdorferi has been reported in patients with early Lyme disease during pregnancy since 1985. These patients were either untreated or inadequately treated, and all demonstrated adverse outcomes of pregnancy including various congenital abnormalities, premature birth and even fetal death**. However, some follow-up studies indicated that maternal Lyme disease was not directed implicated as a cause of fetal malformations, and no association could be found between the presence of IgG antibody to B. burgdorferi in the cord blood and congenital malformations.'*

2001: Abramowsky C, Beyer-Patterson P, Cortinas E. Nonsyphilitic spirochetosis in second-trimester fetuses. Pediatric Pathology, 11:827-838, 2001. (58)

*"**Congenital infection with Borrelia burgdorferi, the agent of Lyme disease was first reported in 1985. Confirming reports have appeared since**."*

2001: Elliot D, Eppes S, Klein, J. Teratogen Update: Lyme Disease. Teratology 64:276-281, 2001. (59)

"***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**."*

2001: Gardner, T. Lyme disease in pregnancy. Program and abstracts of the 14th International Scientific Conference on Lyme Disease and other Tick-Borne Disorders; April 21-23, 2001, Hartford, Connecticut. (60)

"The prognosis for gestational Lyme disease is good if diagnosed and treated adequately. ***The prognosis for neonates with early congenital Lyme disease depends on prompt diagnosis****, especially in severe early cases. Similarly, the prognosis in late congenital Lyme depends not only on prompt diagnosis and treatment, but also on the extent of irreversible damage present at the time of diagnosis.* ***Long term follow-up is important for detecting possible recurrence of disease****."*

Table. Signs and Symptoms of Congenital Lyme Borreliosis

Stage	*Mild Early*	*Severe Early*	*Late*
Onset	*Usually first two weeks of life*	*Usually first week of life*	*Usually >2 weeks and< 2 years of age*
Maternal Gestational LB	*Usually first or second trimester*	*Usually first or second trimester*	*Usually second or third trimester*
Signs and Symptoms	• *Mild suspected sepsis or meningoencephalitis* • *hyperbilirubinemia* • *adenopathy* • *rash* • *intrauterine growth retardation* • *miscellaneous anomalies (eg. genitourinary (GU) skeletal, cardiac)*	• *Severe suspected sepsis or* • *meningoencephalitis* • *respiratory distress* • *preinatal death* • *intrauterine growth retardation* • *Fever* • *Rash* • *Adenopathy* • *Hepatosplenomegaly* • *Hyperbilirubinemia* • *Miscellaneous anomalies (eg GU, skeletal, cardiac)*	• *Subacute illness* • *developmental delay/meningoencephalitis* • *Growth retardation/failure to thrive* • *Prematurity* • *Fever* • *Adenopathy* • *Rash* • *Hepatosplenomegaly* • *Miscellaneous anomalies (eg GU, skeletal, cardiac)*
Prematurity?	*< 4 weeks*	*<5 weeks*	*--*

2001: Mattman LH. Cell Wall Deficient Forms. 3rd Edition. Chapter 37: The Placenta. CRC Press, Taylor and Francis Group, 2001. (61)

"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."*

*"****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."*

2001: 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 (62)

"A review of the congenital and gestational Lyme borreliosis literature yielded 259 reported cases for which the outcome of the individual episode of gestational Lyme borreliosis was noted, and addition of four of the authors cases which brought the total to 263 cases."

"A total of ***66 cases of the 263 were found that the author considers to represent an adverse event at least associated with an episode of gestational Lyme borreliosis including miscarriage, stillbirth, perinatal death, congenital anomalies, systemic illness, early onset fulminant sepsis and later-onset chronic progressive symptoms****."*

2001: 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 (62 cont)

*"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**."*

"In the larger population-based studies or serologic surveys, individual outcomes of gestational Lyme disease were not provided for all patients, which made difficult the recognition of a small number of individual adverse outcomes associated with gestational Lyme disease."

*"Several reports that involved serologic screening of large populations of obstetric patients, but **provided no information about the occurrence, treatment or specific outcomes of any clinically symptomatic cases of gestational Lyme borreliosis, could not be used in evaluation of outcomes of gestational Lyme borreliosis**; however, they provided data on sero-prevalence in the obstetric population."*

"*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."*

*"**Therefore, in order for infants with congenital Lyme borreliosis and therefore initiation of prompt antibiotic therapy of the congenitally infected infant usually depend on suspicion or confirmation of Lyme borreliosis in the mother**. Therefore, in order for infants with congenital Lyme borreliosis to be recognized, it is **essential for clinicians caring for newborns and infants to become familiar with the various manifestations of Lyme borreliosis in the adult**, as well as in the congenitally infected infant."*

"Large scale prospective studies of sufficient numbers of patients with gestational Lyme borreliosis, with follow-up to determine the pregnancy outcome of each enrolled patient: B. burgdorferi specific evaluation of any fetal or neonatal demise; and long-term follow-up of each infant born to determine the occurrence of possible early and late sequelae are needed."

*" Only one infant was found to be positive for B burgdorferi antibody (patient 24), and this was transient; therefore this **does not appear to be a sensitive method of diagnoses and reliance on sero-positivity leads to misdiagnosis of the majority of congenitally infected infants**."*

*"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 eliminate the B. burgdorferi infection, these infants may present the dilemma of seronegative late Lyme borreliosis**."*

*"It is uncertain **how many episodes of gestational toxemia, spontaneous miscarriage and abortion, stillbirth, culture negative neonatal sepsis, failure to thrive, developmental delay, congenital heart disease or sudden infant death syndrome may be due to unrecognized gestational Lyme borreliosis**."*

1999: Kochevar JM, Liegner KB. The Incidence of Lyme Disease Affecting Several Members of Families. Abstract P252. 8th International Conference on Lyme and other Emerging Tick-Borne Diseases, Munich, Germany, June 20-24, 1999. (63)

"100% of the 40 families evaluated through our office have demonstrated at least one other member of the family, besides the index case, was also exposed to B. burgdorferi, the causative organism of Lyme disease, and also required treatment."

"In Lyme endemic areas, when one patient having the illness is identified, evidence of Lyme disease should be sought in family members so that appropriate intervention can be made."

1999: Braun-Falco O, Plewig G, Wolff HH, Burgdor WHC (eds.) Dermatology, 2nd ed., Springer-Verlag Berlin Heidelberg, 2000. Chapter 4, Bacterial Diseases-Spirochetal Infections-Lyme Disease, p.185. (64)

*"**Borrelia burgdorferi can cross the placenta**. Fetal death, spontaneous abortions and congenital malformations may all occur but are quite uncommon. This risk of fetal involvement is apparently greatest if the infection occurs early in pregnancy."*

1999: 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. (mouse model) (65)

*"Vertical transmission of Bb was confirmed with **Bb isolated from foetuses** of Apodemus agrarius and Rattus edwardsi. The results showed that **Lyme disease spirochete Bb might be naturally maintained in an enzootic cycle by transplacental transmission**."*

1999: Norris C, Danis P, Gardner T. Aseptic meningitis in the newborn and young infant. Am Fam Physician. 15:59(10):2761-2770. 1999. (66)

*"**Although congenital Lyme disease is rare, it may cause neurologic symptoms in 20 percent of infants and, in areas where Lyme disease is endemic**, should be considered if there is maternal exposure history to ticks." "Congenital Lyme disease can be treated with ceftriaxone."*

1999: 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. (67)

"Because it has been established that maternal syphilis, also caused by a spirochete, is associated with stillbirth and with congenital malformations in live-born infants, there has been speculation regarding whether Lyme disease is also associated with the development of congenital abnormalities."

***"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**."*

*"This was a retrospective study, and a criterion for exposure was that a woman have Lyme disease diagnosed and treated. **We therefore cannot evaluate the risks to the fetus associated with undiagnosed and untreated Lyme disease**."*

"Only episodes of Lyme disease that were diagnosed and treated by a physician were included in this analysis."

1999: Maraspin V, Cimperman J, Lotric-Furlan, S et al. Erythema migrans in pregnancy. Wein Klin Wochenschr (1999) 111/22-23:933-940. (68)

*"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**."*

"It is known that in erythema migrans (EM), the early localized stage of borrelial infection, spirochetes may disseminate by the hematogenic or lymphogenic route to various organs and organ systems."

*"Our first patient with probably fetal borrelial involvement was recognized in 1986: a 33-year-old woman delivered a stillborn female infant six weeks before term. She **did not remember any tick or insect bite, did not recall any signs or symptoms suggestive for Lyme borreliosis** and had taken no medications during gestation. On autopsy the fetus showed early cutaneous macerations, fluid thorax, ascites, and hepatosplenomegaly. Histological examinations of tissues revealed only mild, predominantly perivascular lymphocyte infiltration. **Spirochetes were seen by dark-field examination of lung, liver, and brain tissue specimens**. Serologic tests for syphilis on post-partum maternal blood were negative. B Burgdorferi IgG antibody titres were positive on indirect immunofluorescence assay without absorption (IFA)."*

*'Concern is aroused by the fact that **an unfavourable outcome of pregnancy was even registered in cases of maternal Lyme borreliosis treated with oral antibiotics**. In these cases intrauterine fetal death, neonatal death, syndactyly, cortical blindness and hydrocephalus with spina bifida have been observed. Recently cavernous hemangioma, cheilognathopalatoschysis, dysplasia coxae and hypospadias have also been associated with borrelial infection during pregnancy. The described cases show no uniform pattern of abnormalities.'*

1998: 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. (in cows) (69)

"Spirochetes were cultured from the placentas in 2 of 10 cows and from the uterine fluid of 1 in 8 cows. B. burgdorferi DNA was detected in the colostrum in 4 of 12 cows. Three of 15 calves were stillborn; B. burgdorferi was detected by PCR in 3 of 3 and spirochetes cultured from 2 of 3 stillborn calves. Fetal tissue from which B. burgdorferi DNA was detected include blood, spleen, bladder, kidney, synovial fluid and tissue, heart, cerebrum and aqueous humor."

"B. burgdoferi was cultured from the spleen of one stillborn calf and the kidney of another."

"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. burgdoferi in naturally infected dairy cattle."

1997: Trevison G, Stinco G, Cinco M. Neonatal skin lesions due to a spirochetal infection: a case of congenital Lyme borreliosis? Journal of Dermatology, 1997, 36, 677. (70)

*"**In the present report, we observed the clinical manifestations of a congenital spirochetosis. Many clues suggest that the baby boy may be affected by congenital cutaneous LB**."*

"The disease appeared approximately 3 weeks after birth, with manifestations of the second stage of the LB, similar to that observed in syphilis."

*"**The early and late transplacental transmission of Bb has been documented** in over 30 pregnancies all over the world and fatal and adverse outcomes have been reported.."*

"Affected mothers may deliver normal infants, but sometimes Bb infection during pregnancy can result in abortion, stillbirth, preterm delivery intrauterine growth retardation and congenital malformations and manifestations in the newborn."

1997: Silver H. Lyme disease during pregnancy. Infect Disease Clinics of North America, Vol 11(1), 1997. (71)

*"The first case of perinatal transmission of presumed B. burgdorferi was reported by Shirts et al in 1983. The infant was born at 38 weeks to a mother who had two episodes of high fever of unknown origin at 30 weeks and 32 weeks of gestation. The mother was initially treated with erythromycin and then cefamandole. At deliver the neonate was pale, had hepatosplenomegaly, petechiae, severe thrombocytopenia and hyperbilirubinemia. **On a peripheral smear, spirochetes were seen and a diagnosis of borreliosis was made. Histologic evaluation of the placenta revealed spirochetes within the villous capillaries**. Serologic testing and specific antigen testing of the spirochete were not performed, and results of syphilitic testing were not reported. The patient, however, lived in an area endemic for Lyme disease and remembered moving a woodpile 10 days before the onset of symptoms."*

"The first well-documented case of perinatal transmission of B. burgdorferi was reported by Schlesinger et al in 1985. The infant was born at 35 weeks to a mother with a clinical history consistent with erythema migrans in the first trimester, which subsequently resolved without further antibiotic therapy. The infant had severe congenital cardiac defects resulting in neonatal death at 39 hours of life. Spirochetes compatible with B. burgdorferi were found in the spleen, kidneys and bone marrow."

*"In 1988 however, a disturbing case was reported by Weber et al of a poor perinatal outcome in a woman diagnosed in the first trimester with erythema migrans and treated with oral penicillin. She delivered her infant by vacuum extraction at term following an uncomplicated pregnancy. The infant developed respiratory distress at 23 hours of life and died within 30 minutes of respiratory failure. The diagnosis was respiratory failure secondary to perinatal brain damage. **Spirochetes were found in the brain and liver and were confirmed by immunohistochemical techniques to be B. burgdorferi."***

1997: Weis JJ, Yang L, Seiler KP, Silver R. Pathological Manifestations in Murine Lyme disease: Association with Tissue Invasions and Spirochete Persistence. CID 1997;25 (suppl 1). (Mouse model) (72)

"Forty-six percent of acutely infected mice had at least one fetal death, compared with none of the control animals (p=.0002)."

"PCR analysis revealed the presence of B. burgdorferi DNA in the uteri of acutely infected mice but not in uteri of controls. Spirochete DNA was only rarely detected in fetal tissues, and its presence was not required for fetal death."

"Acute but not chronic infection was also associated with the presence of spirochete DNA in the uterus on day 16 of gestation. This supports the contention that pathological involvement in Lyme disease requires the invasion and persistence of spirochetes in tissues."

*"Clinically, B. burgdorferi infection resembles many aspects of syphilis. Infection with Treponema pallidum during pregnancy is associated with devastating perinatal outcomes (22). **Severe adverse perinatal outcomes, including preterm delivery, fetal death and malformation, and congenital infection have been observed in pregnant woman infected with B. burgdorferi (23-26)."***

1996: Maraspin V, Cimperman J, Lotric-Furlan S et al. Treatment of Erythema Migrans in Pregnancy – found in Clinical Infectious Diseases 1996; 22, 788-93. (73)

*"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**."*

"Among the infants of untreated women who had symptoms and/or signs of Lyme borreliosis during pregnancy, researchers have noted cardiovascular malformations, stillbirth, and neonatal rash."

1996: Altaie SS, Mookherjee S, Assian E, Al-Taie F, Nakeeb SM, Siddiqui SY. Transmission of Borrelia burgdorferi from Experimentally Infected Mating Pairs to Offsprings in a Murine Model. Abstract #1-17. 1996 FDA Science Forum. (Mouse model) (74)

'This transmission model suggests that Bb can be transmitted in-utero.'

'Transmission to offspring was indicated when Bb was isolated from any tissue from a given pup.

'From the experimentally infected in which milk was cultures, 2 (8%) transmitted Bb to their pups on day one via their milk.'

'Among 49 infected from groups A and C, 5 (10.2 %) transmitted Bb to their pups either in-utero or intrapartum. 4 of the litters from the mating pairs in Group B had infected pups.'

*'**These results indicate that Bb can transmit by other modes than the tick bite**.'*

1996: 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. (75)

"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."

"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."

1995: Schmidt B, Aberer E, Stockenhuber C, Breier K, 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;21:121-128. (76)

*"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."*

1995: 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. (77)

"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****."*

"In addition to sample size constraints, this study has limited follow-up with respect to any long-term sequalae of prenatal exposure to Lyme disease. ***Developmental problems may not be detected until after the first year of life****."*

1995: Alexander JM, Cox SM. Lyme Disease and Pregnancy. Infectious Diseases in Obstetrics and Gynecology 3:256-261 (1995). (78)

"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****."*

"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****."*

1995: Silver RM, Yang L, Daynes RA, Ware Branch D, et al. Fetal Outcome in **murine** Lyme disease. Infection and Immunity, Jan, 1995 pp.66-72. Mouse model (79)

"*Clinically, B. burgdorferi infection most resembles syphilis, which has long been associated with devastating perinatal out-comes (33). This led to concern by obstetricians regarding possible untoward fetal effects of B. burgdorferi. Indeed,* ***several adverse perinatal outcomes, including preterm delivery, fetal death, and malformations, have been noted*** *(15, 17, 26, 32).* ***Congenital infections from transplacental transmission of B.burgdorferi have also been documented*** *(14, 15, 26, 32)."*

"A sensitive PCR technique detected B. burgdorferi in the ***uteri of acutely infected mice*** *but did not detect DNA in the uteri of controls or chronically infected mice."*

"We ***cannot exclude the possibility of occasional murine transplacental transmission of B. burgdorferi under these or other conditions****. In fact,* ***we detected a faint band of B. burgdorferi DNA in one fetal sample*** *taken from an animal that had been infected 5 days prior to mating."*

1994: Gerber M, Zalneraitis E. Childhood neurologic disorders and Lyme disease during pregnancy. Pediatric Neurology Vol 11(1), 1994. (80)

"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."

1994: 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 (81)

"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."*

*"****There are reports of several cases of stillbirths, spontaneous miscarriages, heart defects and other congenital anomalies in newborns. In 25% of affected women, pregnancy was accompanied by development of early-onset late toxicosis****."*

*"****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."*

1994: Gasser R, Dusleag J, Reisinger E, Stauber R etal. A most unusual case of a whole family suffering from late Lyme borreliosis for over 20 years. Angiology. Vol 45, No 1. 1994 (82)

"A son was born in 1969, who, at birth, suffered from several minor abnormalities like a huge sacral hemangioma, gluteal atrophy, and others. He was generally weak, had recurrent episodes of fever throughout his life and showed minor mental abnormalities like extreme irritability and depressions."

"Much larger controlled studies are needed to assess the risk to the fetus when a pregnant woman becomes infected with borrelia burgdorferi."

"Bb has been isolated from a variety of tissues and body fluids, and the possibility of person to person transmission cannot be rejected without absolute proof of the contrary."

"The present case report represents the only report in the literature of a whole family infected and ill with Lyme disease for such a long period of time, and it raises the question of sexual and transplacental transmission. The latter question certainly warrants further attention.

1994: Bleiweiss, JD. (MD) When to Suspect Lyme. Personal Essay. 1994. http://cassia.org/essay.htm (83)

"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."

1994: Remy JM, Chevrant-Breton O, Logeais B, Patoux-Pibouin M, Chevrier S, Chevrant-Breton, J. Traitement de la maladie de Lyme pendant la grossesse: a propos d'un cas. Nouv. Dermatol, 1994;13:682. **translated from French (84)

"14 cases of fetal or perinatal death have been reported (1, 2,3,4,5,6) and at least 56 other cases of gestational Lyme disease are known (5, 7, 8, 9, 10, 11, 12) with an absence of abnormality in the child in case and an absence of link proved in ten cases. It is likely that favorable cases will be less published if the risk of a complication is low, based on epidemiological studies (7, 11, 12, 13, 14, 15); nevertheless, it is possible that these studies underestimated spontaneous miscarriages and miscarriages: in 1989, Mac Donald in a study conducted between 1978 and 1988, ***14 cases of Lyme disease during pregnancy with 11 fetal of perinatal deaths showing Borrelia burgdorferi in fetal tissues or placenta****. In this study, six cases were associated with abnormalities in cardiac organogenesis with our deficiencies in the interventricular wall, finding the autopsy data of the Schlesinger case."*

1994: Bussen S, Steck TH. Manifestation einer Lyme-Arthritis im Wochenbett. Z. Geburtsh. u. Perinat. 198(1994). **translated from German (85)

"The transplacental transmission of Borrelia burgdorferi was demonstrated in two newborns whose mothers had acute borreliosis in the first trimester. Both children died during the first week of life, one as a result of heart failure (aortic valve and isthmus stenosis) (Schlesinger et al., 1985), the other due to encephalitis (Weber et al., 1985).

"In a retrospective compilation, four out of 19 newborns with serologically confirmed maternal Borrelia infection in the first or second trimester recorded intrauterine fetal death, premature birth, syndactyly and cortical blindness (Markowitz and co-workers 1986)."

"In a recent prospective study, 3 out of 11 children with maternal Borrelia infections in early pregnancy were diagnosed with congenital malformations (one clubfoot, gastro-esophageal reflux and VATER association) (Strobino et al., 1993). In both studies, the mothers were adequately treated with antibiotics during pregnancy. A causal connection between the maternal Borrelia infection and the diverse, childish malformations cannot be reliably established on the basis of these observations. However, the congenital abnormalities and damages that have occurred in 9 of 32 support this suspicion."

1994: Trevison, G. Lyme borreliosis, a general survey. Acta Dermatovenerologica A.P.A. Vol 3, 94, No 1/2. (86)

*"**Borreliae can cross the placental barrier and contaminate the conceptus during the first months of pregnancy**; the risks of contamination during the first three months of pregnancy is higher."*

"Malformations, fetal death in uterus, pre-term deliveries and rashes in the newborn are possible consequences of the infection during pregnancy. Congenital Lyme disease is possible though rare, and reports are scarce."

1993: Sicuranza G, Baker DA. Lyme Disease in Pregnancy, Chapter 23, p 184-186. Found in: Mosby Year Book, eds: Coyle P. Lyme Disease. (87)

"Maternal infection may involve transmission of the invading microorganism to the fetus. This may have no adverse consequences or may produce a range of sequalae from minor transient problems to fetal death and abortion."

*"A **body of evidence suggest that the causative agent of Lyme disease, B. burgdorferi can cross the placenta and infect the fetus**. There are also several reports that suggest that this may be associated with a poor fetal outcome. However, the majority of studies have not been able to identify B. burgdorferi as the cause of spontaneous abortions, congenital abnormalities, or neurologic sequelae in infants."*

1993: Christen HJ, Haneford F, Eiffert H, Thomssen R. Epidemiology and Clinical Manifestations of Lyme Borreliosis in Childhood. Acta Pediatr Suppl 386:1-76, 1993. (88)

*"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."*

1993: 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 (89)

"The etiological agent of Lyme Disease, a spirochete Borrelia burgdorferi, has a proven transplacental transmission and for that reason can affect the outcome of the pregnancy, thus it represents an important prenatal problem."

"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."

1993: 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. (90)

*"**there are case reports <u>that have demonstrated the potential of B Burgdorferi to cross the placenta and infect fetal tissue</u>**."*

*"these case reports **<u>clearly indicate</u>** 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."*

*"**the number of women was too small to draw** conclusions about the risk of having a child with a congenital malformation if the woman is seropositive."*

*"**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**."*
*"**tick bites within 3 years preceding conception were significantly associated with congenital malformations**."*

*"It was hypothesized that adverse pregnancy outcomes were most likely to be associated with exposure during pregnancy or exposures recent to conception. However, **because the numbers of exposed patients were small and <u>because it is possible that the infection is reactivated</u>**, we also examined the effects of any past exposure to Lyme disease versus no exposure."*

1993: Christen H, Hanefeld F. Lyme Borreliosis in Childhood and Pregnancy. Chapter 17. In: Aspects of Lyme borreliosis. Weber K, Burgdorfer W, Schierz G (editors). Springer-Verlag Berlin Heidelberg; 1993. (91)

*"It is well known that spirochetes cause congenital infections. Transplacental transmission of Treponema pallidum, Leptospira and Borrelia recurrentis is associated with a wide spectrum of adverse outcome of pregnancy including abortion and stillbirth. **The same risk might possibly be expected for infection with B. burgdorferi during pregnancy**."*

"There is only one well-documented case of congenital Lyme borreliosis in Europe described by Weber et al (1988) in which the mother suffered from erythema migrans in early pregnancy and the child died on the first day of life. B burgdorferi was detected in the brain by means of monoclonal antibodies and liver by sliver staining. Another case of this type was reported by Schlesinger et al. (1985) in the USA."

*"According to the experiences of Weber et al. (1988) **orally administered penicillin does not seem to be sufficient to avoid transplacental transmission of B. burgdorferi**."*

1993: Burgess EC, Wachal MD, Cleven TD. Borrelia burgdorferi infection in dairy cows, rodents and birds from four Wisconsin dairy farms. Veterinary Microbiology, 35, (1993) 61-77. (In mice) (92)

"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 1/2 fetuses from the P. leucopus. The spirochetes from all three cultures were positive by PCR analysis."

*"**<u>Transplacental transmission was shown</u>** in M. musculus and P. leucopus."*

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

1993: 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. (In dogs) (93)

"Maternal-fetal transmission of B. burgdorferi has been reported in horses, human beings, coyotes and Peromyscus leucopus."

"In human beings, maternal infection during pregnancy has been associated with fetal death, congenital cardiac defects, early neonatal death, cortical blindness, syndactyly and a neonate delivered with erythema chronicum migrans."

*"Intrauterine infection by B. burgdorferi does **occur in dogs** and is a potential means by which the **spirochete can be transmitted in a breeding population in the absence of a tick vector**."*

"Intrauterine infection with B. burgdorferi is a mechanism by which pups can become infected in the absence of a vector. Furthermore, 6-week-old pups that were delivered by an infected female had Bb specific DNA detected in their tissues."

1992: Stechenberg BW. Rheumatology - Lyme Disease. Current Problems in Pediatrics, Oct 1992. (94)

*"**Maternal-fetal transmission of Borrelia burgdorferi has been documented** in two infants, one with congenital heart disease and the other with encephalitis. Prospective studies of Lyme disease have not revealed a specific pattern of adverse outcomes."*

1992: 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. (95)

*"**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**"*

"Markowitz et al. reported on 19 pregnancies with clinical B. burgdorferi infection. Five of the 19 patients (26%) had an adverse outcome of pregnancy: premature delivery, intrauterine demise, syndactyly, and cortical blindness."

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

1992: ACOG Committee Opinion: Committee on Obstetrics: Maternal and Fetal Medicine. Lyme disease during pregnancy. Int J. Gynecol Obstet 1992, 39; 59-60 (96)

*"**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."*

1992: 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 (97)

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

1991: Schutzer SE, Jannigan CK, Schwartz RA. Lyme Disease During Pregnancy. CUTIS. Volume 47, April 1991. pp 267-268. (98)

"..fatal and adverse results have been described resulting from both early and late infections. Cortical blindness, syndactyly, and heart defects have been described. ***Cited in particular have been deaths and complications in the infants when the mother was treated with oral as well as intravenous antibiotics****."*

"Although infected mothers may deliver normal healthy infants in some cases and infants with congenital pathologic condition in others, the full effect of Lyme disease in pregnancy is not known and no universal agreement on guidelines has been reached. Nevertheless, early diagnosis and treatment are most likely to be associated with favorable outcomes in both the mother and child."

1991: Dorward D, Schwan T, Garon C. Immune Capture and Detection of Borrelia burgdorferi Antigens in Urine, Blood or Tissues from Infected Ticks, Mice, Dogs and Humans. Journal of Clinical Microbiology, June 1991 p. 1162-1170). (99)

"Human urine and blood samples, which were collected from patients with suspected Lyme borreliosis, were graciously provided by Paul Duray. The donors were chosen from among patients with histories of erythema migrans, arthritis, neurologic involvement, and/or ***congenital Lyme borreliosis****."*

1991: Lakos, A. Lyme borreliosis in the years 1984 through 1989. Parasit. Hung., 24:5-51, 1991. Hungarian Society of Parasitologists. (100)

"Bb infection may also cause carditis, chronic arthritis and several other forms of neurological disorders. Most recently, otoneurological and ophthalmological complications ***as well as fetal injury have been reported****. The disease is famous for* ***protean, chronic, fluctuating manifestations resembling another spirochetal illness, syphilis*** *and is a candidate for the award of the 'great imitator.'*

1991: Cryan B, Wright DJM. Lyme disease in Paediatrics. Archives of Disease in Childhood; 66:1359-1363. (101)

"The isolation of B burgdorferi from the blood has raised the possibility of transplacental transfer of the organism. ***To date, borreliae have been isolated from one stillbirth and one newborn infant*** *but congenital abnormalities resulting from Lyme disease during pregnancy have not been unequivocally demonstrated.* ***The abnormalities that have been recorded were associated with serological evidence of infection in retrospective studies****."*

1991: Burgdorfer W. Lyme Borreliosis: Ten Years after Discovery of the Etiologic Agent, Borrelia burgdorferi. Infection 19 (1991) No. 4:257-261. (102)

'The past ten years have shown considerable broadening of the clinical spectrum of Lyme borreliosis, making it one of the most complex bacterial diseases ever known. ***Thus transplacental transmission of B. burgdorferi has resulted in stillbirths or malformed fetuses****. Although invasion of the placenta by spirochetes is well documented, malfunction and/or death of the fetus appear to be rare.'*

'A culture-positive neonatal death was recently recorded in California; B. burgdorferi was grown from the frontal cortex and spirochetes were found in silver stained sections of the brain and heart.'

'After ten years of intensive investigations and more than 2,500 scientific publications, Lyme borreliosis is now recognized as the most prevalent tick-borne disease that every year affects thousands of people – children and adults alike. Indeed, as in many regions where it is endemic, ***the disease has been considered second only to AIDS in public interest and concern****.'*

1990: Drulle, John (MD) Pregnancy and Lyme Disease. December 1990. Reprinted by the John Drulle, MD Memorial Lyme Fund Inc. in 2006. (103)

*"When a pregnant woman is infected with Lyme disease, not only is she **subject to its devastation**, but **her baby is too**. **I have seen a number of babies born with congenital Lyme** and am quite aware of the devastating effects it can cause."*

1990: Cryan B, Wright DJM. Antimicrobial agents in Lyme disease. Journal of Antimicrobial Chemotherapy 25, (1990), 187-190. (104)

*"The isolation of B. burgdorferi from the blood has raised the possibility of transplacental transfer of the organisms. **To date, borreliae have been isolated from one stillbirth, and one newborn infant**, but congenital abnormalities resulting from Lyme disease during pregnancy have not been unequivocally demonstrated."*

1990: Horst, H. (abstract no W/TH-P-20). In: Abstracts (book 1) of the 4th International Conference on Lyme borreliosis. Stockholm, Sweden, p 56. (105)

"Within one year (1987-1988), 1600 cases of Lyme borreliosis were registered with the following disease manifestations. Because approximately only 25 % of the practicing physicians participated in the survey it seems reasonable to multiply the incidence rate by 2-4 to get a realistic number."

*"**Gestational Lyme Borreliosis** - 1"*

"It therefore might be concluded that these data represent the average epidemiological situation for large parts of Middle-Europe."

1990: Edly S. Lyme Disease During Pregnancy. New Jersey Medicine. Vol 87 (7), July 1990. (106)

*"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**."*

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

*"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**."*

1990: Stiernstedt G. Lyme Borreliosis during Pregnancy. Scand J Infect Dis, Suppl. 71:99-100, 1990. (107)

"Naturally the question of Lyme borreliosis, in analogy with syphilis, may cause congenital disease has been raised."

"Three cases of congenital Lyme borreliosis have been described in which the organism has been identified or cultured from fetal tissue. In two cases the mother was untreated during pregnancy and delivered a stillborn and premature child respectively."

1990: 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. Stockholm, Sweden, p 128. (108)

*"**We report a culture positive neonatal death occurring in California**, a low endemic region. The boy was born by C-section because of fetal distress. He initially appeared normal. He was readmitted at age 8 days with profound lethargy leading to unresponsiveness. Marked peripheral cyanosis, systemic hypertension, metabolic acidosis, myocardial dysfunction and abdominal aortic thrombosis were found. Death ensued. **Bb was grown from a frontal cerebral cortex inoculation.** The spirochete appeared similar to the original Long Island tick isolate. **Silver stain of brain and heart was confirmatory of tissue infection**. The family was **seronegative for LB** by ELISA at Yale."*

1989: Dattwyler R, Volkman D and Luft B. Immunologic aspects of Lyme borreliosis. Review of Infectious Diseases Vol 11(6) 1989. (109)

*"Lyme borreliosis is a **chronic infectious disease caused by the spirochete Borrelia burgdorferi**."*

*" **Neonatal Lyme disease:** In **humans, B burgdorferi is capable of infecting the fetus** (35). Sequelae (including abortion and fetal abnormalities) have been associated with infection (36,37). The time, incidence, and morbidity of in utero infection are not known.*

*However, both **humoral and cellular B burgdorferi-specific responses can be detected in cord blood of previously infected neonates** (authors' unpublished observations).*

*In addition, **Borrelia-specific antibodies have been found in the CSF of an infant with evidence of neonatal neurologic dysfunction** whose mother had been **infected in the second trimester**.*

***The mother, who was asymptomatic, had been treated with oral antibiotics** and did not have diagnostic levels of antibodies to B burgdorferi at the time of parturition (authors' unpublished observations).*

*Effective therapy to eradicate borreliae on both the maternal and the fetal side of the placenta is essential, as **persistent infection may be difficult to diagnosed after the initial course of antibiotics**."*

1989: 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. *in coyotes (110)

"Transplacental infection of B. burgdorferi has been shown in humans, cows and horses and has been associated with abortions and fetal mortality (Schlesinger et al. 1985, Burgess, 1988). The effect of transplacental transmission in the coyote is unknown. The case of an antibody negative coyote have a B. burgdorferi 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."

"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."

1989: Nadal D, Hunziker UA, Bucher HU, Hitzig WH, Duc G. Infants born to mothers with antibodies against Borrelia burgdorferi at delivery. Eur J Pediatr. 1989; 148(5):426-7. (111)

*"**The spirochete Borrelia burgdorferi, the causative agent of Lyme disease, also appears to cross the placental barrier**. Adverse outcomes of pregnancies in women with Lyme disease have been reported and include fetal death, prematurity, infants with complex cardiac malformation, ventricular septal defect, cortical blindness, syndactyly or neonatal rash."*

1989: Hamilton, D. Lyme Disease. The Hidden Pandemic. Postgraduate Medicine. Vol 85, No 5, April 1989. pp. 303-314. (112)

"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."

"Long-term persistence of the spirochete in humans, characterized by periodic activation, multiplication and dissemination over ten years or longer, may be responsible for the episodic nature of this disease."

1989: Luft, BJ, Gorevic, PD, Halperin JJ, Volkman DJ, Dattwyler, RJ. A Perspective on the Treatment of Lyme Borreliosis. (113)

"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. reported the congenital transmission of B burgdorferi to an infant whole mother had been treated with 1 million units of oral penicillin for 7 days."

*"****Persistent B. burgdorferi infection can produce various insidious and chronic dermatologic, neurologic and rheumatologic manifestations****. The pathophysiologic mechanisms involved in the chronic phase of this illness remain incompletely defined."*

1989: Schmidt R, Goller E, Zunser R, Kruger J, Ackermann R. Prevalence of Erythema migrans Borreliosis in Blood donors. Infusionstherapie 16: 248-251 (6/1989). (114)

"Since intrauterine transmission of Borrelia infection has been described, the inevitable question of whether this disease can also be transmitted as a result of blood transfusion becomes a major concern."

"Even though borreliemia seems to be most probable in the presense of distinct clinical signs and in the beginning of disease when antibody titres are still low, the pathogen may persist and relapses may occur despite high antibody titres."

"Though intrauterine transmission of Borrelia infections has been demonstrated, the occurrence of Erythema migrans Borreliosis through blood transfusions has not yet been described. The absence of reports linking Borrelia infection and blood transfusion, however, may convey a false impression of safety."

1989: Medical Science Steps up its assault on Lyme Disease. In Science section. The New York Times. July 4, 1989. (115)

*"****We do know that the Lyme bacteria crosses the placenta****," said Dr. David Axelrod, the New York State Health Commissioner."*

1989: 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. * in horses (116)

"Transplacental transmission of B. burgdorferi has been demonstrated in humans, associated with abortions, fetal deaths, and possible heard defects."

"This study shows that B. burgdorferi can cause in utero infections in horses and can be associated with foal mortality. The kidney lesions in the foals that died soon after birth and in the yearling contributed to the deaths of the animals. The lesions were attributed to B. burgdorferi infection as B. burgdorferi was isolated from the kidneys of three of the four animals and spirochetes were identified in the kidneys of histologic sections."

"B. burgdorferi was demonstrated in the proximal convoluted tubules of the kidney and in the spleen of a premature infant of woman positive for B. burgdorferi antibody (Schlesinger et al, 1985).

"The demonstration of antibodies in the serum of Foal 2 and the isolation of spirochetes from Foal 1 suggest infection took place in-utero."

1989: Luft BJ, Dattwyler RJ. Lyme Borreliosis. Current Clinical Topics Infectious Disease. 1989; 10:56-81. (117)

*"Although the **potential for B. burgdorferi to cause congenital disease has clearly been establishe**d, 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."*

*"**Two cases of congenital Lyme borreliosis have been described** in which the organism was isolated or identified from fetal or neonatal tissue. Both mothers reported EM during the first trimester. In the first reported case, the baby was born to a mother who was untreated for her EM. The infant had widespread congenital cardiovascular abnormalities and subsequently died of respiratory distress. Pathological examination revealed no evidence of inflammation in any organ. However, spirochetes were identified in the spleen, renal tubules and bone marrow. Subsequently, Weber et al described a pregnant woman who developed EM and was treated with a short course of oral penicillin. She subsequently gave birth to a baby who died of respiratory failure as a consequence of perinatal brain damage. B burgdorferi was identified histopathologically in the brain and liver."*

1989: Cartter M, Hadler J, Gerber M, Mofenson L. Lyme Disease and Pregnancy. Connecticut Medicine. Volume 53 (6), June 1989. (118)

"In 1985 Schlesinger et al reported the first case of transplacental transmission of Lyme disease. They identified spirochetes morphologically compatible with B. burgdorferi in multiple organs or an infant who had died of complications of congenital heart disease shortly after premature delivery."

"Similarly, Weber et al described post-mortem detection of B. burgdorferi in the brain and liver of a child who had died at 24 hours of age from the consequences of perinatal brain damage."

"Macdonald et al observed B. burgdorferi in multiple organs including the myocardium of a stillborn infant

whose mother had not sought medical attention for EM in the first trimester of pregnancy. Although there was no significant tissue inflammation, the authors felt the infant had died of overwhelming spirochetosis."

"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."

1989: Steere, A. Medical Progress, Lyme Disease. The New England Journal of Medicine. Vol 321, No. 9. pp 586-596. Aug. 31, 1989. (119)

Congenital Infection:

*"The **transplacental transmission of B. Burgdorferi has now been reported** in two infants whose mothers had Lyme borreliosis during the first trimester of pregnancy."*

"Both infants died during the first week of life, one because of congenital cardiac malformations and the other of encephalitis. In both, spirochetes were seen in various fetal tissues stained with Dieterle's silver stain, but cultures and serologic testing were not done."

*"Although **it is likely that the Lyme disease spirochete can probably cause an adverse outcome**, it seems to be unusual."*

"A pregnant woman in Europe whose erythema migrans was treated with oral antibiotics had an infant who died of possible Lyme encephalitis."

*"**Clinically, this borrelial infection is most like syphilis in its multisystem involvement, occurrence in stages and mimicry of other diseases**."*

"After hematogenous spread, B. burgdorferi seems to be able to sequester itself in certain niches.'

1989: Lebeaut A, Bourrillon A. La maladie de Lyme chez l'enfant. Arch Fr Pedia 1989; 46:287-92. ** Translated from French. (120)

"Maternal-fetal transmission was first documented in 1985 in association with the occurrence of congenital malformations, particularly heart defects (56). In a recent study (57), surveillance of pregnancy in 19 women with Lyme has highlighted the possibility of prematurity, cortical blindness, syndactyly [noted also in another prospective study (58)], died in utero (59). The direct relationship of causality between the spirochete and the occurrence of such abnormalities is however not certain, justifying the continuation of epidemiological and clinical studies in this context. Most authors (56, 57, 59) currently propose to routinely treat any suspicious pregnant woman with Lyme, regardless of which trimester is recognized. The treatment is based on oral or parenteral penicillin therapy for some (60), to prevent infection of the fetus."

1989: *Berger B. Dermatologic Manifestations of Lyme Disease*. Reviews of Infectious Diseases, Vol II, Supplement 6, Sept-Oct 1989. (121)

*"**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."*

1989: Adams FG. Connecticut Epidemiologist. Epidemiology Section. State of Connecticut Department of Health Services. Pregnancy and Lyme Disease. March 1989, Vol 9(2). (122)

"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."

*"**Several case reports suggest that Lyme disease can be transmitted congenitally**. However, two follow-up studies of small numbers of women diagnosed with acute Lyme disease during pregnancy, most of whom received some treatment, failed to document adverse outcomes."*

"Additional research is needed to define the risk of congenital transmission of Lyme disease, the clinical consequences of such transmission, and to guide treatment recommendations."

1989: Macdonald, AB. Gestational Lyme borreliosis. Implications for the fetus. Rheum Dis Clin North Am. 1989;15(4):657-77. (123)

"From a biologic perspective, most of the fatal cases of Lyme borreliosis in pregnancy were reactive either in titres in the borderline region or were completely non-reactive in serologic tests. ***The tendency toward sero-negativity in pregnancy makes maternal serology a less satisfactory discriminator or maternal infection and useless as a practical tool to predict the actual state of the fetus****.'*

"If we seek the truth, we must seek the spirochete directly by pathologic study of available tissues from the products of conception."

"A 7-year retrospective analysis of perinatal autopsies performed from 1978-1985 and a 3-year prospective study of perinatal deaths from 1985 to 1988 ***has yielded evidence that Borrelia Burgdorferi is detectable in some perinatal autopsy tissues****."*

*"**Maternal blood is seronegative for specific antibodies against Borrelia burgdorferi in cases where the spirochete can be demonstrated in the fetus or placenta****."*

*"**Great diversity of clinical expression of signs and symptoms of gestational Lyme borreliosis parallels the diversity of prenatal syphilis**. It is documented that transplacental transmission of the spirochete from mother to fetus is possible."*

"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****."*

"*The tissue IFA method can be applied to the retrospective and prospective study of the possible role of B. burgdorferi as the etiologic agent of fetal demise of uncertain cause, congenital heart defects, and miscarriage following maternal toxemia of pregnancy."*

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

1989: Belani K, Regelmann WE. Lyme Disease in Children. Rheum Dis Clin North Am. 1989;15(4):679-689. (124)

*"**Transplacental transmission of the spirochete <u>from mother to fetus has been documented</u>**"*

*"Perinatal borreliosis of Lyme disease occuring in pregnancy **<u>may result in transplacental transmission of the spirochete and cases with adverse perinatal outcomes have been reported</u>**. 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."*

"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."

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

*"**<u>Oral antibiotic treatment has failed in preventing transplacental transmission in one reported case</u>** leading to fatal perinatal borreliosis."*

1988: Duray, P, Steere, A. Clinical Pathologic Correlations of Lyme disease by stage. Annals of the New York Academy of Sciences, Vol 539:65-79, 1988. (125)

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

1988: Burgess E.C. Borrelia burgdorferi infection in Wisconsin horses and cows. Annals of the New York Academy of Science, Lyme disease and related disorders, Vol 539: p. 235-243. (126)

*"Transplacental transmission of B. burgdorferi was demonstrated in the cows. B. burgdorferi was cultured from the blood of a newborn calf, and an aborted calf had antibodies to B. burgdorferi, indicating in utero infection. There is no in utero maternal transfer of antibodies in cows. I3 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. **<u>Transplacental transmission of B. burgdorferi has been demonstrated in humans</u> and has been associated with abortions, early infant death, and possible heart defect**."*

1988: Health and Welfare Canada. Lyme Disease in Canada. Canada Dis Wkly Report, June 4, 1988. (127)

*"**Transplacental transmission of B. burgdorferi <u>has been documented</u>** and may be associated with an increased risk of adverse outcome if pregnancy."*

1988: Barbour A. Laboratory Aspects of Lyme Borreliosis. Clinical Microbiology Reviews, Oct. 1988, p 399-414, Vol 1, 4. (128)

"The organism, like other pathogenic spirochetes, is probably transmissible via the placenta to the fetus. ***B. burgdorferi infection of fetuses has been documented****."*

"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 titres to the organisms (57).

"Family members of Lyme disease patients have high stimulation indices than unrelated controls, indicating either a hereditary predisposition or shared exposure to the infectious agent *(152)."*

1988: Williams CL, Benach JL, Curran AS et al. Lyme Disease During Pregnancy, a cord blood serosurvey. Annals New York Academy of Sciences, 1988;539(1):504-6. (129)

*"**Human transplacental transmission of spirochetes of the genus Borrelia has also been reported to result in fetal infection and sometimes death**."*

*"**Transplacental transmission of B. burgdorferi has now been reported by several investigators**. In two cases of untreated first trimester maternal Lyme disease, both newborns at autopsy were found to have malformations of the heart (one baby was stillborn; one expired at 39 hours of life)."*

1988: In Epidemiologic Report written by Elly Bollegraaf- Lyme Disease in Canada - found in the Canadian Medical Association Journal (CMAJ) Vol 139. August 1, 1988. (130)

*"**Transplacental transmission of B. burgdorferi has been documented** and may be associated with an increased risk of adverse outcome if pregnancy."*

1988: Johnson RC. Vaccine against Lyme disease. Patent # 4,721,617. January 26, 1988. http://www.patents.com/us-4721617.html (131)

"The chronic forms of the disease such as arthritis (joint involvement), acrodermatitis chronica atrophicans (skin involvement), and Bannwart's syndrome (neurological involvement) may last for months to years and are associated with the ***persistence of the spirochete****.* ***A case of maternal-fetal transmission of B. burgdorferi resulting in neonatal death has been reported****. Domestic animals such as the dog also develop arthritis and lameness to this tick-borne infection.* ***For every symptomatic infection, there is at least one asymptomatic infection****. Lyme disease is presently the most commonly reported tick-borne disease in the United States."*

1988: 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 (132)

*"**We now demonstrate B Burgdorferi in the brain and liver of a newborn whose mother had been treated with oral penicillin during the first trimester of pregnancy**."*

*"**B. burgdorferi was identified in rare paraffin sections of the brain when the monoclonal antibody.. supplied by Dr. A.Barbour was used**"..*

*"**We have found B Burgdorferi in the human neonatal brain and liver**"*

"Application of an immunohistochemical method allowed for us to identify the spirochete as Borrelia Burgdorferi"

1988: Carlomagno V, Luksa V, Candussi G et al. Lyme Borrelia Positive Serology associated with spontaneous abortion in an endemic Italian Area. Acta Europaea Fertilitatis, Vol 19, n.5, 1988. (133)

"Concern about the effect of maternal Lyme Borreliosis on pregnancy outcome was justified being the etiologic agent a spirocheta. Lyme Borreliosis during pregnancy was documented to our knowledge in 22 cases… In 2 of these cases a transplacental transmission of borrelia burgdorferi was also documented."

"Necessity for routine serological screening of pregnant patients living in an endemic area 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."

*"**Paraffin 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 trans placental transmission**."*

1987: Lavoie PE, Lattner BP, Duray P. H et al. Culture positive, seronegative, transplacental Lyme borreliosis infant mortality. Arthritis Rheum; 1987. p. S50. (134)

*"**We report a culture positive neonatal death occurring in California**, a low endemic region. The boy was born by C-section because of fetal distress. He initially appeared normal. He was readmitted at age 8 days with profound lethargy leading to unresponsiveness. Marked peripheral cyanosis, systemic hypertension, metabolic acidosis, myocardial dysfunction and abdominal aortic thrombosis were found. Death ensued. **Bb was grown from a frontal cerebral cortex inoculation.** The spirochete appeared similar to the original Long Island tick isolate. Silver stain of brain and heart was confirmatory of tissue infection. The family was **seronegative for LB by ELISA** at Yale."*

1987: MacDonald A, Benach J, Burgdorfer W. Stillbirth following Maternal Lyme Disease. New York State Journal of Medicine vol 87, November 1987. (135)

*"**Transmission of the spirochete Borrelia Burgdorferi from mother to fetus during the first trimester of pregnancy was followed by overwhelming spirochetosis in the fetus with intrauterine death near term**."*

*"**Two cases of transplacental transmission of Borrelia Burgdorferi have been associated with fetal death and cardiac malformation**."*

*"**The clinical examination of the patient and the clinical diagnosis of probably Lyme disease must be the 'gold standard of diagnosis'** because Lyme serologic studies may be non-diagnostic due to intra-laboratory variation in detection of serum antibody or due to delay between primary infection and the production of serum antibody, which is recognized for every serologically defined infectious disease."*
"We recommend that pathologists search for spirochetes in tissues of stillborn fetuses who show malformations in the cardiovascular system."

1987: Burgdorfer W. Lyme Disease. Current Views. Lecture presented at Allergy and Asthma Symposium, May 9, 1987. Oshkosh, Wisconsin. (136)

*'I may add here that **maternal-fetal transmission of the Lyme disease spirochete has been documented in the United States**. The first report concerned a woman who contracted the disease during the first trimester. The child was premature and died of congenital heart disease during the first week of life. Of 19 additional women with Lyme disease during pregnancy, 14 were normal but in the remaining five there were cases of intrauterine fetal death, prematurity and developmental delay with cortical blindness.'*

1987: MacDonald AB. Lyme Disease. A Neuro-ophthalmologic View. Journal of Clinical Neuro-opthamology 7(4): 185-190, 1987. (137)

*'**Lyme disease in pregnancy way 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.'*

1987: Mikkelsen A, Palle C. Lyme Disease during Pregnancy. Acta Obstet Gynecol Scand 66:477-478. (138)

"Schlesinger et al reported transplacental transmission of Borrelia burgdorferi in a pregnant woman who developed Lyme disease during the first trimester of pregnancy. No antimicrobial therapy was given and at term she gave birth to an infant with congenital heart defect, causing the death of the child after a week. At autopsy the spirochetes were seen in the spleen, kidney and bone marrow."

"In the USA, 19 pregnancies complicated by Lyme disease have been evaluated. The outcome of 14 was normal. The others resulted in fetal demise in the second trimester, in prematurity, and in developmental delay with cortical blindness. As Lyme disease during a pregnancy seems responsible for the adverse outcome, it is important to recognize and treat this condition."

1987: Anderson JF, Johnson RC, Magnarelli LA. Seasonal Prevalence of Borrelia burgdorferi in Natural Populations of White Footed Mice, Peromyscus leucopus. (in mice) (139)

*"One culture was obtained from a **fetus of a pregnant white-footed mouse** from which **spirochetes also were cultured from spleen and kidney tissues**."*

1986: Schlesinger PA. Rheumatology Corner, Lyme Disease. Minnesota Medicine, Vol 69, June 1986. (140)

"Recently, transplacental transmission of Borrelia burgdorferi has been documented."

1986: Macdonald, AB. Human fetal borreliosis, toxemia of pregnancy and fetal death. Zentralbl Bakteriol Mikorbiol Hyg (A). 1986;263(1-2):189-200. (141)

*"**Spirochetes were cultured from fetal liver in four stillborn human fetuses, three of whom demonstrated congenital malformations of the heart or great vessels**. Toxemia of pregnancy was found in two of the cases of the series. **Spirochetes were identified by paraffin embedded formalin fixed fetal tissues in each case in this series using a simple indirect immunofluorescent microscopic method**."*

*"**Spirochetes were cultured from fetal liver tissue in each of the four cases, from fetal heart in one case**."*

*"**Spirochetes were detected in fetal liver, heart, adrenal, brain, kidney, meninges, and subarachnoid space. Spirochetes were reactive against the pooled human serum lot described above in all cases and against a monoclonal mouse antibody specific for B. Burgdorferi**."*

1986: Weber K, Neubert U. Clinical Features of Early Erythema Migrans Disease and Related Disorders. Zbl. Bakt. Hyg. A 263, 209-228, 1986. (142)

"Three women were pregnant. One woman was treated with propicillin during the 12th week of pregnancy for an erythema migrans of one-week duration, ***had negative antibody titers at first visit*** *and 2 months after therapy, delivered a normal child, but the child died 23 hours after delivery; post mortem examination (Drs. H. Bratzke and M. Eder, University of Miinchen) revealed signs of aspiration in the lung and mild hemorrhage in the brain;* ***borreliae were found in brain and liver by silver stain and/or immunofluorescence with monoclonal antibodies*** *(with Dr. P. H. Duray, Yale University)."*

"Three of our women were pregnant. One was still pregnant at the cut-off time of this study, and one having contracted EMD shortly before term delivered a normal child. ***The newborn of the third woman had a few borreliae in brain and liver despite antibiotic therapy during pregnancy****. Congenital heart disease has been reported recently (36)."*

1986: Markowitz L, Steere A, Benach J, Slade J, Broome C. Lyme Disease during Pregnancy. Respiratory and Special Pathogens Epidemiology Branch, Division of Bacterial Diseass, Centers for Disease Control, Atlanta GA, USA. J AM. MED ASSOC. 255/24 (3394-3396), 1986 (143)

"In a recent case report, transplacental transmission of the Lyme disease spirochete was documented, but was not linked directly to the congenital cardiac abnormalities found in the infant."

"In this study we investigated cases of Lyme disease during pregnancy to detect any adverse outcomes. Five of the 19 pregnancies complicated by Lyme disease had adverse outcomes. ***These outcomes were not birth defects: prematurity, intrauterine fetal death and rash illness in a newborn****."*

"the ***frequency of adverse outcomes reported here warrants further surveillance and epidemiologic and laboratory studies of pregnant women with Lyme disease****."*

"It appears that ***many patients are bacteremic early in Lyme disease and that the later manifestations are due to tissue invasion and persistence of the organism****."*

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

*"A four-year-old girl with neonatal onset of chronic diffused urticarial rash, head enlargement, protruding eye balls, bilateral arthritis of the knees, growth and mental retardation and signs in the blood and cerebrospinal fluid of chronic inflammation is presented and compared with two similar cases reported by us previously****. In the present case, however, elevated antibody titres against I. ric Borrelia antigen were found in the serum****."*

*"****The mother (asymptomatic) also had positive ELISA titres****, the father was negative." "The patient was born in March (thus conceived and in early embryonic development the previous summer).* ***Thus, it cannot be ruled out, that our patient developed this specific syndrome as a self-propagating inflammatory host response after an intrauterine infection with Lyme disease spirochetes****."*

1986: World Health Organization, Geneva. Weekly Epidemiological Record. No. 39. 26 September, 1986. Page 297-304. (145)

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

"In an effort to assess the risk of Lyme disease during pregnancy, the state and territorial epidemiologists and CDC have established a registry to enrol cases of Lyme disease in pregnant woman before the outcome of pregnancy is known. Of the 19 pregnancies evaluated to date, none resulted in a child with a congenital heart defect. However, other adverse outcomes were found, including intra-uterine fetal death in the second trimester, prematurity, and developmental delay with cortical blindness. None of the adverse outcomes have been documented to be caused by Lyme disease."

*"****Since transplacental transmission has been documented****, it will be important to determine whether maternal infection with B. burgdorferi is associated with an increased risk of adverse pregnancy outcome. Cases of Lyme disease during pregnancy should also be reported to state health departments and CDC before delivery so the types and approximate frequency of any adverse outcomes can be determined, and appropriate diagnostic tests obtained."*

1986: Burgdorfer, W. The Enlarging Spectrum of Tick-Borne Spirochetosis: R. R. Parker Memorial Address. Reviews of the Infectious Diseases, Vol 8, No. 6. Nov/Dec 1986 (146)

*"…****now we have found a spirochete capable of spreading transplacentally to the organs of the*** *fetus, causing congenital heart disease and possible death of the infant."*

1985: In MMWR. 'Lyme disease and cases occurring during pregnancy' Vol 34, No 25, June 28, 1985), pp. 376-378. Published by Centers for Disease Control and Prevention (CDC). (147)

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

1985: 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. (148)

"We report the case of a woman who developed Lyme disease during the first trimester of pregnancy. She did not receive antibiotic therapy. Her infant, born at 35 weeks gestational age, died of congenital heart disease during the first week of life. ***Histologic examination of autopsy material showed the Lyme disease spirochete in the spleen, kidneys, and bone marrow****.'*

*"The Lyme spirochete has been cultured from blood, skin and cerebrospinal fluid and has been seen in synovial lesions****..it is clear that the organism may invade and persist in many different sites****."*

*"****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****."*

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Compiled by Sue Faber RN BScN, updated June 26, 2019 - **Co-Founder LymeHope**

Note: Citation boxes highlighted in light green refer to animal studies

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CTV National News Coverage, January 21, 2019

'Mothers on a Mission..'