Tick Borne Infections in Pregnancy,

DrJohn Lambert, Full Professor of Medicine and Infectious Diseases,
Mater Hospital and UCD, Dublin. jlambert@mater.ie

A complex partnership

- The complex interactions at the materno-fetal interface is poorly understood
- Immune modulation in pregnancy includes reduced CD/CD8 cells, decreasing cytotoxic T cells, and a shift from Th1 to Th2 Helper T cells, all increasing susceptibility to infection.
- The role of the placenta as both a protective barrier from infection but also from maternal immune recognition, while also supplying the fetus with all of the essential nutrition for human development, needs more research

Differing perinatal outcomes:

- Minor, self limiting illnesses
- Pregnancy loss from spontaneous abortion
- Invasive fetal infection
- Congenital syndromes
- The timing of fetal infection in utero may determine the extent of disease manifestations and the outcomes for the unborn child

Outcome in pregnancy

- Wide variation in outcomes, depending on the timing of infection, the type of infection, the interaction between the infecting organism and the immune system, and indeed certain host factors including the placenta.
- Peri- and post partum infection may represent mucosal exposure, breast feeding. Infections occurring in this period may not manifest until later in childhood or beyond

Vertical/Transplacental Transmission of Disease

A vertically transmitted infection is caused **by active pathogens** such as bacteria or viruses that are **transmitted directly from the mother to an embryo, fetus or baby** during pregnancy or childbirth.

The term **congenital/gestational infection** can be used if the vertically transmitted infection persists in the baby after childbirth – causing postnatal infection.

Clinical evidence of infection: may be seen at birth, soon afterward, or not until years later – this latency (absence or pause of symptoms) has been well described with other congenital infections.

November 1977 – Boston Children's Hospital

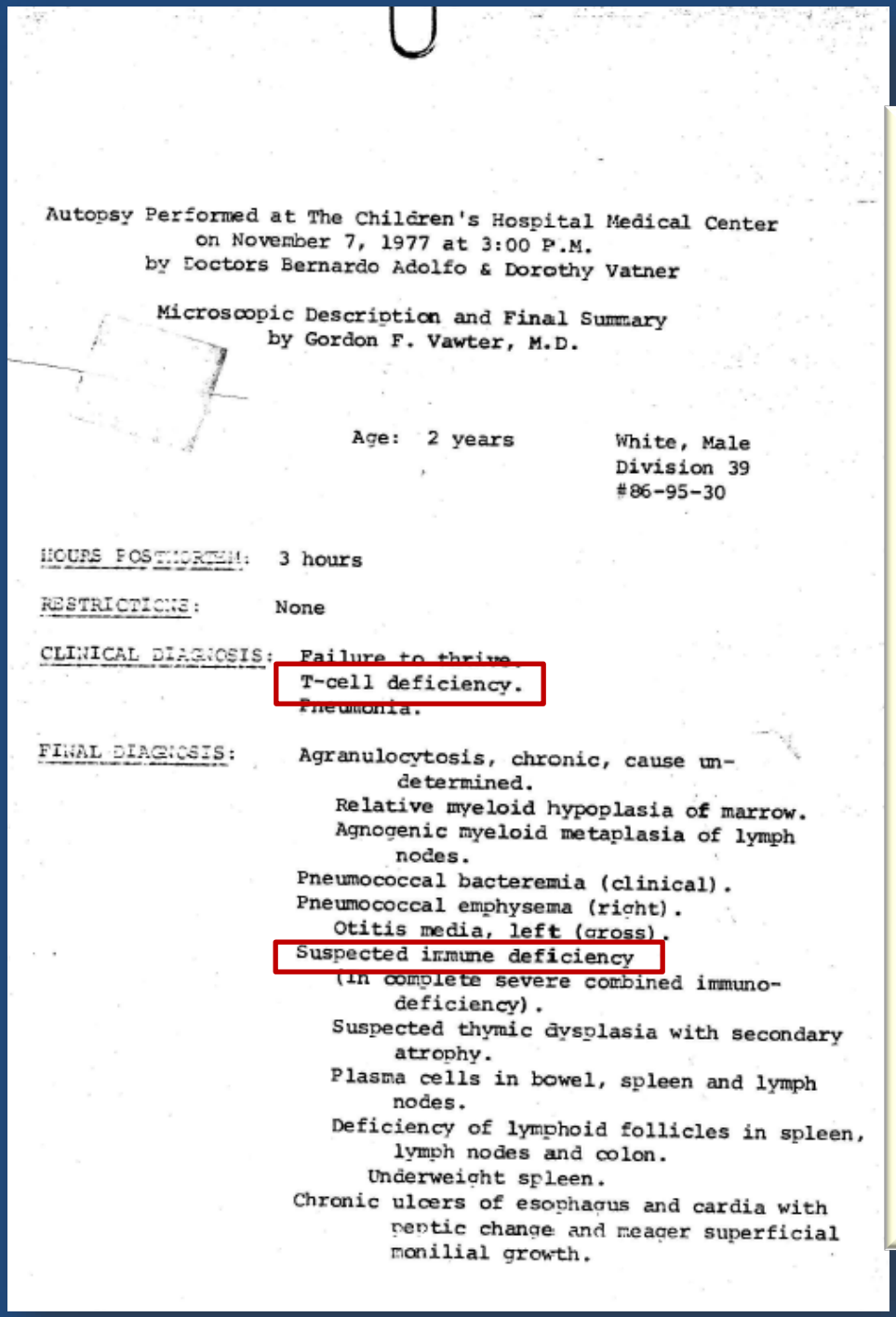
Boston Children's Hospital
Until every child is well

- 2 year old male
- Severe malnutrition
- Developmental delay
- Thrush
- Recurrent infections/fevers unresponsive to antibiotics
- Persistent diarrhea without etiology
- Parents alcohol, drug abuse, social problems
- Admitting dx: "Psychosocial failure to thrive"

- Anemia/leukopenia
- Low T-cell (then called e-rosette forming cells) number and function
- Hypergammaglobulinemia

→ after a month on hyperal, extensive negative work-up but persistent severe disease

- Developed hypoxia
- Diffuse infiltrates & acidosis
- Pneumococcal bacteremia
- Despite broad spectrum antibiotics, he died.



Autopsy Performed at The Children's Hospital Medical Center
on November 7, 1977 at 3:00 P.M.
by Doctors Bernardo Adolfo & Dorothy Vatner

Microscopic Description and Final Summary
by Gordon F. Vawter, M.D.

Age: 2 years

White, Male
Division 39
#86-95-30

HOURS POSTMORTEM: 3 hours

RESTRICTIONS: None

CLINICAL DIAGNOSIS: Failure to thrive.
T-cell deficiency.
Pneumonia.

FINAL DIAGNOSIS:
Agranulocytosis, chronic, cause undetermined.
Relative myeloid hypoplasia of marrow.
Agnogenic myeloid metaplasia of lymph nodes.
Pneumococcal bacteremia (clinical).
Pneumococcal emphysema (right).
Otitis media, left (gross).
Suspected immune deficiency
(in complete severe combined immunodeficiency).
Suspected thymic dysplasia with secondary atrophy.
Plasma cells in bowel, spleen and lymph nodes.
Deficiency of lymphoid follicles in spleen, lymph nodes and colon.
Underweight spleen.
Chronic ulcers of esophagus and cardia with peptic change and meager superficial monilial growth.

Autopsy showed

- Chronic esophageal ulcers, candida
- Myeloid hypoplasia
- Deficiency lymphoid follicles in spleen, lymph nodes, thymus
- Thymic dysplasia with secondary atrophy/fibrosis
- Blood, pleural fluid grew pneumococci

→

- T-cell deficiency unknown etiology

Brief History of the Evolution of the Pediatric HIV Epidemic

–The beginning

Jim Oleske and Long-Term Survivors
UMDNJ Newark 2003

–The middle

GLOBAL PLAN TOWARDS THE ELIMINATION OF NEW HIV INFECTIONS AMONG CHILDREN BY 2015 AND KEEPING THEIR MOTHERS ALIVE

–The end?

Pediatric HIV Infection

- The first case of pediatric AIDS reported to CDC in 1982, 18 months after 1st report in adults.

Immune Deficiency Syndrome in Children. James Oleske et al. *JAMA.* 983;249(17): 2345-2349.

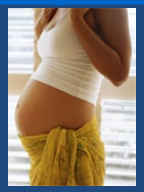
Acquired Immuno-deficiency With Reversed T4/T8 Ratios in Infants Born to Promiscuous and Drug-Addicted Mothers . Arye Rubinsteinet al. *JAMA.* 1983;249(17):2350-2356.

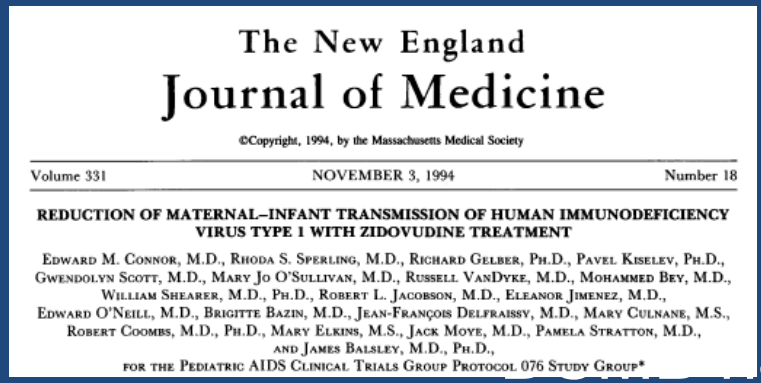
- By 1983, reports of AIDS among children of parents with recognized risk factors were published.

"…since 1979…children with an otherwise unexplained immune deficiency syndrome and infections of the type found in adults with AIDS….. 8 children from the Newark, NJ…born into families with recognized risks for AIDS. These patients have had recurrent febrile illnesses, failure to thrive, hypergammaglobulinemia, and depressed CMI. Four of these children have died."

PACTG 076: AZT Regimen Was Designed to Target Multiple Potential Time Points of Transmission

CD4 >200

Pregnancy	Labor/Delivery	Infant
		
AZT 100 mg 5 times daily	AZT IV 2 mg/kg 1 mg/kg/hr	AZT 2 mg/kg q 6 hr x 6 weeks
TARGET: *In Utero* (after 1st trimester)	TARGET: Intrapartum	TARGET: Postpartum
	Pre-Exposure Prophylaxis (PrEP)	**Post-Exposure Prophylaxis (PEP)**

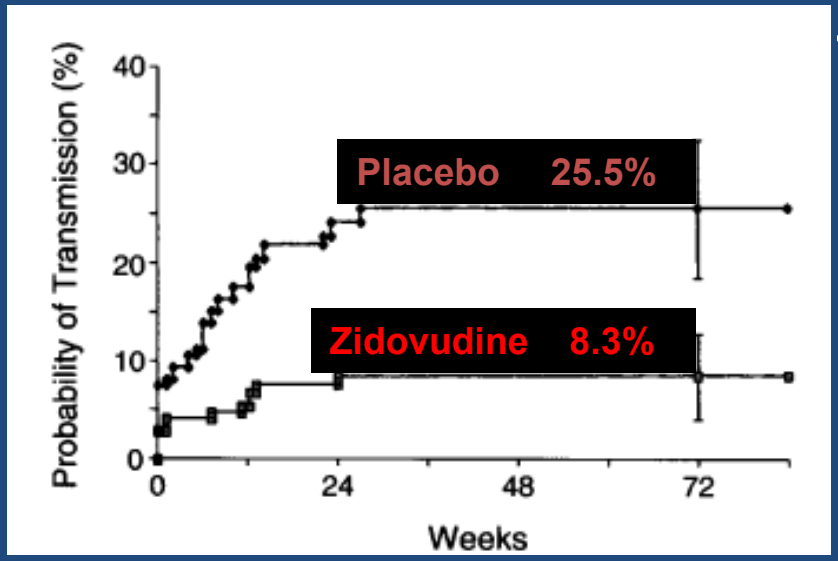


The New England
Journal of Medicine

Volume 331 NOVEMBER 3, 1994 Number 18

REDUCTION OF MATERNAL–INFANT TRANSMISSION OF HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 WITH ZIDOVUDINE TREATMENT

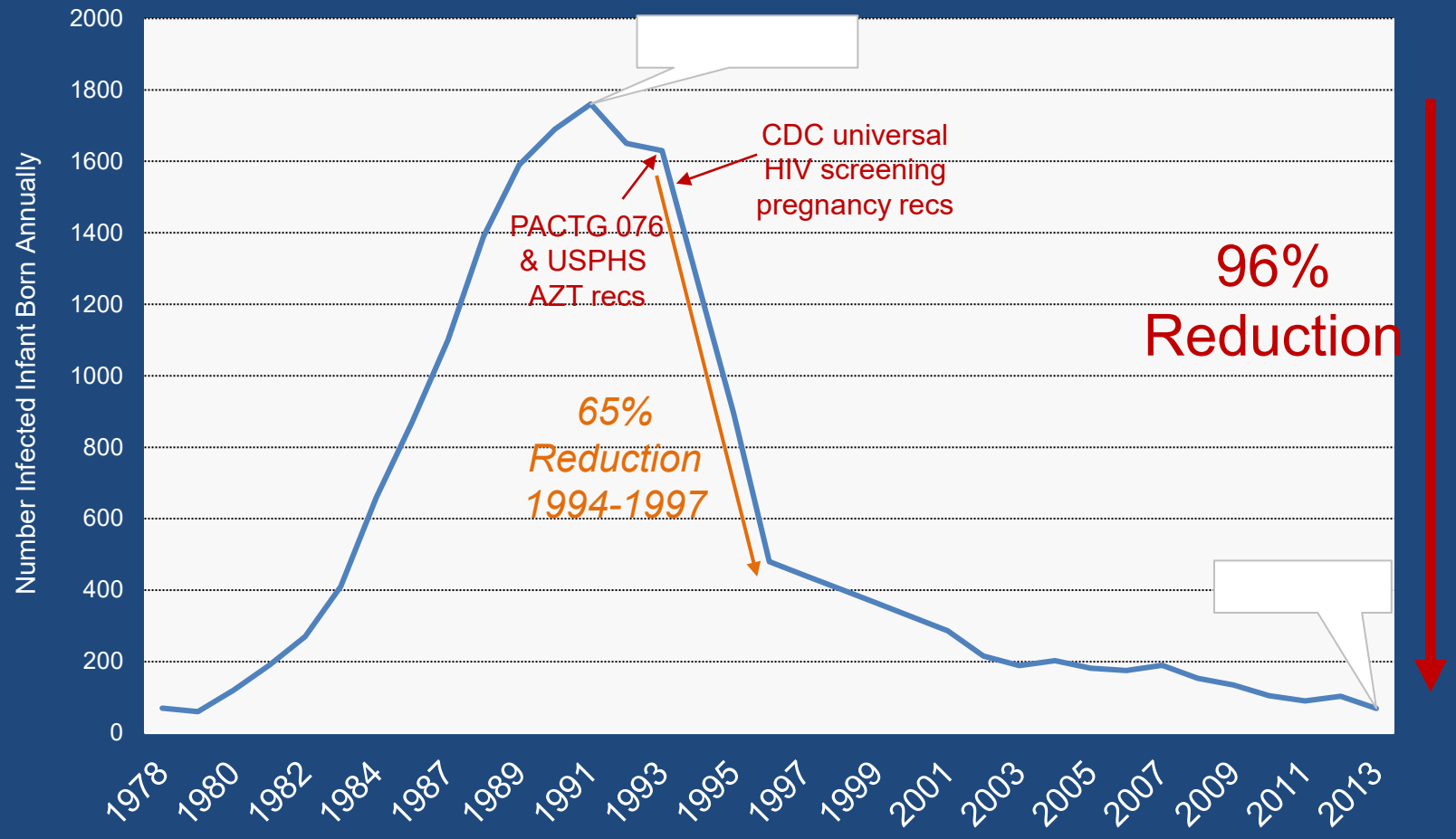
EDWARD M. CONNOR, M.D., RHODA S. SPERLING, M.D., RICHARD GELBER, PH.D., PAVEL KISELEV, PH.D., GWENDOLYN SCOTT, M.D., MARY JO O'SULLIVAN, M.D., RUSSELL VANDYKE, M.D., MOHAMMED BEY, M.D., WILLIAM SHEARER, M.D., PH.D., ROBERT L. JACOBSON, M.D., ELEANOR JIMENEZ, M.D., EDWARD O'NEILL, M.D., BRIGITTE BAZIN, M.D., JEAN-FRANÇOIS DELFRAISSY, M.D., MARY CULNANE, M.S., ROBERT COOMBS, M.D., PH.D., MARY ELKINS, M.S., JACK MOYE, M.D., PAMELA STRATTON, M.D., AND JAMES BALSLEY, M.D., PH.D., FOR THE PEDIATRIC AIDS CLINICAL TRIALS GROUP PROTOCOL 076 STUDY GROUP*



First demonstration of treatment as prevention!

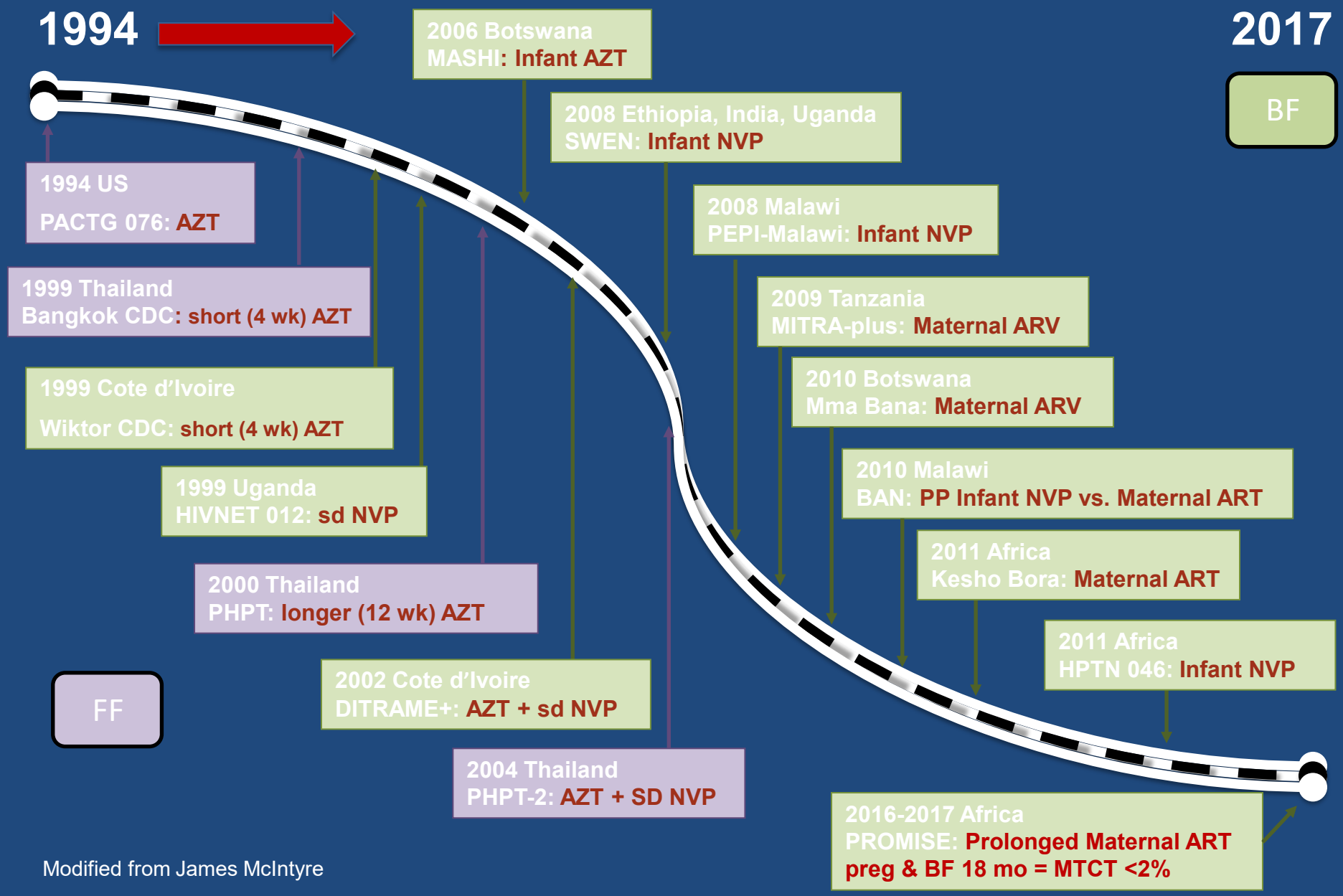
Rapid Translation of Trial Results Into Practice

Estimated number of perinatally-infected infants born annually in the United States 1978-2013



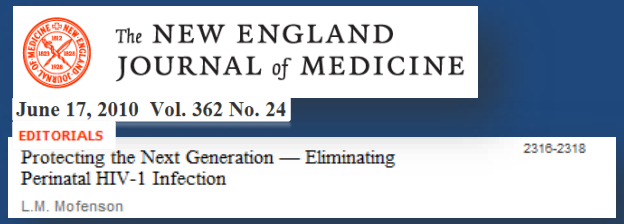
Nesheim S et al. JAIDS 2017;76:461-4

Building the Evidence Road for PMTCT



Modified from James McIntyre

2010: Potential Elimination



The End?
Elimination?
Cure?

Global MTCT Eliminati nges

- Number of ge (15-
- ntries,
- C in
- Tre ing
- Issue even with pre-

The major issue is no longer WHAT to do…

The major issues are health care access and health care system barriers to implementation

conc lead to less optimal PMTCT.

How was the mother to child transmission of HIV approached?

- Identifications of a ‘mystery’ illness
- Further investigation and resources applied to develop this investigation.
- Investigation into the timing of infection, and the factors involved in infection. Prospective studies (WITS, HERS)
- Controlled trials to identify interventions (ACTG076)
- Roll out of successful interventions, and an ‘elimination strategy’ for congenital HIV

Congenital Lyme?

- What has happened in the last 30 years?
- What research has been done?
- What can we learn from other diseases (ie HIV)
- How can we prevent congenital infections?
- What are the challenges?
- How would ICD11 codes help?

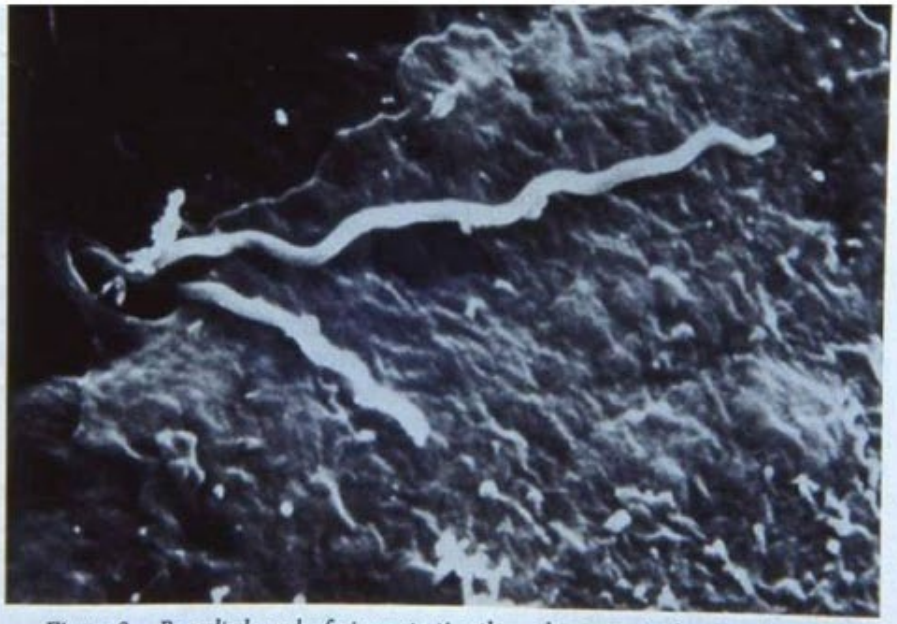
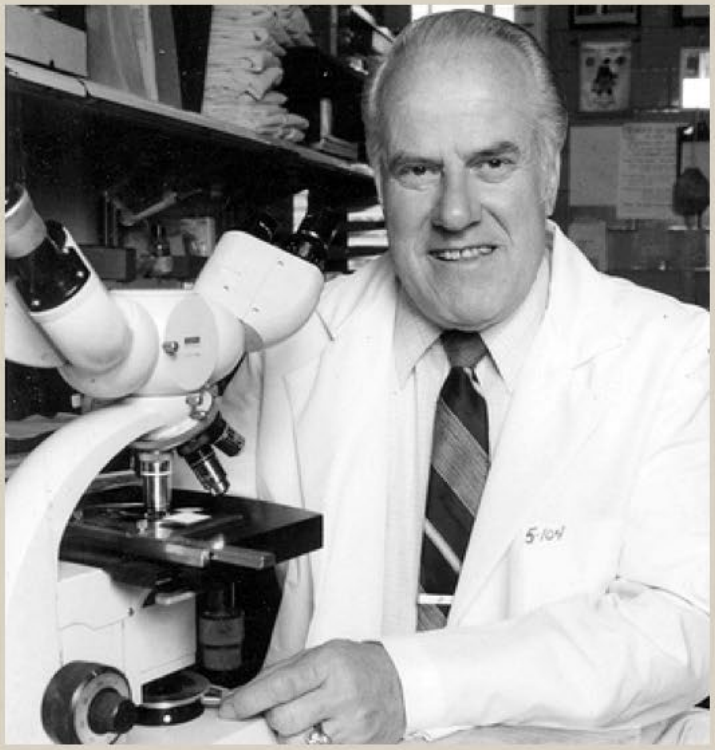


Figure 2. *Borrelia burgdorferi* penetrating through an opening between human umbilical cord endothelial cells grown on human amniotic membrane. Photo courtesy of Dr. Andrew Szczepanski, Department of Pathology, State University of New York at Stony Brook, New York (×16,400)

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

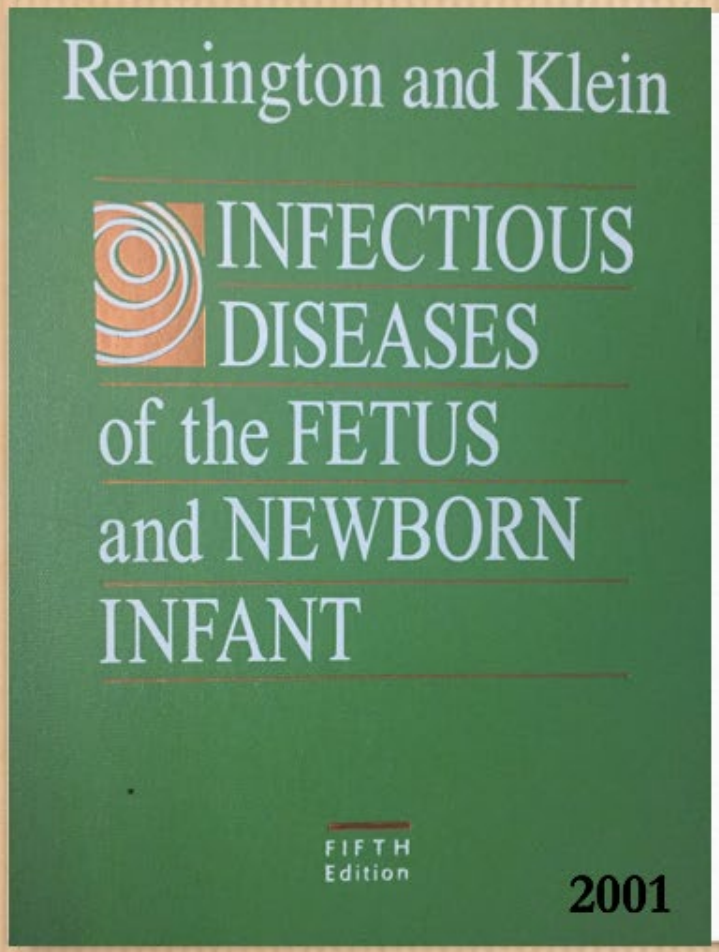


The Enlarging Spectrum of Tick-Borne Spirochetoses: R. R. Parker Memorial Address

... 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



- 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

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

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

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).

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

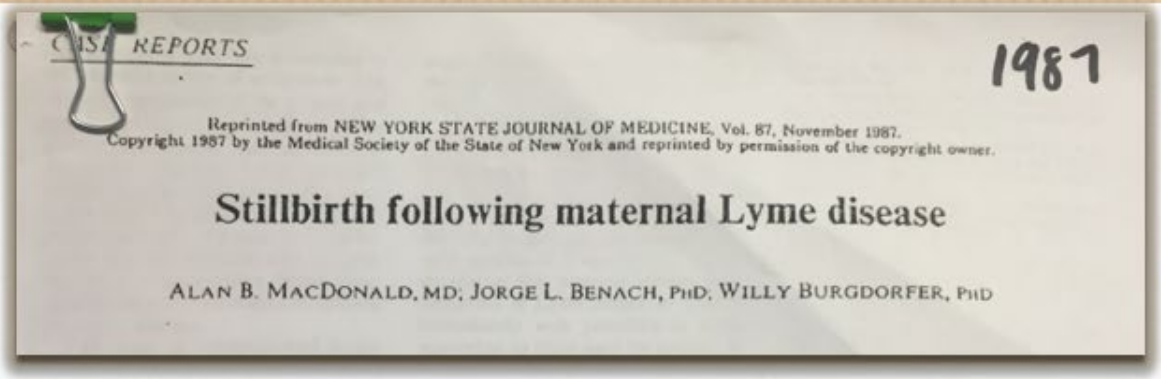
Southampton Hospital, Long Island, New York, U.S.A.

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.



CASE REPORTS

1987

Reprinted from NEW YORK STATE JOURNAL OF MEDICINE, Vol. 87, November 1987.

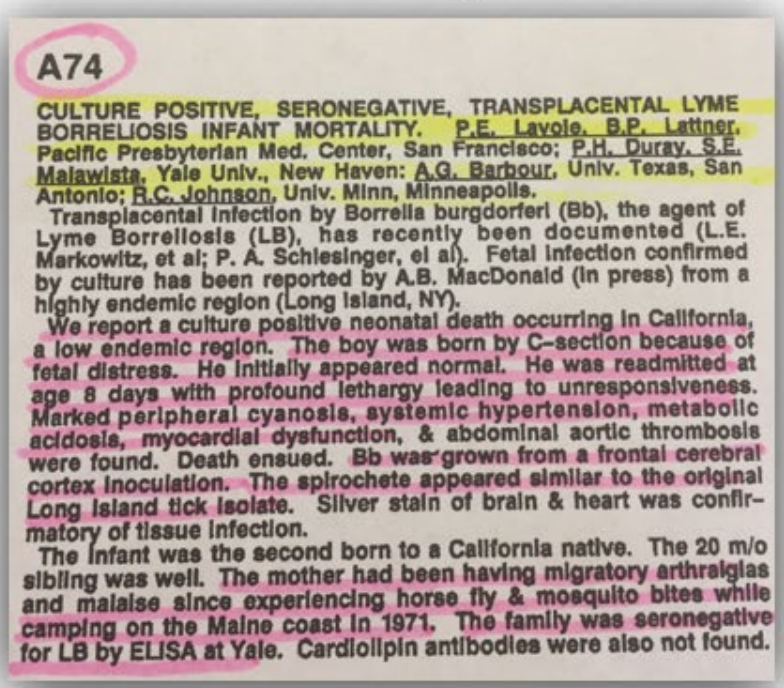
Stillbirth following maternal Lyme disease

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

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, et 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

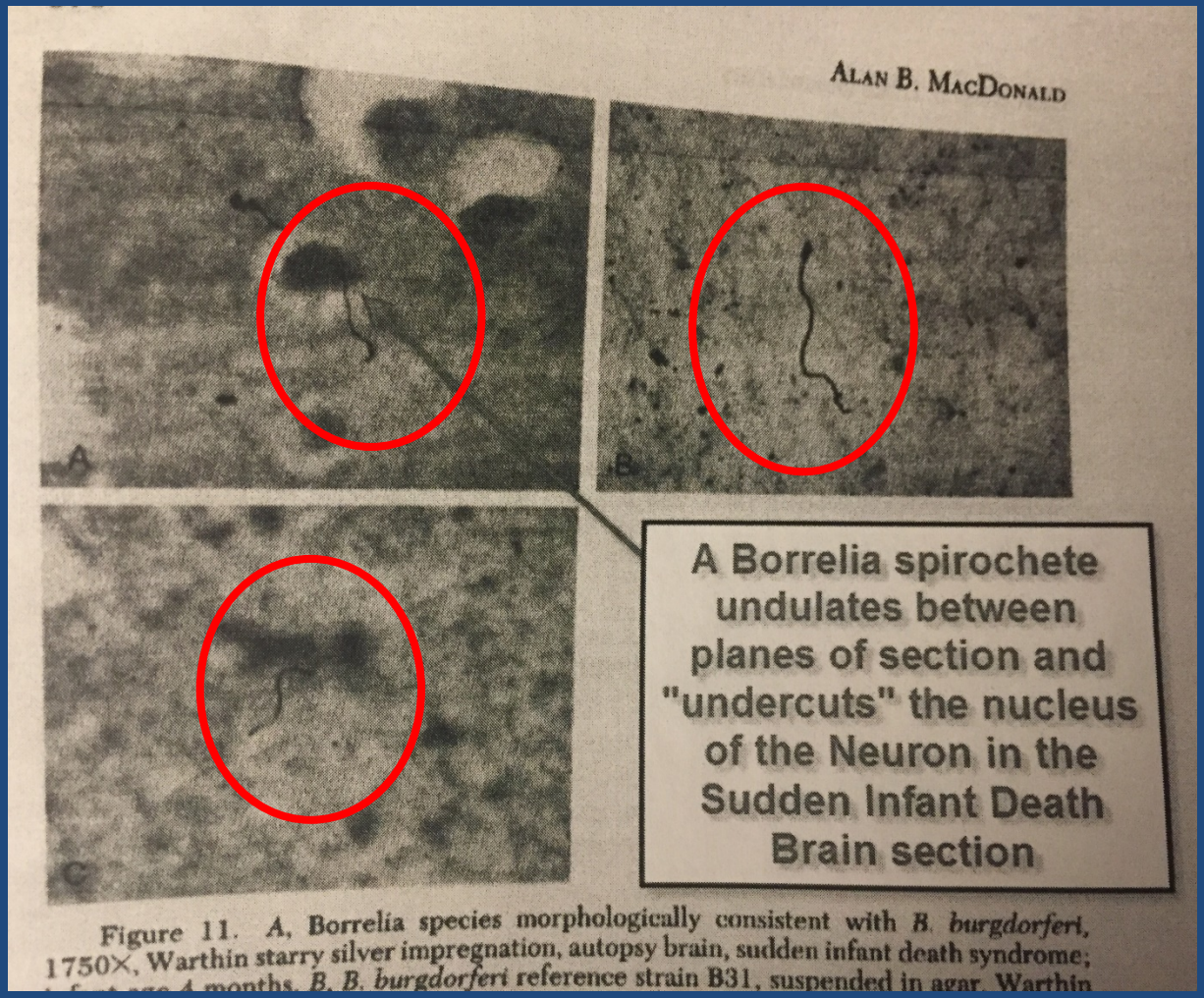


Figure 11. *A*, Borrelia species morphologically consistent with *B. burgdorferi*, 1750×, Warthin starry silver impregnation, autopsy brain, sudden infant death syndrome; [illegible] months. *B*, *B. burgdorferi* reference strain B31, suspended in agar, Warthin

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

Maternal Lyme Borreliosis and Pregnancy Outcome - 2010

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."*

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

'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'

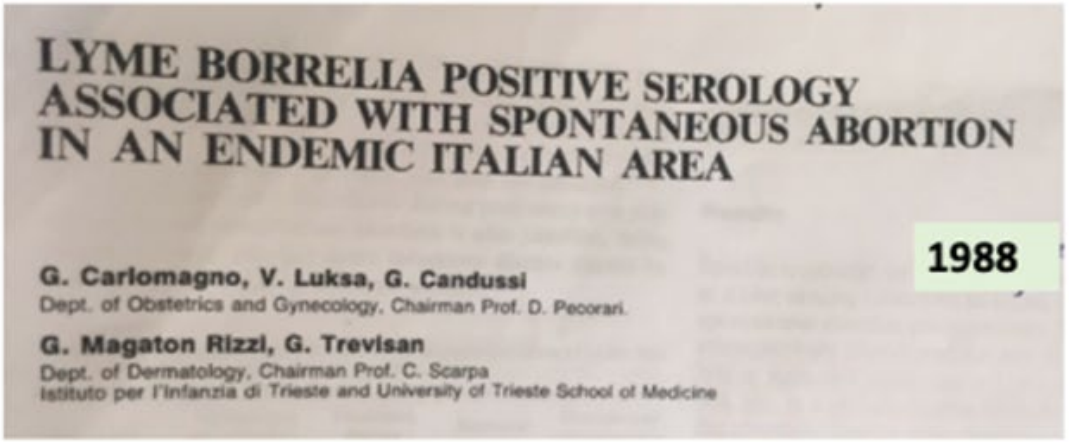
- Miscarriage during the first 20 weeks gestation with high frequency of fetal cardiac abnormality, stillbirth, perinatal death
- **Severe early congenital infection** with neonatal sepsis and meningioencephalitis and high frequency of cardiac abnormality
- **Mild early congenital infection** with growth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

Late congenital infection with

- growth retardation,
- developmental delay,
- neurologic,
- cutaneous,
- dental and
- skeletal involvement.

Page 521-522

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



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.

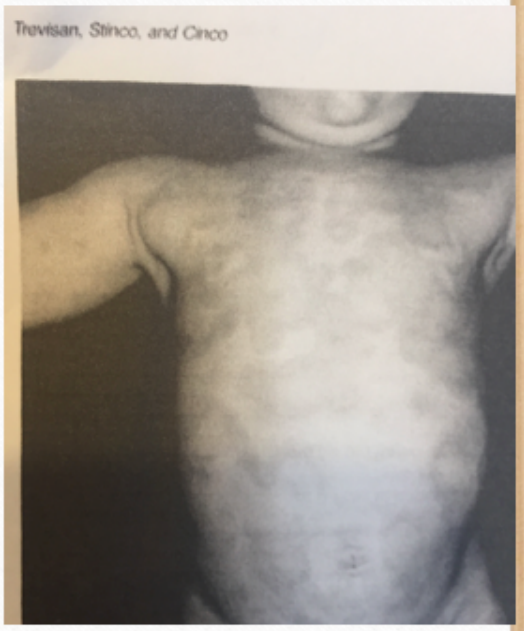
3 sera (6%) from the 49 term pregnancy were positive – none of these patients remembered a tick bite or EM rash and all had healthy infants.

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%)

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

Trevison et al - 1997

- 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**



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

Treatment of LD in pregnancy

- Treatment of gestational LD has been associated with reduced adverse outcomes for the fetus (11%) vs women not treated for infection in pregnancy (50%) (Waddell)
- A 2010 study authored by Lakos et al reported adverse outcomes in parenterally treated (12%), orally treated (31.6%), and of untreated women (60%) with LD in pregnancy.

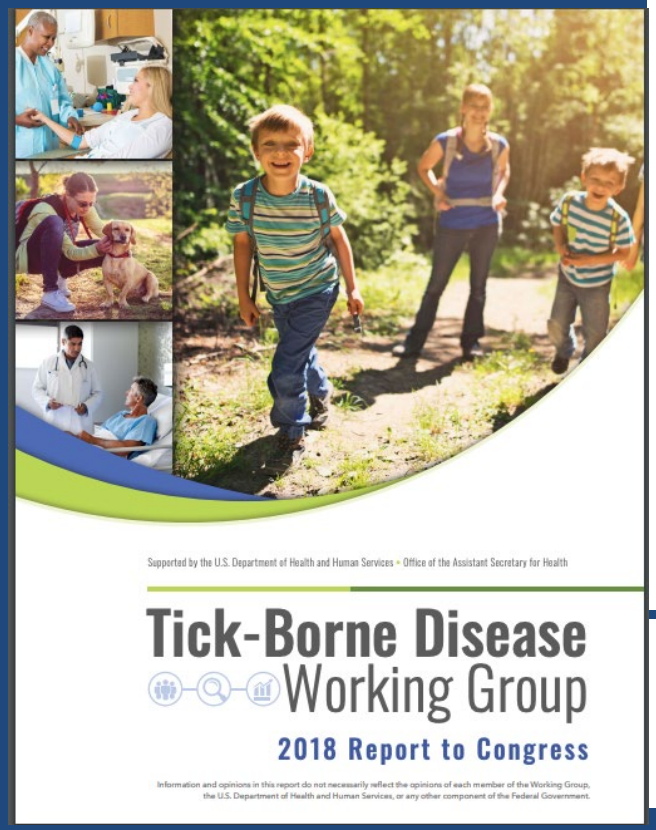
https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg55/

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++).

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.

Government of Canada | Gouvernement du Canada

Lyme disease during pregnancy

There is not enough evidence to confirm that Lyme disease during pregnancy has adverse effects for the fetus. In addition, no adverse effects for the fetus have been observed when the pregnant woman receives appropriate antibiotic treatment for her Lyme disease.

Evidence to-date includes:

- Case reports, which study individual cases

  Case reports have raised the possibility that Lyme disease in pregnant women may have adverse outcomes for the fetus or newborn. However, it is not clear if and how the adverse outcomes were caused by the Lyme disease bacteria.

- Epidemiological studies

  Epidemiological studies have not found a consistently higher rate of adverse outcomes of pregnancy in women with, or at risk of, Lyme disease, compared to pregnant women who are not infected or at risk. These studies cannot rule out the occurrence of adverse outcomes of Lyme disease in pregnancy.

Further research is required to better understand if there may be adverse effects of Lyme disease during pregnancy.

https://www.canada.ca/en/public-health/services/diseases/lyme-disease/pregnancy.html

'Not enough evidence to confirm that Lyme disease during pregnancy has adverse effects for the fetus.'

Note: There is **no mention of in-utero or transplacental transmission of Lyme** from an infected mother to her baby.

The Ad Hoc Committee was invited to meet with the Special Rapporteurs for: Health Human Rights & Defenders of Human Rights

JUNE 5, 2018. Corruption and Human Rights Violations Against Lyme Doctors, Scientists and Parents Now on United Nations Record

Meeting with
Special Rapporteur
Michel Forst

June 2018

The New Global Face of Lyme

ICD10 Codes		ICD11 Codes	
A69.2	Lyme Disease	1C1G	Lyme borreliosis
M01.2	Arthritis due to Lyme	1C1G.0	Early cutaneous Lyme borreliosis
G01	Meningitis due to Lyme	1C1G.1	Disseminated Lyme borreliosis
G63.0	Polyneuropathy due to Lyme	1C1G.10	Lyme Neuroborreliosis
		1C1G.11	Lyme Carditis
		1C1G.12	Ophthalmic Lyme borreliosis
		1C1G.13	Lyme arthritis
		1C1G.14	Late cutaneous Lyme borreliosis
		1C1G.1Y	Other specified disseminated Lyme borreliosis
		1C1G.1Z	Disseminated Lyme borreliosis, unspecified
		1C1G.2	Congenital Lyme borreliosis
		1C1GY	Other specified Lyme borreliosis
		6D85.Y	Dementia due to Lyme Disease
		9C20.1	Infectious panuveitis in Lyme disease
		9B66.1	Infectious intermediate uveitis in Lyme disease
		8A45.0Y	Central Nervous System demyelination due to Lyme borreliosis

The New Global Face of Lyme

JUNE 2018 RELEASE

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CODE FOR CONGENITAL LYME

IS DELETED DECEMBER 2018

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**."

"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.'

There is some evidence to suggest that it is **biologically plausible** for *B. burgdorferi* to be **vertically transmitted to the fetus**, however these studies have been unable to define a characteristic pathological effect of *B. burgdorferi* infection in the fetus, thus there are significant knowledge gaps about the relationship of *B. burgdorferi* infection and adverse birth outcomes

Infections of the fetus or newborn

Inbox ×

[redacted]

Dec 18, 2018, 6:07 PM (3 days ago)

to me

Dear Jenna

This was in response to a request for the removal of Congenital Lyme borreliosis by the Public Health Agency of Canada who stated that there was little evidence of a specific syndrome resulting from congenital B. burgdorferi infection (in contrast to congenital syphilis, for example) but rather that there was some evidence of an increased risk of adverse outcome or fetal abnormality. The matter was then discussed in detail by the ICD-11 Medical and Scientific Advisory Committee and sent out for expert opinion. It

[redacted]

KA00.3 Foetus or newborn affected by maternal infectious diseases & XN13C Borrelia Burgdorferi

[redacted]

I shall, however, suggest to WHO that appropriate post-coordination options be incorporated explicitly into ICD for neonatal infections where the organism is not specified (KA61.Y*, KA62.Y, KA63.Y, KA64.Y, children of KA65, EH10, EH11, EH12, KA003, KA6Y)

* Please add residual KA61.Y Other specified bacterial infections of the **fetus** or newborn

I am sorry that you were not informed of this decision. I am forwarding this message to WHO for their information.

With kind regards

[redacted]

Time to recognise congenital Lyme: an open letter to the WHO

- Submitted to Lancet for publication
- CDC first recognised in 1985, where they quoted Schlesinger ‘Transplacental transmission of B burdorferi has been documented in a pregnant woman with Lyme disease who did not receive antimicrobial therapy’
- However this recognition was removed subsequently from CDC website as well as from textbook Remington and Klein
- Open letter was rejected by Lancet, never acknowledged by the WHO as being received

The Effect of the Waddell (non) 'systematic review'

- Much of the medical literature on congenital Lyme was discounted.
- Provide statement on 'one case' that possibly provides supporting evidence that Borrelia can transmit from mother to child 'biologically plausible'
- They did not include Willy Burdorfer's case (the ECM rash was not seen by a GP so it did not meet the requirements of their review)
- States there is no epidemiological evidence to support congenital abnormalities more common in Lyme endemic areas, though studies suggest the opposite.
- The members of the Waddell paper are non-clinician members of the Canadian public health agency, with co- authors from the USA CDC
- Emails from WHO support Canadian involvement in reversing the ICD11 recognition of Congenital Lyme.
- Lack of ICD11 for Congenital Lyme will hurt future data collection

Finally a response from WHO

- May 11, 2020 Dr Samira Asma, Assistant Director General, Division of Data, Analytics and Delivery for Impact, WHO
- jakobr@who.int
- ‘There needs to be sufficient evidence that a health condition exists’.
- The concept of ‘congenital Lyme disease’ was removed from ICD-11 based on a systematic review conducted by the UK NICE. The decision was later also supported by an independent systematic review by Waddell et al and information available from the CDC
- When future research would provide evidence for ‘congential Lyme disease’ a proposal for amendment of ICD could be submitted.

Clinical Infectious Diseases

Human Granulocytic Anaplasmosis During Pregnancy: Case Series and Literature Review

Abhay Dhand,[1] Robert B. Nadelman,[1] Maria Aguero-Rosenfeld,[2] Fadi A. Haddad,[1,a] Daniela P. Stokes,[3] and Harold W. Horowitz[1,a]

[1]Department of Medicine, Division of Infectious Diseases, and [2]Department of Pathology, New York Medical College, Valhalla, and [3]Hudson Valley Infectious Diseases P.C., Poughkeepsie, New York

We describe the clinical and laboratory manifestations and pregnancy outcomes of 6 women who received a diagnosis of human granulocytic ehrlichiosis during pregnancy. Human granulocytic ehrlichiosis did not seem to present in a fulminant fashion, and all treated patients had excellent responses to rifampin or doxycycline therapy. Perinatal transmission was documented in 1 neonate, who responded well to treatment. There do not appear to be any long-term adverse sequelae in children born from these pregnancies (mean follow-up duration, 21 months).

2007

‘Perinatal transmission was documented in one neonate’.

Ehrlichosis in Pregnancy

- Gram negative obligate intracellular organisms which include Anaplasma and Ehrlichia.
- Human granulocytyci anaplasmaosis causes flu like illness, , low white cells (morulae and intracellular inclusions seen) . Cases of miscarriage have been reported and vertical transmission reported.
- Human monocyctic ehlichosis, get intracellular invasion of organism, association with adverse outcome not well described

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EMERGING INFECTIOUS DISEASES®

EID Journal > Volume 18 > Number 8—August 2012 > Main Article

Volume 18, Number 8—August 2012

Dispatch

Vertical Transmission of *Babesia microti*, United States

Julie T. Joseph✉, Kerry Purtill, Susan J. Wong, Jose Munoz, Allen Teal, Susan Madison-Antenucci, Harold W. Horowitz[1], Maria E. Aguero-Rosenfeld[1], Julie M. Moore, Carlos Abramowsky, and Gary P. Wormser

Author affiliations: New York Medical College, Valhalla, New York, USA (J.T. Joseph, K. Purtill, J. Munoz, H.W. Horowitz, M.E. Aguero-Rosenfeld, G.P. Wormser); New York State Department of Health, Albany, New York, USA (S.J. Wong, A. Teal, S. Madison-Antenucci); University of Georgia, Athens, Georgia, USA (J.M. Moore); and Emory University School of Medicine, Atlanta, Georgia, USA (C. Abramowsky)

Cite This Article

Abstract

Babesiosis is usually acquired from a tick bite or through a blood transfusion. We report a case of babesiosis in an infant for whom vertical transmission was suggested by evidence of *Babesia* spp. antibodies in the heel-stick blood sample and confirmed by detection

Babesiosis in Pregnancy

- Babesia is a protozoa, usually microti in USA and divergens in the EU.
- More common in immunocompromised patients, including splenectomised, so pregnant women thought at higher risk. Can cause HELLP syndrome in pregnancy.
- A congenital syndrome has been suggested, with fever, thrombocyctopenia, and anemia.

TBE in Pregnancy

- Tickborne encephalitis is a neurotropic flavivirus.
- A case report of infection in the third trimester of pregnancy resulted in a self limiting infection.
- Cases in non pregnant individuals start with a non specific flu followed by neurological sequelae including meningitis, myelitis, encephalitis, and paralysis.
- A vaccine is available and should be considered in endemic areas.

Repapsing Fever in Pregnancy

- Another Borrelia strain not well recognised in the ‘West’ and in North America, but may be there!
- Thought to cause up to 10-15% of neonatal deaths worldwide.
- Associated with decreased birth weight, preterm delivery, or alternatively severe damage and miscarriage or neonatal death.
- Mouse studies show impaired fetal circulation, direct invasion of placenta, intrauterine growth retardation.

Rickettsiae in Pregnancy

- RMSF caused by rickettsia rickettseii is the most pathogenic of the Rickettsiae and causes a febrile illness with mortalities as high as 30% without treatment.
- In pregnancy the ‘rash’ is often missed, and outcomes are similarly poor if not treated.
- No cases of vertical transmission have been reported. Risk is maternal/fetal death

Perinatal transmission of Bartonella

JOURNAL OF CLINICAL MICROBIOLOGY, June 2010, p. 2289–2293 Vol. 48, No. 6
0095-1137/10/$12.00 doi:10.1128/JCM.00326-10

2010

CASE REPORTS

Molecular Evidence of Perinatal Transmission of *Bartonella vinsonii* subsp. *berkhoffii* and *Bartonella henselae* to a Child[▽]

Edward B. Breitschwerdt,[1]* Ricardo G. Maggi,[1] Peter Farmer,[2] and Patricia E. Mascarelli[1]

Intracellular Pathogens Research Laboratory, Center for Comparative Medicine and Translational Research, College of Veterinary Medicine, North Carolina State University, Raleigh, North Carolina,[1] and Department of Pathology, North Shore University Hospital, 300 Community Drive, Manhasset, New York[2]

Received 18 February 2010/Returned for modification 16 March 2010/Accepted 6 April 2010

***Bartonella vinsonii* subsp. *berkhoffii*, *Bartonella henselae*, or DNA of both organisms was amplified and sequenced from blood, enrichment blood cultures, or autopsy tissues from four family members. Historical and microbiological results support perinatal transmission of *Bartonella* species in this family. It is of clinical relevance that *Bartonella* spp. may adversely influence human reproductive performance.**

Bartonella in Pregnancy

- Classically from fleas, lice, and flies, but ticks implicated.
- In pregnancy, high mortality, miscarriages, preterm births and fetal deaths caused by Carrion's disease in the acute phase.
- Only one case suggested vertical transmission.

Understanding the Impact of Tick Borne Infections in Pregnancy and their Offspring

- Paucity of well designed prospective studies and little investment in the accurate surveillance and monitoring of these infections worldwide.
- Having an ICD11 code 1C1G.2 for congenital borreliosis would assist in the ability of researchers and advocates to petition for better studies and better funding. ICD11 code dropped based on NICE review that only included publications from 2000 and after. Canadian paper by Waddell is 'selective' and 'cherry picks' studies
- To develop prospective studies, monitor pregnant women, follow babies after delivery (LWITS)

What are the consequences of 'Missed' diagnoses in Pregnancy

- We may be missing many unknown cases of Tickborne infections transmitted infections in pregnancy.
- One unknown but plausible explanation for Autism Spectrum Disorder is the possibility of a vertically transmitted infection in pregnancy.
- Of the 20 USA states that report the highest occurrence of autistic disorders per 10,000, 15 states reported higher than average number of Lyme disease cases. Conversely, in 20 states with lowest Autism, no Lyme disease reported.
- Another 'mystery' childhood illness, spinal muscular atrophy, attributed to Borrelia.

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.'

Teratogenicity: '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 – 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.

Does Lyme Spread from Mother to Child?

- Yes, it is transplacentally transmitted and it may cause adverse outcomes.
- We have only small studies but it is clear that the bacteria can spread to the placenta and to the baby.
- It is likely that early in utero infection causes more severe damage ? Placental insufficiency, large volume bacteremia may be important factors.
- Lack of ‘inflammation’ in baby does not mean infection is not significant (inflammation may come later)
- Having an ICD 11 code for congenital Lyme would facilitate recognition and better prospective studies and encourage future research
- USA ‘pediatric RED Book’ does not describe this entity
- If we dealt with HIV like we have Borreliosis, we would have Pediatric HIV epidemic of massive proportions, rather than success.

Denial of Congenital Lyme: science will never win, so lets focus on human rights violation

Vertical/Transplacental Transmission of Disease

A vertically transmitted infection is caused **by active pathogens** such as bacteria or viruses that are **transmitted directly from the mother to an embryo, fetus or baby** during pregnancy or childbirth.

The term **congenital/gestational infection** can be used if the vertically transmitted infection persists in the baby after childbirth – causing postnatal infection.

Clinical evidence of infection: may be seen at birth, soon afterward, or not until years later – this latency (absence or pause of symptoms) has been well described with other congenital infections.

ITS COMPLICATED