

Gestational Lyme

Dr. Charles Ray Jones

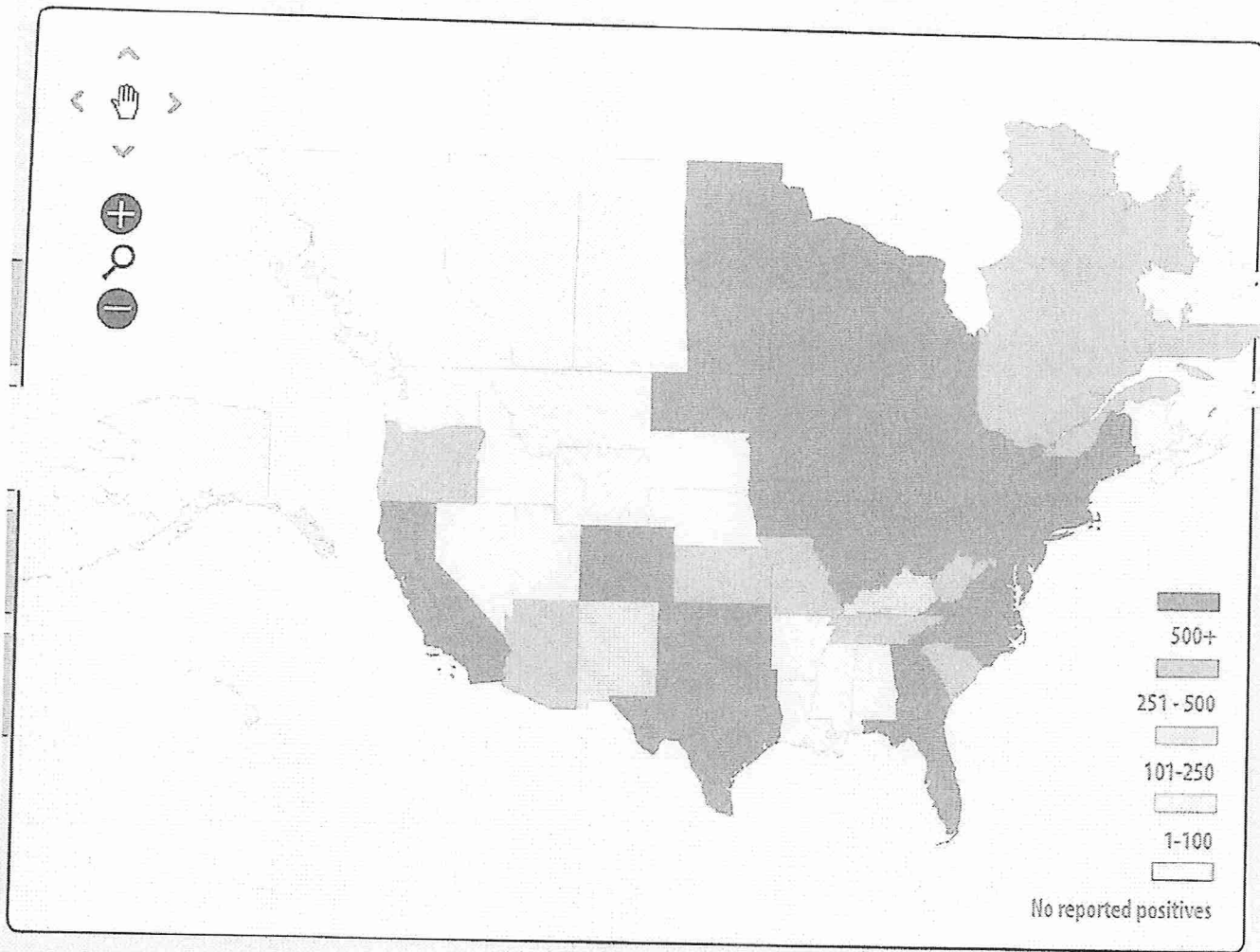
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ILADS

Toronto, Canada

Lyme Disease:

- ▶ Spirochete pathogen: *Borrelia burgdorferi* (Bb)
- ▶ Multisystem (primarily nerve, joints, cardiovascular, endocrine, skin)
- ▶ All ages and ethnic groups
- ▶ Both genders
- ▶ Can be active, acute, dormant, localized, disseminated, recurring, relapsing, or chronic
- ▶ Transmitted:
 - Ticks (mostly Ixodes but others implicated)
 - Gestational
 - Through breast milk



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These maps indicate reported *Ehrlichia*, Lyme, heartworm and *Anaplasma* positives from more than 10,000 veterinary clinics, telephone surveys and IDEXX Reference Laboratories' results. All data was collected from 2001 to December 2009 except for *Anaplasma* data, which was collected from 2006 to December 2009. Data on file at IDEXX Laboratories, Inc., Westbrook, Maine USA.

Gestational transmission of disease:

The infection of the fetus by active pathogens in the mother from the time of conception to birth.

Congenital disease:

Disease present at birth

Note: Approximately 10% of the patients in my TBI-only practice are currently gestational Lyme.

Hypotheses around gestational transmission of Lyme:

- ▶ *Borrelia burgdorferi*, a spirochete, moves across the placental barrier infecting the fetus
- ▶ Bb may be pathophysiologically similar to the spirochete that causes syphilis which is well known to be transmitted from an infected mother to the child
- ▶ Lyme parallels the diverse presentation of prenatal syphilis
- ▶ A number of other pathogens including HIV, CMV, and Toxoplasma are well known to cross the placenta and cause infection.
- ▶ Essentially any infection in the mother has the potential to affect the fetus.

Parallel Cases:

In 2 separate cases of IVF, the embryos were infected. One child with gestational Lyme was born to a surrogate mother who had no known association with Lyme. The other mother had cryopreserved embryos implanted sequentially about 2 years apart. Each child was born sick. Association to Lyme was not made until after the third child.

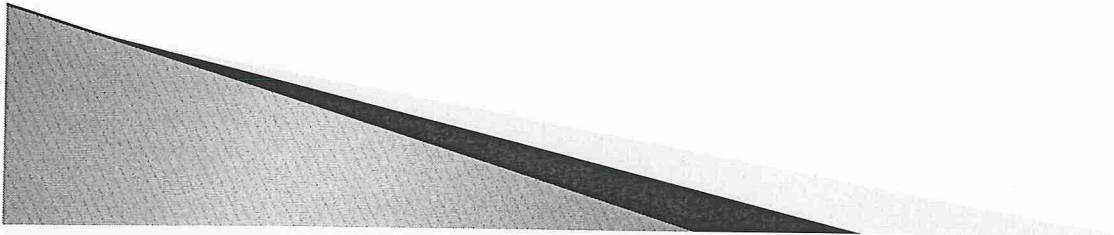
Gustafson and Burgess demonstrated the intrauterine transmission of *Borrelia burgdorferi* in dogs in 1993

Inoculated females with Bb: 80% of the mothers became infected and 80% of those gave birth to infected pups as shown by DNA-positive tissues in PCRs and cultures. Interestingly: Most, but not all, of the pups were infected

Retrospective Study:

Gestational Lyme Disease Case Studies of
102 Live Births

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Methods:

- ▶ 102 case studies of children with gestational Lyme
- ▶ Diagnosis was clinical: based on history and physical
- ▶ Lab results were used only to support clinical diagnosis or to help describe the study population
- ▶ Children in the study were typically diagnosed between 1 and 5 years of age.

Study population:

- ▶ All mothers in the study had either untreated or partially treated Lyme
- ▶ 16% had been treated prior to pregnancy
- ▶ Some bitten by tick during pregnancy, some prior
- ▶ Majority of mothers diagnosed prior to the child's diagnosis
- ▶ 66% reported a difficult pregnancy
- ▶ Many mothers had Lyme symptoms that continued beyond the pregnancy
- ▶ 41% breast fed
- ▶ A number of the children had subsequent tick bites after diagnosed with congenital Lyme
- ▶ A number had tick-borne co-infections
- ▶ All children in the study improved with appropriate antibiotics

Most common sxs and sxs of gestational Lyme include:

- 90% Hypotonia
- 80% Irritability*
- 80% Cognitive problems including learning disabilities and mood swings
- 72% Fatigue and lack of stamina
- 69% Pain
- 60% Low grade fevers, pallor, sickly, and dark circles under eyes
- 50% Arthritis or painful joints (stiffness or decreased ROM)
- 45% Unspecified rashes
- 40% GERD and vomiting with coughing (nausea, diarrhea, constipation, abdominal pain)
- 40% Frequent URI and otitis
- 40% Noise, light, and skin sensitivity
- 30% Eye problems (cataracts, myopia, astigmatism, conjunctival erythema (Lyme eyes), optic nerve atrophy, optic neuritis, uveitis)
- 30% Developmental delay including language and speech problems
- 30% Cavernous hemangiomas (dilated bvs especially in brain but can be anywhere, can be asx or sx)
- 23% Secondary Lyme rashes
- 23% Night sweats
- 23% General muscle pain or spasms
- 23% Cardiac abnormalities (palpitations, PVCs, murmurs, mitral valve prolapse, etc.)

* The irritability referred to here is a persistent irritability associated with impulsivity

Hypotonia

Tone: A normal tension or responsiveness. In muscles, normal tone is a constant slight contraction that helps maintain posture and coordination.

Hypotonia:

- ▶ Present in over 90% of the cases of gestational Lyme
- ▶ Children described as floppy, limp, rag dolls, or pillows full of pudding.
- ▶ Variety of possible causes
- ▶ In Lyme, Bb is thought to impede sensory input or the activation of muscle or other functions, or directly impact the cerebellum.
- ▶ Features of hypotonia:
 - Arms and legs hang by sides
 - Decreased DTRs
 - Little resistance to passive motion
 - Decreased muscle tone
 - Delay in gross and fine motor skills
 - Excess flexibility
 - Drooling
 - Speech difficulties due to decreased muscle strength
 - Rounded shoulders
 - Leaning

Persistent irritability associated with impulsivity is present in @ 80% of cases.

This irritability is not garden-variety crabbiness that may accompany long-term illness. Rather, this is a persistent irritation that often accompanies impulsive acts. While this irritability is improved with appropriate treatment, the impulsivity may never completely resolve. The irritation may result from the frustration associated with the impatience and impulsivity.

Features:

- Acts without thinking
- Does not think things through
- Takes unnecessary risks
- Short fuse
- Can't wait for turn
- Blurts
- Says the wrong thing
- Interrupts
- Intrudes
- Emotional liability

Case:

- ▶ Male child presented with:
 - ▶ Significant hypotonia manifested by:
 - ▶ Poor muscle control
 - ▶ Stooped gait
 - ▶ Could not control toe movement
 - ▶ Irritation and impulsivity severe
 - ▶ Extreme sensitivity– slightest stimulation of senses toxic to him
 - ▶ Problem with sensory integration (could not process all incoming stimuli)
 - ▶ Daily fevers of 101 or 102
 - ▶ Severe joint pain
- ▶ **History:** Mother had Lyme during pregnancy and child had innumerable tick bites over the years in endemic area. Had been diagnosed with a virus that he would grow out of eventually. When he did not improve and doctors were out of ideas, grandparents hired a priest.
- ▶ **Work-up:** Clinical diagnosis of gestational Lyme with WB bands all positive supporting Lyme diagnosis. Also positive for multiple other TBDs including Babesia, Bartonella, and *Mycoplasma fermentans*.
- ▶ **Treatment:** Appropriate antibiotics that hit Lyme and known co-infections.
- ▶ **Outcome:** 3 month follow-up: Normal gait, good muscle movement, improvement on impulsivity and irritability and sensory integration. Doing well in school and athletic. “I didn’t know I wasn’t supposed to hurt.”
- ▶ **Plan:** Continue treatment since improvement is on-going.

Neurologic signs and symptoms are also especially common in gestational Lyme including:

Irritability	Cognitive problems
Headache	Speech delays
Poor memory	Articulation difficulty
Developmental delay	Reading/writing issues
Vertigo	Word selections
Tics	Auditory or visual processing
Involuntary movements	Dyslexia
Broad neuropsychiatric problems	Anxiety
Anger or rage	Aggression or violence
Mood swings	Emotional lability
Depression	Suicidal thoughts
ADD, ADHD, lack of concentration	OCD
Sensory sensitivity	Photophobia
Motion sickness	Seizures

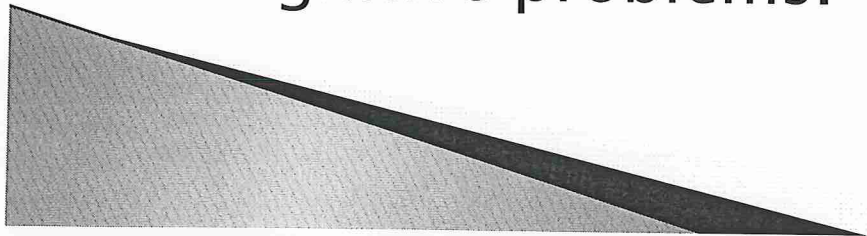
Note: About 10% had symptoms consistent with the autism spectrum.

Additional study results from the retrospective study:

Results of lab tests:

ELISA	25 % positive
Western blot	58 %
Bb culture	37 %
PCR (urine)	4 %
PCR (blood)	7 %

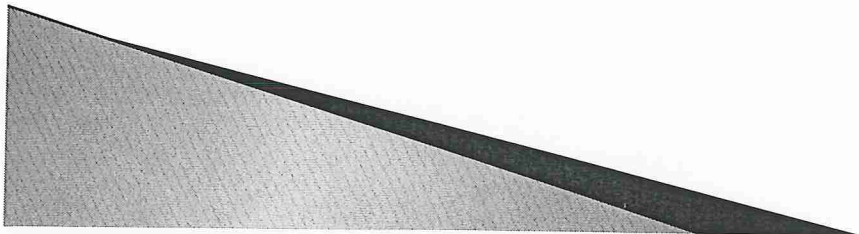
The testing most correlated with a diagnosis of congenital Lyme was neuropsychological evaluations with 80% confirming suspected cognitive problems.



Additional study results from the retrospective study:

Rate of co-infections:

Strep	7 %
Leptospirosis	5 %
Fungus or yeast	4 %
Ehrlichiosis	6 %
Babesiosis	14 %



There are two treatment considerations in these cases:

1. If the mother has Lyme disease, she needs to be treated in a way that gives the best chance of protecting the fetus from contracting the infection.
2. If born with congenital Lyme, the neonate must be treated to give the best chance to eliminate the infection and reduce the potential for long-term damage.

In both cases, antibiotics must be selected that will hit both the active and dormant states of the Bb and will not cause damage to the developing fetus or newborn.

Treatment of the pregnant woman with Lyme:

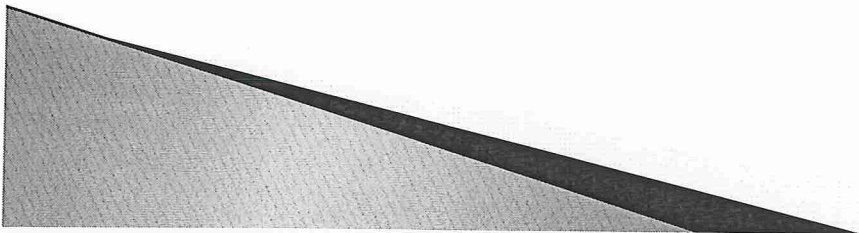
- ▶ A Lyme pregnancy registry was maintained for a number of years
- ▶ If the Lyme-infected mother was on adequate doses of antibiotic therapy during gestation then NO babies were born with Lyme
 - mother treated with 2 antibiotics... NO Lyme babies
 - mother treated with 1 antibiotic ... ~25% Lyme babies
 - mother not treated with antibiotics... ~50% Lyme babies
- ▶ Unfortunately, many cases are not recognized or are undertreated

Oral options:

Amoxil (amoxicillin) 1000 mg q 8, OR
Ceftin (cefuroxime) 500 q 12, OR
Omnicef (cefdinir) 300 to 600 mg bid

PLUS

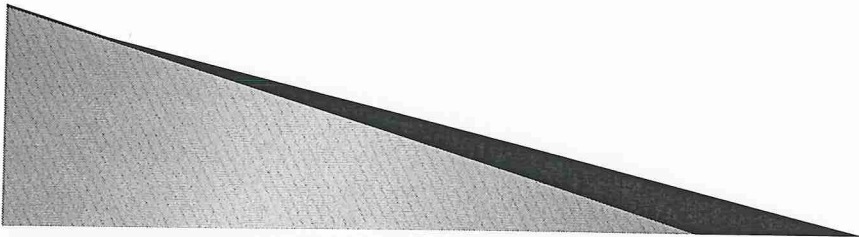
Zithromax (azithromycin) 500 mg bid



Parenteral options:

In mothers who are very ill or who can't tolerate or achieve adequate levels with oral medications, consider:

- Benzathine PNC (Bicillin): 1.2 million units IM 1 to 3 times a week
- Ceftriaxone (Rocephin): 2 g IV daily
- Cefotaxime (Claforan): 6 g daily either continuous infusions or as 2 g IV q 8



After birth, the maternal Lyme may no longer be mollified by the pregnancy hormones and symptoms may return in full force. There may be profound fatigue and these women may need additional help post-partum.

Continue to treat the mother's Lyme as appropriate.

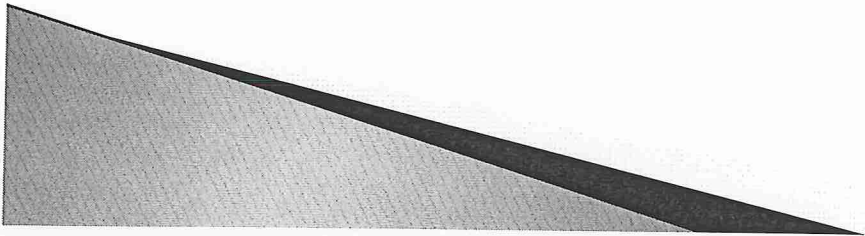
Breast feeding can **ONLY** proceed in actively ill Lyme patients **IF** the mother is on appropriate antibiotics, since live spirochetes have been isolated from breast milk.

Treatment of the neonate with congenital Lyme:

- ▶ Have a high index of suspicion
- ▶ Although only subtle symptoms may be present at birth, **SERIOUS NEUROLOGIC SEQUALAE** may result if not promptly diagnosed and treated.
- ▶ These problems can be severe and debilitating.
- ▶ Patients often have entrenched and chronic Bb neurologic manifestations by the time the diagnosis is made.
- ▶ Kids do well if treatment is aggressive and for sufficient duration.
- ▶ Some patients respond and have a disease-free period and think the disease is gone, only to recur. Recurrence could be due to a new bite or flare of old disease. Retreat.

Treatment options for the child with gestational Lyme:

Combination of PCNs, CSs, and macrolides.
TCNs are not usually used in children under 8.



If you are unsure whether to treat a mother or child:

Gardner: 1995 study of Lyme disease of the fetus and newborn: 161 cases

In mother with active Lyme:

Treated with antibiotics: 85 % of the neonates were normal (15% abnormal)

No antibiotics: 33 % of the neonates were normal (67% abnormal)

Many of these untoward events were significant including miscarriage, stillbirth, perinatal death, congenital anomalies, sepsis, or chronic progressive infection.

In 1989, Alan MacDonald documented the adverse outcomes in cases of Lyme infection during pregnancy. These adverse events were found to occur irrespective of trimester of initial infection and appear to be in excess of adverse outcomes compared to what is observed in matching uninfected populations.

Untoward outcomes documented in Lyme infected mothers:

Prematurity

Blindness

Toxemia

CVS anomalies

Respiratory distress

Hydrocephalus

SIDS

Fetal death

Growth retardation

Hyperbilirubinemia

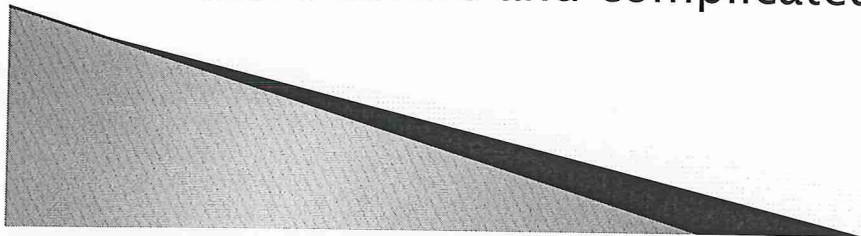
Case:

Mother of a child with congenital Lyme relays her story of being severely ill with Lyme when 5 months pregnant. Her obstetrician agreed she had Lyme and, although he was not convinced she needed any treatment, went into the supply closet coming out with a handful of doxycycline samples which would last her 4 days. "This should be plenty." Four months later, her baby was born with Lyme.

Many mothers of congenital Lyme children feel they should have done more to prevent transmission. How were they to know when HCPs often do not know?

Confounders in recognizing congenital Lyme

- ▶ May be asymptomatic at birth
- ▶ First signs and symptoms may be delayed for varying periods causing the mother's Lyme during pregnancy to be forgotten
- ▶ When sxs noted, commonly overlooked or attributed to something else
- ▶ Signs and symptoms may mimic other conditions leading to misdiagnosis
- ▶ Co-morbidities are common
- ▶ Manifestations may affect multiple systems leading to pursuing wrong leads
- ▶ Symptoms may wax, wane, and change with varying degrees of severity
- ▶ Difficulty in gathering supportive laboratory data (many false negatives)
- ▶ Negative lab results do not rule/out the disease
- ▶ Mother may have Lyme but if not currently active, may not know the child is at risk
- ▶ In general, the longer the child goes without appropriate diagnosis, the more severe and complicated the clinical course

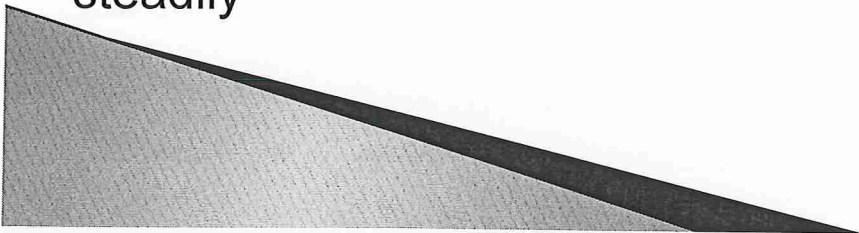


Case: A 6 y/o boy presented with an ankle monitor, a consequence of repeated run-ins with the police. He had been in juvenile lock-up 4 times for larceny, arson, attempted murder, and cruelty to animals. He had frequent rages, significant anxiety, emotional liability, and many fears. He had been seen by a number of HCPs with diagnoses of OCD and ODD. The child was about to be jailed. There was not much hope until the mother recalled that she had had Lyme prior to the pregnancy.

Work-up: As usual, multiple ELISA tests were negative, but other tests for Lyme were positive as were tests for other TBIs. (Not sure if these were gestationally transmitted or due to subsequent tick bites.) Undergoing extensive neuropsychiatric testing.

Treatment: Rapid response to antibiotic therapy. Now all As and superb athlete. While fears and anxiety not completely gone, much improved. Because he had so much delay in diagnosis and treatment, considering IV gamma globulin to address potential autoimmune component.

Lesson: Today there is more recognition of the possible infectious basis for a number of cases of intractable neuropsychiatric complaints. Had this mother not recalled her Lyme, the child would be incarcerated instead of improving steadily



Interesting questions:

1. Does Bb affect the genetic material of the fetus?
2. What happens to the fetus if the spirochete causes teratogenic affects during organogenesis?
3. Does infection in the father matter?

Answers:

We aren't sure.

1. Does Bb affect the genetic material of the fetus?

- Recent work has demonstrated that protozoal parasites, certain viruses such as HIV, and some bacteria can affect gene structure or expression in the host.
- Xiao demonstrated significant changes in rodent behavior due to alteration in gene expression after infection with the protozoal parasite *Toxoplasma gondii*. “*T. gondii* can play its infected rodent hosts like a piano, ...”
- HIV and other viruses, and bacteria such as *Helicobacter pylori* are known to alter gene structure and expression. Why not Lyme?

2. What happens to the fetus if the spirochete causes teratogenic affects during organogenesis?

Children with congenital Lyme seem to be born with certain congenital anomalies at a rate in excess of those in matching uninfected populations such as: syndactyly, congenital eye problems, prematurity, cardiac abnormalities, and congenital urologic anomalies.

Are these problems due to gestational Lyme, genetics, co-morbidities, environmental influences, or a combination of factors?

3. Does infection in the father matter?

We know that the father can infect the mother. We know that an infected mother can infect the child. There are anecdotal reports that an infected father contributed sperm in IVF to a mother previously uninfected and the child was born with gestational Lyme. We do not know if Bb active in the father at the time of spermatogenesis causes genetic defects in the child.

Challenge:

Do not make the same mistakes in Canada that have been made in the US. Please:

- Recognize that Lyme disease exists and is becoming more prevalent.
- Understand that Lyme can be a serious illness especially in children.
- Congenital Lyme can result in severe and permanent disabilities.
- When you have a pregnant patient with Lyme, you must also protect the fetus.
- Understand that there may be more than one infection active at a time and multiple non-infectious co-morbidities.
- Keeping a high index of suspicion is half the battle. You can't manage a disease you don't even consider. If the mind doesn't know, the eyes don't see.
- Never underestimate the damage that can be done by Lyme or the other TBDs.

Needed: Prospective studies

Note: Blinded, placebo-controlled studies may be difficult to design given what we know about the potential for gestational Lyme to cause serious and permanent problems in the fetus. Who would get the placebo?

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Bibliography, CALDA, www.lymedisease.org

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Pediatric Tick-Borne Disease*

Lyme Disease

Can pass from

mother to baby.

ASK ME!

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