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Annals of Clinical Cytology and Pathology

Short Communication

Borreliosis Infection during Pregnancy

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Submitted: 28 September 2017

Accepted: 16 October 2017

Published: 23 October 2017

ISSN: 2475-9430

Keywords
- Borrelia burgdorferi
- Lyme disease
- Pregnancy
- Adverse fetal outcomes

Abstract

Congenital Lyme disease is an ongoing area of interest in the medical literature. While there have been case reports, animal studies, and epidemiological investigations, there continues to be a paucity of information and consensus regarding potential devastating fetal outcomes. In addition to case reports, obstetrical concerns stem from the known adverse fetal outcomes associated with congenital syphilis, another bacterial species of the spirochete class. There is insufficient evidence through these limited case and epidemiological studies to demonstrate a causal relationship between *Borrelia burgdorferi* infection and adverse outcomes by delivery, however, many obstetricians and authors remain concerned regarding cases of acute asymptomatic infection and their potential obstetrical complications.

INTRODUCTION

Lyme disease is caused by infection with *Borrelia burgdorferi*, which as a systemic infection, has been well documented to have serious medical implications in the non-pregnant adult. Borreliosis is an infection of animals, transmitted to humans via Ixodes ticks, with an incidence that can vary according to the occurrence of infected animals and vectors. Since *Borrelia burgdorferi* is a spirochete infection similar to syphilis, consequences of congenital infection should be predictable [1].

Lyme disease first gained attention in 1975 in the town of Lyme, Connecticut, United States, with a reported increased incidence of juvenile arthritis. This increased incidence was traced back to tick bites, and a common and unique pathological agent was suspected [2]. It was however not until 1981, that the spiral shaped bacterial pathogen, *Borrelia burgdorferi*, was identified as responsible for Lyme disease [2]. Since then, three *Borrelia* species are known to be pathogenic in humans, as well as eight minimally pathogenic or nonpathogenic species. They all belong to the genus *Borrelia burgdorferi sensu lato*. The three species of *Borrelia* are additionally endemic to different regions of the world, with *Borrelia burgdorferi sensu stricto* being seen in North America, and *Borrelia afezelii* and *Borrelia garinii* infecting the European subcontinent [2].

Between 60,000 – 100,000 cases of Lyme disease occur annually across the world [2], with more than 20,000 cases annually reported in the United States of America. In the United States, Lyme disease is considered the most common tick borne illness, concentrated heavily in the Northeast and Midwest [3]. Information that has been released by the Centers for Disease Control and Prevention lists the states of Vermont, Maine, Pennsylvania, Rhode Island, Connecticut, New Jersey, Massachusetts, Delaware, New Hampshire, and Minnesota as the states with the highest reported incidence of disease [4]. The number of reported cases in the United States have steadily increased over the past 20 years, from approximately 11,000 cases in 1995, to approximately 28,000 cases reported in 2015 [5]. Similar incidences are now being reported across the European subcontinent. In Canada, populations of infected ticks are established in Nova Scotia, southeastern Quebec, southern Ontario, southeastern Manitoba, and parts of British Columbia [6].

Lyme disease is generally divided into three clinical stages of disease. Stage 1 is considered early localized infection, occurs days to weeks after infection, and is heralded by erythema migrans of the skin, with associated symptoms such as headache, fever, myalgia, arthralgia, lymphadenopathy, and conjunctivitis [2]. Stage 2 is considered early disseminated infection, occurring weeks to months of infection, and is associated with neurological manifestations (most commonly asymmetric flaccid palsy), which are indicative of early disseminated infection [2]. Stage 3 of the disease is persistent infection months to years after exposure and is consistent with polyradiculoneuritis [2].

There are additionally different manifestations of disease associated with the three different *Borrelia* pathogenic species. *Borrelia burgdorferi* is known for likely dissemination, association with chronic and refractory arthritis, and more frequent oligoatriular arthritis with more intense joint inflammation [7]. *Borrelia garinii* typically does not disseminate, but is associated with neurotropic properties including encephalomyelitis, while *Borrelia afzelii* typically only has cutaneous manifestations [7].

The general standard practice of treating pregnant women, who become infected with one of the pathogenic *Borrelia* species causing Lyme disease, is simply a course of antibiotics, when

there is high clinical suspicion of disease and when it has been appropriately diagnosed. Unfortunately, concern continues to grow regarding pregnant women who are asymptomatic with an acute infection, and therefore never received antibiotic treatment. There has been multiple case reports published which have alluded to serious fetal outcomes in the setting of acute infection.

METHODS

A literature search was completed through www.pubmed.org and www.medline.com in order to review publications regarding the potential adverse impacts of Lyme disease in pregnancy. Journals and book chapters from 1987 through 2012 were considered. Articles was searched through the use of keywords such as "Lyme disease", "adverse fetal outcomes", "Borrelia burgdorferi infection", "pregnancy", "neonatal death", and "congenital malformations". The Centers for Disease Control from the United States of America, www.cdc.gov, as well as the Infectious Disease Society of America's guidelines on Lyme disease, www.idsociety.org/guidelines, were additionally reviewed for the most updated information.

DISCUSSION

The first case reports that gained attention were published in the 1980's, with Dr.'s Schlesinger, MacDonald, and Weber at the forefront. The first confirmed case of tranplacental passage of *Borrelia burgdorferi* was reported in 1985 by Schlesinger, a physician practicing in the state of Wisconsin. He described a woman who experienced a tick bite during the first trimester of pregnancy. She did not receive the diagnosis of Lyme disease, despite cutaneous manifestations consistent with Stage 1 disease, and therefore did not receive antibiotic treatment. She delivered preterm at 35 weeks gestational age [8]. The neonate expired on hour thirty-nine of life due to congestive heart failure. Autopsy revealed several major congenital cardiac malformations including aortic valve stenosis, patent ductus arteriosis, as well as a coarctation of the aorta [8]. In addition to spirochetes being isolated from cardiac tissue, they were also isolated from the neonate's spleen, kidneys, and bone marrow. It is notable that this mirrors the findings of the spirochetes *Treponema pallidum* dissemination to fetal organs. The mother subsequently tested positive for Lyme disease [8]. Although the cardiac complications could not be traced back directly to the *Borrelia* infection, a teratogenic effect could not be excluded [2].

MacDonald followed in 1987 with a similar case report of first trimester infection and lack of appropriate antibiotic treatment. The mother reported that she was an avid hiker in an endemic region, and experienced cutaneous and joint manifestations after experiencing a tick bite. She carried to full term, but vaginally delivered a 2,500 gram stillborn fetus. Again autopsy revealed a significant ventricular septal defect, with Lyme spirochetes isolated from the fetal brain, heart, adrenal glands, and placenta. The mother's blood tested positive for the Lyme spirochete [9].

One year later, Dr. Weber described a case of a woman diagnosed with Lyme disease in the first trimester, who was treated with antibiotics, but for only one week. She delivered at term, but the neonate experienced significant respiratory distress, was later found to have significant intracranial hemorrhaging, and demised on hour twenty-three of life. Spirochetes consistent with *Borrelia* were isolated from brain tissue [10].

Later in 1989 MacDonald released a publication through the Rheumatic Disease of North America, which reviewed a total of 14 cases of adverse fetal outcomes associated with congenital Lyme disease, but also stated that epidemiology, serology, and histopathology perspectives, which had since been investigated, offer a non-convergent view on the potential impact of congenital Lyme disease [11].

Animal studies conducted on other mammals, have demonstrated infection with *Borrelia burgderfori* during pregnancy being associated with reproductive failure and well as fetal wastage [12-14]. Due to these case reports published by the late 1980's, which suggested Lyme disease could be responsible for adverse fetal and neonatal outcomes, animal investigations began to gain popularity. These animal studies demonstrated that the likelihood of transplacental infection is higher in the beginning of pregnancy than in later pregnancy [2].

Sine concern surrounded acute infection not treated with antibiotics; murine experiments were conducted by Silver and colleagues in 1995 comparing acute verses chronic infection with *Borrelia*. Acutely infected mice were inoculated 5 days prior to mating, while chronically infected mice were inoculated 3 weeks prior to mating. Gestational sac deaths occurred in 14% of acutely infected mice, compared to no gestational sacs in the chronically infected mice [15]. Furthermore, Silver's experiment additionally documented that 46% of acutely infected mice had at least one fetal death occur, while no fetal deaths occurred in those considered to be chronically infected [15], supporting the human case reports with documented increased risk of spontaneous miscarriage and stillbirth.

While transplacental transmission has been confirmed in humans, and case reports document adverse outcomes in inadequately treated mothers, case series and epidemiological studies offered scarce information to support the argument for congenital malformations and adverse obstetrical outcomes. A study conducted in 1996 reviewed sixty placentas from asymptomatic women who were residing in an endemic region for Lyme disease, and who had either negative or equivocal serologic testing. Three out of sixty placentas, 5%, returned positive for the spirochete *Borrelia burgdorferi* when undergoing Warthin-Starry silver staining. All of these pregnancies were noted to have an uncomplicated antenatal course and normal neonatal outcomes [15].

An additional case study that was conducted in 1999 on 105 women, in 1999, which again failed to show an increased association with infection with *Borrelia* and an increased incidence of congenital malformations. Ninety three of the 105 women had health infants who delivered at term. Four of these infants were born with congenital anomalies; however, infection with *Borrelia* could not be directed implicated as the cause [16]. Furthermore, their incidence of congenital anomalies 3.8%, is similar to the baseline risk of a congenital malformation in the general obstetrical population.

Multiple epidemiological studies from the 1980s and 1990s

additionally offer conflicting views regarding the increased risk of congenital malformations with fetal infection with *Borrelia*. A study in which twelve seropositive women were identified, only one had a documented history consistent with Lyme disease during her pregnancy. Of the twelve women, two neonates had hyperbilirubemia, one had transient hypotnia, one was small for gestational age, and one had transient supraventircular heart beats (which resolved). The infant born to the women with a clinical diagnosis of Lyme infection was noted to have a ventricular septal defect [17]. However, up to seventeen months later, all of the remaining children had no evidence of infection with *Borrelia burgdorferi* [17].

Conversely and more recently, in 2010, Lakos and Solymosi conducted a review of 95 cases of maternal diagnosis of Lyme disease occurring during pregnancy. Seven out of ninety-five women experienced either fetal death or a stillbirth [18], which is significantly higher than the baseline risk of stillbirth (~6/1,000), supporting the association between acute infection and fetal loss and stillbirth. Furthermore, it has been reported in the United States that there are twice as many cases of congenital heart disease in women who reside in endemic regions with a high incidence of Lyme disease [19].

This finding contradicted a 1999 retrospective case control study that was conducted in an area considered endemic for Lyme infection, in which 769 cases of children with congenital heart defects were reviewed, and compared to 704 children born without congenital heart defects. Lyme disease in the mothers during or before pregnancy was then additionally reviewed. There was no association found between congenital heart defects and Lyme disease in the mothers either within 3 months of conception or during pregnancy [20].

It is crucial for obstetrical patients residing in, or traveling to endemic regions to be educated by their providers regarding safeguards to protect themselves from acute infection. Protection and prevention can be optimized through the use of insect repellent with 20-30% DEET and by performing a thorough tick examination and showering as soon as possible after outdoor activities associated with possible tick exposure [21]. No adverse effects have been documented with the use of DEET insect repellents in the obstetrical population [22].

If an obstetrical patient develops signs and symptoms which are consistent with a possible exposure and acute infection with *Borrelia*, laboratory testing should be promptly initiated. Therapeutic treatment should not be delayed while awaiting results, since an intrauterine death is possible following acute borreliosis [2]. It is appropriate to treat with oral antibiotics for stage 1 of disease, but stages 2 and 3 should have treatment initiated with IV antibiotics. The Centers for Disease Control and prevention currently recommend a three week course of antibiotic therapy for obstetrical patients with suspected Lyme disease, with the standard antibiotic regimen being Amoxicillin 500mg three times daily or Cefuroxime axetil twice daily for women with a penicillin allergy [20]. Other publications have recommended as high as 1,000mg Amoxicllin orally for 3 weeks. Other appropriate oral regimens include Cefuroime axetil 500mg twice daily for three weeks, Roxithromycin 300mg daily for three weeks, or Clarithromycin 250mg twice daily for three weeks. Intravenous regiments include Ceftriaxone 2-4g daily or Penicillin G 5 million units four times daily for two to three weeks' duration [2]. There is no indication for termination of pregnancy in the setting of a diagnosis of acute infection [2].

Additional surveillance with ultrasound is appropriate in the setting of an acute infection with *Borrelia*. An ultrasound assessing for evidence of congenital spirochete infection, as is performed in cases of syphilis infection is recommended. Evidence of congenital spirochete infection includes hepatomegaly, ascites and other signs of hydrops, fetal anemia evidence by abnormal middle cerebral artery Doppler studies, and a thickened placenta [23]. It has additionally been recommended for a fetal echocardiogram to be performed between 20-22 weeks' gestational age in suspected cases of Lyme disease exposure early in the first trimester during cardiac organogenesis, due to the increased risk of potential fetal cardiac complications [24].

There are additional considerations in the post-partum period. Evaluation of a pregnancy that has been complicated by Lyme disease should include pathologic examination of the placenta to detect evidence of spirochetes within the umbilical cord [25]. Cultures, immunohistochemistry, and indirect immunofluorescence may be additionally beneficial in confirming *Borrelia* during pregnancy [25]. New mothers should also be informed that it is possible to obtain *Borrelia* DNA via PCR from breast milk [26], and it is unclear whether this represents intact bacterium. Due to this lack of data in the literature, there is a relative contraindication to breast feeding in the setting of an acute infection [26].

CONCLUSION

Intra-human transfer of *Borrelia* can be initially silent or unrecognized, and if not successfully treated, infection can be life long, and latency, late activation, and reactivation are common [27]. Therefore, continued investigation into new cases of pregnancies acutely afflicted by Lyme disease and reporting of such cases is warranted in order to add to the growing body of evidence regarding the pathophysiology and clinical outcomes of congenital Lyme disease. Thankfully, through the already available case reports, animal studies, and epidemiologic studies, we have gained valuable insight. The similarities of the clinical presentation of congenital syphilis to pregnancies with acute Lyme disease helps guide ante partum management. Due to the severity of previously documented cases, there should be a low threshold of suspicion to diagnose cases of Lyme disease in pregnancy. Particularly in endemic area, serologic testing for women with symptoms of acute infection should be considered. In the interim, as more data emerges, emphasis should be placed on protection and prevention, and educating obstetrical patients on signs and symptoms.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the Department of Obstetrics and Gynecology and Division of Maternal Fetal Medicine at Pennsylvania State College of Medicine at the Milton S. Hershey medical center for their continued dedication to patient care.

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Cite this article

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