

Infection with *Borrelia*: Implications for Pregnancy

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ABSTRACT

Infection with *Borrelia burgdorferi* during pregnancy started gaining attention in the 1980's. For the past four decades, there have been multiple case reports, case reviews, epidemiologic and histopathological studies that have been conducted. Literature has focused on other the spirochetes, predominately *Treponema pallidum*, which is responsible for causing congenital syphilis. Multiple cases of poor obstetrical outcomes have been reported in women who were acutely infected and did not receive appropriate antibiotic treatment. These adverse outcomes include miscarriage, growth restriction, fetal death, as well as possible associations with preeclampsia. While it has been well established that *Borrelia* is capable of crossing the placenta, there remains to be a clear correlation between acute infection with *Borrelia* and adverse outcomes and congenital malformations. The majority of women who are acutely infected during their pregnancy have been found to have uncomplicated pregnancies and deliveries of infants who have not been infected. However, given the conflicting current research and data, obstetricians should initiate appropriate antibiotic treatment in all patients who report a history of possible acute infection, regardless of the gestational age of the fetus. Organizations such as the Centers for Disease Control, in the United States, maintain that no adverse outcomes have occurred in obstetrical patients who have been appropriately treated.

INTRODUCTION

Infection with the *Borrelia* spirochete bacterial species continues to be seen on a more global scale, and therefore has started to receive increased attention. Since the 1980's there has been a growing level of concern regarding congenital infection with *Borrelia*, and potential maternal, fetal and neonatal outcomes. While there have been multiple case reports, case series, and epidemiological studies, there continues to be a lack of consensus in the obstetrical community regarding adverse outcomes. The majority of scientific studies and literature surround another well-known spirochete that has significant congenital consequences, *Treponema pallidum*. Since the etiological agent of Lyme disease is also a spirochete, there has been concern about the effect of maternal Lyme infection on pregnancy outcome [1].

The congenital transfer rate of *Treponema pallidum*, the etiological agent responsible for syphilis, has been reported as high as 68% in previous cohorts of treated infected mothers [2]. Multisystem involvement is well documented in fetuses infected with *Treponema* that can result in respiratory symptoms, poor feeding, rhinitis, hoarse crying, generalized lymphadenopathy with fever, and hepatosplenomegaly that may be present at birth or develop within the first 4 weeks of life [3]. It has been well documented that penicillin is effective in preventing transplacental transmission of syphilis as well as treating an infected fetus. It is further recommended that fetuses that have been exposed to *Treponema* should be watched more closely while in utero with serial ultrasound to assess for evidence of spirochete infection such as hepatomegaly, ascites, hydrops, thickened placenta, and fetal anemia [4].

In this chapter, we will review the similar findings that have thus far been established with regard to *Borrelia* infection, and the subsequent management recommendations this has incurred.

DISCUSSION

Case Reports

The first case reports that addressed the possibility of congenital infection with *Borrelia* were seen in the literature starting in the 1980s. Dr. Schlesinger, a physician who was practicing in Wisconsin, United States, described transplacental passage of *Borrelia burgdorferi* in 1985. He described a patient who experienced a reported tick bite during the first trimester of pregnancy. Although she had cutaneous manifestations consistent with possible infection, she never received the diagnosis of an acute infection. Therefore, she did not receive antibiotic treatment. She experienced a preterm delivery at thirty five weeks gestational age, of a neonate which demised at hour of life thirty nine. Autopsy revealed significant congenital heart defects in the form of aortic valve stenosis, patent ductus arteriosus, and coarctation of the aorta [5]. Postmortem spirochetes were isolated from multiple organ systems [5], which parallels the multi-organ involvement seen in congenital infection with *Treponema*. The mother subsequently had positive serology in the post-partum period. Although the congenital cardiac malformations could not be directly linked to

first trimester *Borrelia* infection, a teratogenic effect was highly suspected due to the evidence of borreliosis.

In 1989, Dr. MacDonald released a comprehensive review of gestational borreliosis through the Rheumatic Disease Clinics from America. He notably discussed a patient, who suffered from a term intrauterine fetal demise. Retrospective review of her past medical and obstetrical history was significant for likely first trimester *Borrelia* exposure. Fetal viscera showed *Borrelia Burgdorferi* in the liver, adrenal glands, brain, heart and placenta [6]. Spirochetes were additionally evident on dark field examination. He presented a total of fourteen cases of adverse fetal and neonatal outcomes, in which infection with *Borrelia* was determined in the post-partum period. He notes several cases of second trimester miscarriage, growth restriction, stillbirth, and neonatal deaths of term infants who subsequently had multiple congenital anomalies including congenital heart defects [6].

Shortly thereafter, Dr. Weber described the case of a gravid female who experienced an acute infection with *Borrelia* during the first trimester of her pregnancy. She received antibiotic treatment for the duration of one week. She carried her pregnancy to term, but delivered a neonate that experienced significant respiratory distress and an intracranial hemorrhage. This culminated in a neonatal demise at hour twenty three of life. Spirochetes that were consistent with *Borrelia* were isolated from brain tissue postmortem [10].

A similar case of persistence of Borreliosis despite antibiotic treatment was described in a 28-year-old who was infected during the second trimester of pregnancy. She received 15 days of antibiotics and delivered a term neonate. However, despite negative maternal and neonate serology, placental cultures and staining were consistent with *Borrelia* [6]. The patient retrospectively reported a tick bite two weeks prior to delivery in which she developed a rash and did not receive additional treatment.

Furthermore, Lavole and colleagues from San Francisco, Yale-New Haven, Texas, and Minneapolis, presented an abstract at the 51st Annual Meeting for the American rheumatism Association, of a mother living in California, a non-endemic region for *Borrelia* infection, who experienced an infant demise days after a non-complicated pregnancy. The case was noteworthy due to seronegativity but positive cultures which were obtained from the neonate. The neonate presented on day of life eight with profound lethargy, systemic hypertension, and unresponsiveness, and ultimately demised. Spirochetes were then cultured from both brain and cardiac tissue upon post-mortem examination [11].

In addition to the multiple case reports that are found in the literature, there are case series that explored the association between congenital *Borrelia* infection and adverse outcomes. Two studies have been conducted by the Centers for Disease Control (CDC), in the United States.

A retrospective review was conducted in nineteen women who were infected with *Borrelia* during their pregnancy course. Adverse fetal outcomes included prematurity, cortical blindness,

fetal death, syndactyly and neonatal rashes [12]. However, infection with *Borrelia* was unable to be directly implicated as the exclusive causative agent for these outcomes. A similar prospective case series examined seventeen women who again were acutely infected during their pregnancy with *Borrelia*. Although one woman had a spontaneous abortion, there was no evidence of *Borrelia* infection on tissue cultures or stains. Furthermore fifteen of the seventeen women had uncomplicated pregnancies and delivered normal term infants with no clinical or serological evidence of infection [13]. The conflicting outcomes of these case series demonstrate the lack of full elucidation of pregnancy complications.

Animal Studies

After the increased attention due case reports revealing potential adverse fetal and neonatal events associated with *Borrelia* infection, multiple animal studies have since been conducted. These animal experiments provided direct evidence that infection with *Borrelia* associated with adverse outcomes in other mammals and species.

Research conducted on canines has confirmed trans placental passage of *Borrelia*. Trans placental transmission of *Borrelia* has been documented via polymerase chain reaction in over 47% of pups born to female canines that underwent intra dermal inoculation with *Borrelia* multiple times during their pregnancy [14]. Only 21% of the pups were found to have culture positive tissues, and as reported in human case reports, none of the tissues revealed evidence of inflammation [14], that is typically associated with infection and negatively affect a developing fetus. Several additional studies have revealed a link between *Borrelia* infection and adverse outcomes during pregnancy including fetal wastage, reproductive failure, and severe fetal infection in canines, cows, and horses at the time of delivery [14-16].

Additional studies have confirmed that only acute infection with *Borrelia* is tied to adverse fetal outcomes, specifically of fetal death. Experiments conducted by Silver and colleagues explored the pregnancy risks associated with acute versus chronic infection with *Borrelia* in a murine model. Acutely infected mice were defined as those inoculated five days prior to mating, while those considered to be chronically infected were inoculated three weeks prior to mating. Fetal death occurred in 10 of 72 gestational sacs, or 14% of acutely infected mice, while no deaths occurred in the chronically infected mice [17]. 46% of the acutely infected mice had at least one fetal death occur [17].

Epidemiological Studies

The distribution of *Borrelia* infection continues to be documented as being on much larger scale than previously thought, increasing the risks for obstetrical patients across the globe. Infection has been reported in over thirty countries, spanning six continents, and over several islands [18-20]. Therefore, there have been a multitude of epidemiological studies conducted in order to attempt to show a correlation between infection with *Borrelia* and adverse pregnancy outcomes and congenital infection.

A study conducted by Williams et al in 1995 reviewed cord blood serum from 421 deliveries and determined that there was no association between the presence of IgG antibodies and congenital malformations [21]. A more conclusive study was conducted by Nadal and colleagues in 1989, where they reported outcomes in 1,416 women for the presence of antibodies against *Borrelia* at the time of delivery. Twelve of these women were found to be seropositive for infection with *Borrelia*, although only one of these women reported a history consistent with acute infection. Only the infant of the mother with a clinical history of infection delivered an infant with a congenital malformation, in the form of a ventricular septal defect [22]. Of the remaining women who were seropositive, 2 of the infants had transient hyperbilirubinemia, 1 had transient hypotonia, 1 was post term and considered to be small for gestational age, 1 had transient macrocephaly, and 1 had transient supra ventricular beats. All of these infants were followed until 9-17 months of age, all were reported as thriving, and none were reported to have serological evidence of *Borrelia* infection [22].

Since there are known adverse neurological consequences in adults inflicted with *Borrelia* infection who do not receive adequate treatment, Gerber and Zalneraitis examined whether the same outcome occurs to children born to mothers diagnosed with *Borrelia* infection during their pregnancy. Over 190 adult and pediatric neurologists were surveyed in an endemic region of the United States, and none reported ever seeing a child whose mother reported acute infection during pregnancy. They therefore concluded that congenital neuroborreliosis either did not occur, or was occurring at a very low incidence in endemic regions [23].

An additional retrospective case control study was conducted over seven counties in an endemic region of New York, United States, to investigate the potential relationship between *Borrelia* infection and cardiac defects in children as previously mentioned case reports suggest. 796 children that were born with congenital cardiac defects were compared to 704 children born without defects, and investigated whether there was maternal *Borrelia* infection before or during pregnancy. They were unable to find an association between congenital heart defects and *Borrelia* infection in mothers either within 3 months of conception or during pregnancy [24].

Furthermore a prospective population based investigation conducted in the endemic region of Westchester County, New York, United States, studied approximately 2,000 women for clinical and serologic evidence of *Borrelia* infection at their first prenatal visit, and then again at the time of their delivery. Only 0.7% of the women were found to be seropositive for *Borrelia* infection, and only 4% of the women reported a past medical history of *Borrelia* infection [25]. Fifteen additional women were diagnosed with *Borrelia* infection during the study period. The investigators were unable to find a link between exposure to *Borrelia* and fetal death, prematurity or congenital malformations [25].

However, more recently in 2010, Lakos and Slymosi, reviewed ninety five cases of maternal *Borrelia* infection during pregnancy. They reported that seven out of the ninety five of these

mothers experienced either fetal death or stillbirth [26]. This is appreciably higher than the baseline risk of stillbirth in the general population of approximately 6/1,000. This supports the association between acute infection with *Borrelia* and increased risk of fetal death and stillbirth.

Epidemiological studies have so far shown conflicting results regarding the association between adverse outcomes and congenital borreliosis.

Transmission

Gardner and other authors have conclusively shown that certain individuals infected with *Borrelia* acquired their disease gestationally [5,27,28]. This is further supported by the finding of *Borrelia* in semen, and by the similarity to which *Treponema* transmission has been abundantly documented in the literature [29].

Trans placental transmission has been clearly documented from case reports of infected fetuses. There have additionally been studies directly examining placentas which evidence of trans placental transmission in humans. Sixty placentas of asymptomatic women who were residing in a highly endemic region were examined with Warthin Starry silver stain for evidence of spirochetes. Of note, all these women had serologic testing that was either negative or equivocal. Three of the placentas were found to be infected with spirochetes [12].

Diagnosis

Diagnosis of an acute infection will present similarly in a pregnant patient as in the non-obstetrical population with erythema, fatigue, fever, myalgia, lymphadenopathy and arthralgia. Symptoms may make it difficult to discern infection from normal symptoms experienced during pregnancy. Patients However, especially when dealing with acute infection in pregnancy, is the concern for patients who are asymptomatic. Erythema migrans has been shown to be an unpredictable indicator of acute infection since it may manifest after initial tick inoculation, or may occur months to years later [30]. Furthermore, erythema migrans is not known to be a marker in gestational or congenital *Borrelia* transfer [28].

When the diagnosis of infection with *Borrelia* is suspected, patients will often undergo serological testing. The gold standard is currently considered enzyme linked immunosorbent assay (ELISA) studies. However, due to its association with false positive rates, Western blot testing is used as an additional confirmatory test [31]. IgM antibodies against *Borrelia* are typically present in maternal serum 2-4 weeks after inoculation. IgG antibodies generally appear at 6-8 weeks and will indefinitely remain elevated [32].

Complicating diagnosis even more, as previously displayed via case reports, serologic testing of mothers in the post-partum period and their neonates is often negative. It has been demonstrated that over 70% of neonates that have tissue verified borreliosis at the time of delivery, will not produce antibodies in sufficient quantity to be diagnosed as sero-positive [28]. A review of normal

fetal and neonatal antibody production has displayed a lag in IgG and IgM antibody levels up to one year of age [33].

Association with Pre-eclampsia

Aside from the progressive effects that can occur in a woman with *Borrelia* infection, who has not received antibiotic treatment, there are cases in the medical literature that point to a possible association between pre-eclampsia and acute *Borrelia* infection. While there has been no direct correlation made to pre-eclampsia and *Borrelia* infection, there are reported cases in the literature discussing mothers who develop pre-eclampsia not only in the third trimester, but more concerning, during the second trimester of pregnancy, heightening the risks for also neonatal morbidity in the setting of prematurity.

Cases of second trimester miscarriage have occurred in the setting of pre-eclampsia with diagnosis of Borreliosis in the post-partum period. A 22-year-old residing in an endemic region for *Borrelia* infection developed pre-eclampsia at 17 weeks gestational age with new onset of hypertension and proteinuria. She subsequently miscarried a stillborn infant with a congenital heart defect at 19 weeks' gestation [6]. Maternal serology was negative for infection, however, *Borrelia burgdorferi* was identified in fetal tissue by immunofluorescence [6].

Another instance was reported of a 37-year-old residing in an endemic area who had a known collagen vascular disorder. While this could predispose her to developing pre-eclampsia, it was noted to be in remission during her pregnancy. Pre-eclampsia was diagnosed at 22 weeks with delivery at 23 weeks of stillborn fetus. Fetal autopsy revealed coarctation of the aorta and no inflammation of visceral tissues. *Borrelia burgdorferi* was identified once again via immunofluorescence in the setting of negative maternal serology [6].

While a direct correlation between pre-eclampsia and infection with *Borrelia* cannot be made from these case reports, it could warrant further investigation, since in these cases reports preeclampsia developed significantly earlier than it typically presents.

Sudden Infant Death Syndrome

Sudden infant death syndrome (**SIDS**) is the sudden death of an infant less than 1 year of age that cannot be explained after a thorough investigation has been conducted [7]. It has been established that congenital syphilis is a cause of death in infants, and that diagnosis can be problematic as more than half of infants are asymptomatic and signs in symptomatic infants may be subtle and nonspecific [8,9] It has additionally been suggested that some cases of sudden infant death syndrome could also be associated with subclinical neonatal Borreliosis which were acquired in utero [6].

A retrospective study of ten cases of sudden infant death syndrome were reviewed in an endemic region of the United States. Forensic pathology (including detailed autopsy, routine histology, and toxicology studies), failed to identify the cause of infant death. Sections of the heart,

brain, kidney and liver were prepared with War thin starry silver impregnation. Two of the ten cases showed spirochetes consistent with *Borrelia burgdorferi* in the brain tissue of infants who experienced sudden death at four months [6].

Prevention

The prevention of acute infection with *Borrelia* in the obstetrical population is the same as in the general population. Prevention education is particularly important for women considering pregnancy who reside in areas that are known to be endemic. The United States Centers for Disease control and Prevention maintain that safeguards can be optimized through the use of insect repellent with 20-30% DEET, performing thorough tick examinations after outdoor activities, as well as showering as soon as possible after tick exposure [34]. Obstetrical patients should be reassured that no adverse effects have been documented with the use of 20-30% DEET insect repellents [35].

Treatment and Surveillance

While it is prudent to initiate serological testing as soon as possible in an obstetrical patient that has signs or symptoms associated with acute *Borrelia* infection, initiation of treatment should not be delayed while awaiting results, since an intrauterine death is possible following infection [36]. This is additionally important given the lack of sero-positivity previously documented in women who have delivered infants positive for Borreliosis.

Treatment in the obstetrical population should additionally be guided by the stage of infection that is clinically evident. It is appropriate to treat women with stage I disease with oral antibiotics, however, stages II and III require intravenous antibiotic administration. The United States Centers for Disease Control currently recommend a twenty one day course of antibiotic therapy for obstetrical patients with suspected *Borrelia* infection [34]. Doxycycline, which is routinely used in the treated of borreliosis is contraindicated in the obstetrical population. The standard antibiotic treatment is Amoxicillin 500mg three times daily or Cefuroimeaxetil 500mg twice daily for women who have an allergy to penicillin [34].

Other publications have suggested Amoxicillin 1g, but only for fourteen days duration [36]. Other appropriate oral regimens include both Roxithromycin 300mg daily or Clarithromycin 250mg twice daily, both for a total of twenty one days [36]. For patients that are diagnosed with stages II or III of infection, we suggest treatment with intravenous antibiotics in the form of Ceftriaxone 2-4g daily, or Penicillin G 5 million units four times a day for fourteen to twenty one days duration [36]. It is important to stress to obstetrical patients, who may understandably be concerned about the possibility of adverse outcomes due to conflicting information, that termination of pregnancy is not considered warranted, and should not be offered to the patient by the provider [36]. The United States Centers for Disease Control and Prevention maintain that no life threatening effects on a fetus have been found in cases in which a mother has been appropriately treated in the setting of acute infection with *Borrelia* [34].

Post-Partum Considerations

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 tissues and within umbilical cord blood [31]. The pediatric team caring for the newborn infant should additionally be informed, in order to test infant serology for evidence of disease, which would therefore prompt treatment in the infant. As previously described, negative serology in the infant does not necessarily rule out the risk of congenital infection, since the majority of infants will indeed screen negative. Therefore, final pathology of the placenta, cultures, immunohistochemistry, and indirect immunofluorescence may be additionally useful in confirming *Borrelia* infection.

The decision to breast feed in the setting of acute infection is a discussion that should be between the patient and her practitioners. Patients should be informed that studies have isolated *Borrelia* DNA via polymerase chain reaction from breast milk of mothers who are acutely infected. It furthermore is unclear if the DNA which has been isolated represents infant spirochetes, which could potentially cause a new infection [37]. However, since there has yet to be a diagnosis of *Borrelia* infection obtained from breast milk in an infant, there is only a relative contraindication to breast feeding [31,37].

CONCLUSION

Syphilis and Lyme borreliosis have similar epidemiologic, etiologic, and clinical manifestations. They are both considered multi systemic infectious diseases that are seen on a global scale. The taxonomical relationship between *Treponema* and *Borrelia* likely explains the congenital malformations that are implicated in Borreliosis, and are already well known to be caused by syphilis [3]. Transmission of *Borrelia* infection occurs via both zoonotic vectors and other humans. Congenital transfer is an established fact, and animal data in conjugation with other data support that sexual transfer also can occur [38]. 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 [38].

The most extensive review of literature had been previously conducted by Dr. Tess Gardner, who examined greater than 260 cases of possible congenital *Borreliosis*, and stressed the potential adverse outcomes from 66 of those cases. It had been stressed that although congenital infection with Borreliosis is rare, infection in utero may result in severe adverse outcomes, including possible neurological symptoms in twenty percent of infants [27].

Over the past 4 decades there has been considerable discussion regarding congenital *Borrelia* infection, and adverse fetal outcomes including fetal death and congenital anomalies. While there have been multiple case reports, case series, epidemiological studies, and histological studies, the definitive effects of congenital *Borrelia* remains uncertain. No studies to date have proven the causal relationship between *Borrelia* infection and adverse outcomes by delivery [3].

There are several points, which are evident from the review of 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* [6].

Given the significant potential for adverse pregnancy outcomes, any time an 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. Additional ultrasound surveillance is warranted in the setting of an acute infection during pregnancy, as it is in the setting of acute infection with *Treponema*. Evidence of congenital spirochete infection includes ascites, hepatosplenomegaly, and fetal anemia evidence by elevated middle cerebral artery Doppler studies, non-immune hydrops, as well as placental thickening [39]. Furthermore, if infection has occurred within the early first trimester of pregnancy during cardiac organogenesis, it is not unreasonable to obtain a fetal echocardiogram between twenty to twenty two weeks gestation [40].

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