Maternal Lyme borreliosis and Pregnancy Outcome

András Lakos, M.D., PhD. Norbert Solymosi D.V.M.

The Center for Tick-borne Diseases, Budapest, Hungary;

and

Adaptation to Climate Change Research Group, Hungarian Academy of Sciences,

Budapest, Hungary

International Journal of Infectious Diseases 2010;14:494-498

doi: 10.1016/j.ijid.2009.07.019

PMID: 19926325

Abstract

Objective: There is disagreement regarding whether Lyme borreliosis is associated with adverse pregnancy outcome.

Methods: We performed a review of data from 95 women with Lyme borreliosis during pregnancy evaluated at the Center for Tick-borne Diseases, Budapest, over the past 22 years.

Results: Treatment was administered parenterally to 66 (69.5%) women and orally to 19 (20.0%). Infection remained untreated in 10 (10.5%) pregnancies. Adverse outcomes were seen in 8/66 (12.1%), 6/19 (31.6%), 6/10 (60.0%), of the parenterally, orally treated and untreated women, respectively. In comparison to patients treated with antibiotics, untreated women had a significantly higher risk of adverse pregnancy outcomes (OR: 7.61, p=0.004). While mothers treated orally comparing to iv. treatment had an increased chance (OR: 3.35) to have an adverse outcome, this difference was not statistically significant (p=0.052). Erythema migrans did not resolve by the time of finishing the first antibiotic course in 17 patients. Adverse pregnancy outcome was more frequent among these “slow responder” mothers (OR: 2.69) but it was not statistically significant (p=0.1425). Loss of the pregnancy (N=7) and cavernous hemangioma (N=4) were the most prevalent adverse outcomes in our series. The other complications were heterogeneous.

Conclusion: Our results indicate that untreated maternal Borrelia burgdorferi s.l. infection may be associated with adverse outcomes, although the bacterial invasion of the foetus can not be proven. Characteristic and regular ‘congenital Lyme disease’ similar to the Hutchinson’ triad in syphilis seems to be unlikely.

Key words

Lyme disease, Borrelia burgdorferi sl. infection, pregnancy outcome, pregnancy loss

Introduction

Lyme borreliosis is the most frequent vector-borne illness in the temperate zone of the northern hemisphere. Early publications suggested that like syphilis, maternal Borrelia burgdorferi s.l. infection may seriously influence the outcome of pregnancy. Stillbirth and congenital heart abnormalities have been described.[1-4] With the exception of some publications,[5,6] most early case reports have described patients with adverse outcomes following their pregnancies. Incidence and cross sectional studies on populations of one to five thousand pregnant women and/or their offspring hardly found a case of Lyme borreliosis and, therefore, remained inconclusive with respect to risk for adverse pregnancy outcomes.[7-11] Epidemiological evaluation of treated and untreated patients is also complicated by the low rate of untreated cases present and identified in most populations.[12] Almost every patient in the largest study to date on gestational Lyme borreliosis was treated with ceftriaxone.[4] Many years ago, analysis of our recorded data suggested that untreated Lyme patients had a much greater chance of suffering an adverse outcome in pregnancy, but the number of the patients was too low to achieve meaningful results.[13]

The Center for Tick-borne Diseases, Budapest was opened in 1986 under the leadership of one of the authors (AL). Since then, 8149 erythema migrans (EM) patients were seen, including 97 cases in which Borrelia burgdorferi s.l. infection was clinically evident during pregnancy. Here we report our experience with these cases.

Methods

Patients

From the 97 registered cases of gestational Lyme disease, we were able to analyze 95 cases. Two women were lost to follow up before delivery. All women were seen by the same examiner (AL). The following criteria for inclusion were used:

1- EM rash as defined by the CDC[14] and EUCALB[15] criteria during pregnancy (N=72).

2- Patients were also included if they visited the Center after delivery with EM which commenced before or during pregnancy (N=17), in many of them the inflammation had already resolved at the first visit to the Center (N=12). The condition of the inclusion for these latter patients was a definitive description of the EM made by the family doctor or another institute.

3- Women with clinically diagnosed acrodermatitis chronica atrophicans (ACA) that still had signs of inflammation[15] after delivery which had commenced before or during the pregnancy (N=3).

4- Patients with facial palsy beginning during pregnancy with preceding EM or with presence of intrathecal Borrelia antibody production[16] (N=3).

In cases when a patient had Lyme borreliosis (EM) twice, and both illnesses coincided with two separate pregnancies, only the first pregnancy was included. If a patient presented the active clinical symptoms of late Lyme borreliosis (e.g. ACA) and during this period of the untreated infection more pregnancies occurred, only the first pregnancy was enrolled. Twin pregnancy only concerned a single event. Seventy-nine offspring were examined by one of the authors, a pediatrician who specialized for infectious diseases (AL), and if not, a medical report registered by the family pediatrician was also accepted.

The onset of the first clinical symptom (starting point) and the first day of the antibiotic treatment (end point) were used to calculate the length of the Borrelia infection during pregnancy.

Mothers were asked to report any later problem of their offspring with a suspicion of congenital origin.

Treatment

Some patients remained untreated (N=10). We prefer parenteral antibiotic treatment for pregnant woman with Lyme borreliosis. While we initially used Penicillin iv. 2x10MU (N=9), ceftriaxone iv. 2 g per day was used for the past 17 years (N=57). The length of therapy for both antibiotics was 15 days. Oral treatment was applied in 19 patients; nine of them visited our Center after delivery. The other ten mothers did not show clinical evidence of an ongoing infection after at least 20 days course of oral treatment had been concluded by the time of the visit.

If EM had not resolved by the time an antibiotic course was concluded, then another antibiotic was prescribed. These 17 women were considered as “slow responders”.

Since some patients were treated with more than one antibiotic, if any of these were parenterally administered, then the patient was considered as a case of parenteral treatment for statistical evaluation.

Serology

Every mother and 85 offspring were tested for Lyme borreliosis with a home-made immunoblot using Borrelia afzelii (ACA1) as an antigen[17] at the time of the first visit. The specificity of our test was 99% in infants, 97% in healthy blood donors and 92% in 'problem samples'. The sensitivity of the test was 48% in EM, 75% in lymphocytic meningoradiculitis and 100% in the ACA and arthritis group.[18]

Statistics

The statistical analyses were performed using R statistical software.[19] For comparison of proportions Fisher's exact was used. The association of the outcomes and treatment type was quantified by logistic regression. The p-values are two-tailed.

Results

We registered 23 adverse outcomes in 20 (21.1%) of the 95 offspring; these are listed in Table 1. The frequency of cavernous hemangioma was higher in our study population than expected as compared to the average frequency in Hungary.[20,21] Three of the four patients with hemangioma were treated parenterally and one remained untreated. The latter patient presented with a single hemangioma of the skin complicated with hypospadias. Another offspring of a treated (slow responder) mother showed multiple hemangiomas of the skin. The third patient presented with a nevus flammeus covered almost half of the face. The fourth patient had multiple skin hemangiomas complicated with liver hemangiomas detected by ultrasound examination. Dysplasia coxae in our series is also more frequent than the average incidence in Hungary. Both mothers having children with this outcome were treated with iv. ceftriaxone, one of them was a slow responder. Another slow responder mother delivered a newborn whose left fore-foot was shorter by 2 cm than the right at birth. An x-ray examination discovered later that half of the L 5 vertebra was missing. In our population, spontaneous abortion is less frequent than the average in Hungary. Other complications either do not differ statistically, or the low number of cases does not permit statistical calculation (Table 1).

Table 1. Adverse outcomes in 20 pregnancies

Adverse outcome	Number of cases - frequency % (CI)		Start of infection in pregnancy weeks (average)	Average incidence in Hungary - % (CI) *(19,20)*
Spontaneous abortion	6	6.3 (2.4 - 13.2)	1-5 (2)	14.8 (14.1-15.6)*
Stillbirth	1	1.1 (0.0 - 5.7)	5	0.51 (0.48-0.55)*
Premature birth	1	1.1 (0.0 – 5.7)	17	8.2-9.8**
Small for dates	1	1.1 (0.0 - 5.7)	13	NA
Cavernous hemangioma	4	4.2 (1.2 – 10.4)	13-27 (21)	0.11 (0.08-0.14)**
Neonatal jaundice required exchange transfusion	2#	2.1 (0.3 - 7.4)	13-38 (25)	NA
Dysplasia coxae	2	2.1 (0.3 - 7.4)	18; before conception	0.21 (0.15-0.27)**
Pyloric stenosis	1¶	1.1 (0.0 - 5.7)	before conception	0.02 (0.02-0.03)**
Papulovesicular eruption at birth	1	1.1 (0.0 - 5.7)	38	NA
Cerebral bleeding	1	1.1 (0.0 - 5.7)	4	NA
Muscular hypotonicity	1	1.1 (0.0 - 5.7)	4	NA
Hypospadias	1§	1.1 (0.0 - 5.7)	27	0.21 (0.20-0.23)**
Skeletal anomaly	1	1.1 (0.0 - 5.7)	13	NA

CI: 95 % confidence interval
NA= not available
Some infants were born with multiple anomalies: #One of these newborns also presented with dysplasia coxae. ¶This newborn also had dysplasia coxae. §This complication was accompanied by cavernous hemangioma.
* Data are from 1996-2006[20]
** Data are from 1986-2006.[21]

We have seen one untreated patient whose pregnancy resulted in stillbirth happened in the 5 months gestation. Her 1st visit was four days later, when a 30 cm EM rash was still visible. Two cases of neonatal jaundice required exchange transfusion were observed. One of their mothers was treated with 4x125 mg erythromycin for 30 days but her EM persisted for another 30 days after completion this treatment (slow responder). This mother visited our center only after delivery. The other mother received ceftriaxone treatment. We have seen one newborn with papulovesicular dermatitis which persisted for 1 month. The first visit of his mother was 2 weeks following the delivery. The untreated mother still had an EM rash at that time. In another woman, who visited our Center after delivery, EM was treated with erythromycin 4x125mg for 8 days but it continued to persist for 36 days following completion (slow responder). Her newborn suffered cerebral bleeding. Mental and physical development was delayed. Pyloric stenosis developed in an infant born to a mother treated with ceftriaxone. This case was complicated with dysplasia coxae. One newborn was delivered at the 35th

week; her mother was treated with oral cefuroxim. Another newborn was small for dates (2200g at 39 weeks). Her mother was treated with ceftriaxone.

Adverse outcomes were seen in 8/66 (12.1%), 6/19 (31.6%), 6/10 (60.0%) of the parenterally, orally treated and untreated women, respectively. Untreated (and also the slow responder) patients had a higher likelihood to have an adverse pregnancy outcome when compared with treated patients (Table 2). While mothers treated orally had an increased chance to have an adverse outcome, this difference was not statistically significant.

Six of the 20 women with adverse outcomes had been untreated. The most frequent reason for this was that some patients had not paid attention to their symptoms, or those family doctors or obstetricians had not recognized the erythema migrans. Four of the ten pregnancies where the mothers remained untreated resulted in a favorable outcome. The infection in three of these mothers with ACA had been started years before the conception and remained unrecognized and untreated during the whole period of pregnancy. Their acrodermatitis was still inflamed at their first visit following delivery, indicating that their infection was still active at that time. One patient was worried about the antibiotic treatment and therefore rejected it. She lost her fetus 56 days later in the 13th week of the pregnancy.

Table 2. Association between the treatment and the pregnancy outcome in maternal Lyme borreliosis

	Adverse outcome	**Healthy newborn**	**OR (95% CI)**		**P**
Untreated / treated	6 / 14	4 / 71	7.61	(1.90 - 30.51)	0.004
Untreated / orally treated	6 / 6	4 / 13	3.25	(0.66 – 15.98)	0.14
Untreated / parenterally treated	6 / 8	4 / 58	10.87	(2.51 - 47.08)	0.001
Orally / Parenterally treated	6 / 8	13 / 58	3.35	(0.99 - 11.31)	0.052

CI: 95 % confidence interval

A smaller (postnatal presentation) group (N=20 - 21.1%, 3 ACA and 17 EM) first visited our Center after delivery, presenting with clinical signs of active Borrelia infection in eight of them. The inflammation had already resolved at the first visit in the remaining 12, but these patients had definitive description of the EM made by the family doctor or another institute.

Adverse birth outcome was more frequent (7 out of 20—35.0%) in the postnatal presentation group compared to those seen during their pregnancy (13 out of 75 pregnancies—17.3%), but this difference was not statistically significant (OR: 2.01, 95% CI: 0.60-6.32, p=0.24). We analyzed the data for prenatal and postnatal presentation groups separately, due to the potential for bias (Table 3).

Table 3. Pregnancy outcome and clinical symptoms of Lyme borreliosis analyzed separately concerning the time of the initial visit.

	All patients (n=95)			
	Pregnancy loss	**Other adverse outcome**	**Healthy neonate**	**Total**
Therapy	*P=0.001079*			
No	3 (30.0%)	3 (30.0%)	4 (40.0%)	10
Oral	3 (15.8%)	3 (15.8%)	13 (68.4%)	19
Parenteral	1 (1.5%)	7 (10.6%)	58 (87.9%)	66
Clinical symptom	P=1			
ACA	0 (0.0%)	0 (0.0%)	3 (100%)	3
EM	7 (7.9%)	13 (14.6%)	69 (77.5%)	89
FP	0 (0.0%)	0 (0.0%)	3 (100%)	3

	Patients visiting during pregnancy (n=75)			
	Pregnancy loss	**Other adverse outcome**	**Healthy neonate**	**Total**
Therapy	*P=0.001399*			
No	1 (100%)	0 (0.0%)	0 (0.0%)	1
Oral	3 (30.0%)	1 (10.0%)	6 (60.0%)	10
Parenteral	1 (1.6%)	7 (10.9%)	56 (87.5%)	64
Clinical symptom	P=1			
ACA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0
EM	5 (6.9%)	8 (11.1%)	59 (81.9%)	72
FP	0 (0.0%)	0 (0.0%)	3 (100%)	3

	Patients visiting after delivery (n=20)			
	Pregnancy loss	**Other adverse outcome**	**Healthy neonate**	**Total**
Therapy	P=0.5319			
No	2 (22.2%)	3 (33.3%)	4 (44.4%)	9
Oral	0 (0.0%)	2 (22.2%)	7 (77.8%)	9
Parenteral	0 (0.0%)	0 (0.0%)	2 (100%)	2
Clinical symptom	P=0.6579			
ACA	0 (0.0%)	0 (0.0%)	3 (100%)	3
EM	2 (11.8%)	5 (29.4%)	10 (58.8%)	17
FP	0 (0.0%)	0 (0.0%)	0 (0.0%)	0

ACA= acrodermatitis chronica atrophicans, EM=erythema migrans, FP=facial palsy.

The interval during which the mother was infected in the pregnancy varied widely (0-280 days, average 33.01 days, —SD: 54.59). We observed no relationship between the length of infection during pregnancy and adverse pregnancy outcomes (OR: 1.00, p=0.953).

There was no statistically significant difference in the general state of health between the treated and the untreated mothers. All untreated mothers with an adverse pregnancy outcome were regularly checked by their obstetricians. Only one of the mothers with spontaneous abortion had a history of a similar episode. None of the patients used illicit drugs, smoked cigarettes or regularly drank alcohol during their pregnancies. All were Caucasian. The average age of the women was 29.7 (SD: 4.3) years. Forty-five (47.4%) women had university degree. Fifty-nine mothers (62.1%) recognized tick bite, and 49 (51.6%) were serologically positive for Borrelia antibody at the first visit our Center. All ACA patients revealed an extremely strong reaction in borrelia immunoblot. Neither the age nor the educational status of the women nor the serological result and the recognition of a tick bite correlated with the outcome of the pregnancy.

Pregnancy loss most often occurred when the infection was acquired in the first weeks of the pregnancy. Five of the pregnancy losses happened in the 8^{th} week of the gestation, one in the 13^{th} week and one stillbirth (22^{nd} week) occurred amongst our

patients (Table 4). We have no information of any morphological exams done on these pregnancy losses.

Table 4. Pregnancy outcome as a function of the time of appearance of Lyme borreliosis

Pregnancy outcome	Start of infection before pregnancy (no. of patients)	Start of infection during pregnancy (trimester – no. of patients)			Total
		I	II	III	
Pregnancy loss	1	5	1	0	7
Other adverse outcome	1	1	7	4	13
Healthy newborn	7	24	21	23	75
Total	**9**	**30**	**29**	**27**	**95**

Our patients come to us from all over Hungary. There was no opportunity to make PCR or culture attempts on the placentas or on the fetuses. Borrelia immunoblot from the cord blood was performed on 74 patients, including seven cases with adverse outcomes. None of the tested newborns showed IgM reaction. Moreover, we were unable to detect Borrelia burgdorferi IgM antibodies in neither 6 infants with congenital anomalies (four of them were born to mothers infected in late pregnancy) nor 17 healthy infants who were tested weeks or months after delivery. All newborns born to mothers who were IgG positive at delivery were IgG positive. The IgG reaction of the newborns mirrored the immunoblot pattern of their mothers suggesting that these antibodies were of maternal origin.

Discussion

We see 60-80% of the reported cases of Lyme borreliosis in Hungary, and probably a higher rate of pregnant women with Borrelia infection. Most of our patients were sent by their family doctors, obstetricians, dermatologists or physicians working at departments for infectious diseases.

Our findings demonstrate a statistically significant association between untreated Lyme borreliosis and adverse outcome of pregnancy. The association is also supported by that a similar (but statistically not significant) trend was found with slow responder mothers (whose EM has not resolved by the time of finishing the first course of antibiotic treatment) and adverse outcomes. Many controversial papers have been published (asserting a range of effects, from serious to no adverse effects on the offspring in maternal Lyme borreliosis) and we think that our study is sufficiently heterogeneous and large numbers of mothers were gathered for statistical evaluation.

Observational, retrospective studies have an inherent risk of bias in collecting and selecting patients. EM is a typical early sign of Lyme borreliosis, while ACA is a typical late form of Borrelia infection in Europe. Both dermatological involvements have characteristic inflammation which usually rapidly disappears during or shortly after treatment. In our study, in cases that remained untreated, patients' clinical symptoms were clearly described by other doctors or were still evident and diagnostic (i.e. EM or ACA) at the time of their first visit to our Center.

It may be possible that a selection bias exists in this study as women who had an adverse birth outcome may have been more likely to seek help at the clinic after delivering a baby. Because of obvious reasons, most of the untreated women (all but one, who ultimately rejected all treatment options) visited our Center only after

delivery. The association between the untreated Lyme borreliosis and first visit only after delivery was expected.

We could see no other differences than the application of antibiotic treatment in women with adverse pregnancy outcomes and with healthy offspring, but we can not rule out that other factors might be present to influence the destiny of the neonates. We should stress on that adverse pregnancy outcome is a combination of several perinatal and neonatal indicators with different degrees of severity.

It seems that a specific syndrome representing a 'congenital Lyme borreliosis' is unlikely. However, spontaneous abortion, stillbirth and preterm birth are frequently published in other studies[1,2,4] and also in our series. The miscarriage rate in our cohort is much lower than the average in Hungary. Pregnancy loss was significantly more frequent amongst untreated patients than among the parenterally treated women in our study population. We frequently observed hemangioma, a hitherto unpublished symptom coincidental with maternal Borrelia infection. In contrast, cardiac abnormalities were not found, these have been the most frequently published consequence of maternal Lyme borreliosis in other reports.[3,7,8,22] We found some of the symptoms mentioned in other papers, such as hyperbilirubinemia,[23] cerebral bleeding,[24] generalized rash[2] and congenital urologic malformations.[4,7] One of the infants in the present study had pyloric stenosis, and Strobino et al[7] have described a newborn with gastric reflux.

It is striking that of the three pregnancies where the mothers had late Lyme borreliosis (i.e. ACA) and in which the infection was acquired long before conception and remained untreated before and during the whole period of pregnancy, none resulted in any fetal or newborn harm. This observation is consonant with an animal study where Borrelia infection did not result in fetal death where mice were challenged weeks before

mating in comparison with 12% fetal death when the infection was introduced after mating.[25] Patients with late Lyme borreliosis, especially with ACA always produce strong antibody reaction against B. burgdorferi, while in most of EM patients usually have faint antibody titers.[18] The intensive immune response of ACA patients may play a role in preventing borrelia spread and transmission to the placenta or fetus.

Placentas and offspring were not tested for Borrelia by PCR and culture in our study. Therefore, it can not be concluded that the adverse outcome is a result of a Borrelia invasion of the fetus or placenta. The adverse outcome may be a consequence of the damage of the placenta or a maternal reaction to the infection. There are animal studies that have demonstrated maternal-fetal transmission[26] but others have supported the opposite conclusion.[25]

We preferred parenteral antibiotic treatment for Lyme borreliosis during pregnancy, following the suggestions by some papers that oral penicillin treatment was coincidental with intrauterine embryonic, fetal or newborn death.[2,24] During the last 17 years, intravenous ceftriaxone was preferred to treatment with oral amoxicillin in our practice. This is due to the pharmacokinetics of amoxicillin as compared to ceftriaxone. According to Andrew et al.[27] during pregnancy, amoxicillin has lower plasma concentrations and more rapid elimination than in the postpartum or non-pregnant situation. The pharmacokinetics of ceftriaxone, however, is not significantly influenced by pregnancy.[28] In addition, ceftriaxone in vitro is more effective against Borrelia than other beta-lactams.[29,30]

Our present data are not conclusive to support the superiority of high dose iv. penicillin or parenterally administered ceftriaxone over the oral antibiotic treatment, since we could not show statistically significant difference between the two groups. We had no chance to examine the placenta or fetus for direct borrelia invasion in the cases

of pregnancy loss, therefore the causal relation remains opened in spite of the statistical association. Similarly, we could not find IgM antibody reaction in the offspring in the other cases of adverse pregnancy outcome therefore our data suggest that these heterogeneous symptoms of newborns are not related to Borrelia invasion of the fetus. Ideally, a prospective, multicenter study would be conducted to enrol sufficient numbers of women in order to adequately address these research questions.

Acknowledgements

We are indebted to Michael Webb for revising the English of this manuscript and Gyöngyi Nagy for technical assistance and database management, Melinda Csáky-Szúnyogh and Gabriella Géczi for collecting the data of the average incidence of adverse pregnancy outcomes in Hungary.

None of the authors reported potential conflict of interest.

The study has not been supported financially by any source.

Ethics

This is a retrospective evaluation going back over 22 years; consequently, written informed consent has not been sought from the patients. All examination and intervention was a part of the routine clinical practice. The study was approved by the Expert Committee of the Hungarian Society for Infectious Diseases as a research ethics board.

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