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Maternal Lyme borreliosis and pregnancy outcome

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SUMMARY

Background: There is disagreement regarding whether Lyme borreliosis is associated with adverse pregnancy outcome.
Methods: We performed a review of the 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%). Infection remained untreated in 10 (10.5%) pregnancies. Adverse outcomes were seen in 8/66 (12.1%) parentally treated women, 6/19 (31.6%) orally treated women, and 6/10 (60%) untreated women. In comparison to patients treated with antibiotics, untreated women had a significantly higher risk of adverse pregnancy outcome (odds ratio (OR) 7.61, $p = 0.004$). While mothers treated orally had an increased chance (OR 3.35) of having an adverse outcome compared to those treated parenterally, this difference was not statistically significant ($p = 0.052$). Erythema migrans did not resolve by the end of the first antibiotic course in 17 patients. Adverse pregnancy outcome was more frequent among these 'slow responder' mothers (OR 2.69), but this 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 an untreated maternal *Borrelia burgdorferi* s.l. infection may be associated with an adverse outcome, although bacterial invasion of the fetus cannot be proven. It appears that a specific syndrome representing 'congenital Lyme borreliosis' is unlikely.

1. 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 1000–5000 pregnant women and/or their offspring found hardly any cases of Lyme borreliosis and, therefore, remained inconclusive with respect to risk for adverse pregnancy outcome.[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] In the largest study to date on gestational Lyme borreliosis, almost every patient 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 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 have been seen, including 97 cases in which *Borrelia burgdorferi* s.l. infection was clinically evident during pregnancy. Here we report our experience with these cases.

2. Methods

2.1. Patients

From the 97 registered cases of gestational Lyme disease, we were able to analyze 95. 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 during pregnancy, as defined by the Centers for Disease Control and Prevention (CDC)[14] and the European Union Concerted Action on Lyme Borreliosis (EUCALB)[15] criteria ($n = 72$). (2) Patients were

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included if they visited the center after delivery, with EM that had commenced before or during pregnancy ($n = 17$); in many of them the inflammation had already resolved at the time of the first visit to the center ($n = 12$). The condition for the inclusion of these latter patients was a definitive description of the EM made by the family doctor or another institute. (3) Those with clinically diagnosed acrodermatitis chronica atrophicans (ACA), with signs of inflammation still present[15] after delivery, which had commenced before or during the pregnancy ($n = 3$) were included. (4) Patients with facial palsy beginning during pregnancy with preceding EM or with the presence of intrathecal Borrelia antibody production[16] ($n = 3$) were also included.

In cases where 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 included. Twin pregnancy only concerned a single event. Seventy-nine offspring were examined by one of the authors, a pediatrician who specializes in 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 in their offspring of suspected congenital origin.

2.2. Treatment

Some patients remained untreated ($n = 10$). At our center, parenteral antibiotic treatment for pregnant woman with Lyme borreliosis is preferred. While we initially used penicillin IV 2×10 MU ($n = 9$), ceftriaxone IV 2 g per day was used for the last 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 10 mothers did not show clinical evidence of an ongoing infection after a course of oral treatment of at least 20 days had been concluded by the time of the visit.

If EM had not resolved by the time an antibiotic course was completed, then another antibiotic was prescribed. Further antibiotics were prescribed for 17 women; these women were considered '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 the statistical evaluation.

2.3. Serology

Every mother and 85 offspring were tested for Lyme borreliosis at the time of the first visit, with a homemade immunoblot using *Borrelia afzelii* (ACA1) as an antigen.[17] 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]

2.4. Statistics

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

3. 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 the adverse outcome of 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 covering almost half of the face. The fourth patient had multiple skin hemangiomas complicated with liver hemangiomas detected by ultrasound examination. In our series, dysplasia coxae was also more frequent than the average incidence in Hungary. Both mothers having children with this outcome were treated with IV ceftriaxone and 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 later showed that half of the L 5 vertebra was missing .

Table 1
Adverse outcomes in 20 pregnancies

Adverse outcome	No. of cases	Frequency, % (95% CI)	Start of infection in pregnancy weeks (average)	Average incidence in Hungary, % (95% CI)[19,20]
Spontaneous abortion	6	6.3 (2.4–13.2)	1–5 (2)	14.8 (14.1–15.6)[d]
Stillbirth	1	1.1 (0.0–5.7)	5	0.51 (0.48–0.55)[d]
Premature birth	1	1.1 (0.0–5.7)	17	8.2–9.8[e]
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)[e]
Neonatal jaundice requiring exchange transfusion	2[a]	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)[e]
Pyloric stenosis	1[b]	1.1 (0.0–5.7)	Before conception	0.02 (0.02–0.03)[e]
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[c]	1.1 (0.0–5.7)	27	0.21 (0.20–0.23)[e]
Skeletal anomaly	1	1.1 (0.0–5.7)	13	NA

CI, confidence interval; NA, not available.
[a] One of these newborns also presented with dysplasia coxae.
[b] This newborn also had dysplasia coxae.
[c] This complication was accompanied by cavernous hemangioma.
[d] Data are for 1996–2006.[20]
[e] Data are for 1986–2006.[21]

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

	Adverse outcome	Healthy newborn	OR (95% CI)	*P*
Untreated/treated	6/14	4/17	7.61 (1.90–30.51)	0.00419
Untreated/orally treated	6/6	4/13	3.25 (0.66–15.98)	0.14691
Untreated/parenterally treated	6/8	4/58	10.87 (2.51–47.08)	0.00141
Orally/parenterally treated	6/8	13/58	3.35 (0.99–11.31)	0.0518

OR, odds ratio; CI, confidence interval.

In our population, spontaneous abortion was less frequent than the average in Hungary. Other complications either did not differ statistically or the low number of cases did not permit statistical calculation (Table 1). We saw one untreated patient whose pregnancy resulted in stillbirth at 5 months of gestation. Her first visit was four days later, when a 30 cm EM rash was still visible. Two cases of neonatal jaundice requiring exchange transfusion were observed. One of the mothers was treated with 4×125 mg erythromycin for 30 days but her EM persisted for another 30 days after completion of this treatment (slow responder). This mother visited our center only after delivery. The other mother received ceftriaxone treatment. We saw one newborn with a papulovesicular dermatitis, which persisted for 1 month. His mother first visited the center 2 weeks following 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 4×125 mg for 8 days, but it persisted for a further 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 35 weeks of gestation; her mother was treated with oral cefuroxime. Another newborn was small for dates (2200 g at 39 weeks). Her mother was treated with ceftriaxone.

Adverse outcomes were seen in 8/66 (12.1%) women treated parenterally, 6/19 (31.6%) women treated orally, and 6/10 (60.0%) untreated women. Untreated patients had a higher likelihood of an adverse pregnancy outcome when compared with treated patients (Table 2). Slow responders ($n = 17$) showed higher chance (OR 2.69) to have an adverse outcome ($n = 5$, 29.4%) than the normal responders ($n = 68$ with 9 adverse outcomes, 13.2%) but it was not statistically significant ($p = 0.1425$). While mothers treated orally had an increased chance of adverse outcome compared to those treated parenterally, this difference was not statistically significant.

Six of the 20 women with adverse outcomes had not been treated. The most frequent reasons for this were that patients had not paid attention to their symptoms or that the family doctors or obstetricians had not recognized the EM. Four of the 10 pregnancies in mothers who remained untreated resulted in a favorable outcome. The infection in three of these mothers with ACA had started years before the conception and had remained unrecognized and untreated during the whole period of pregnancy. Their acrodermatitis was still inflamed at the first visit following delivery, indicating that the 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 week 13 of pregnancy.

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

Adverse birth outcome was more frequent (7/20 (35%)) in the postnatal presentation group compared to those seen during their pregnancy (13/75 pregnancies (17.3%)), but this difference was not statistically significant (odds ratio (OR) 2.01, 95% confidence interval 0.60–6.32, $p = 0.24$). We analyzed the data for the prenatal and postnatal presentation groups separately, due to the potential for bias (Table 3).

The interval over which the mother was infected during pregnancy varied widely (0–280 days, average 33.01 days, standard deviation (SD) 54.59 days). We observed no relationship between the length of infection during pregnancy and adverse pregnancy outcome (OR 1.00, $p = 0.953$).

There was no statistically significant difference in the general state of health between the treated and 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 a university degree. Fifty-nine mothers (62.1%) recognized a tick bite and 49 (51.6%) were serologically positive for Borrelia antibody at the first visit to our center. All ACA patients revealed an extremely strong reaction in Borrelia immunoblot. The age and educational status of the women, serological results, and recognition of a tick bite were not correlated with pregnancy outcome.

Pregnancy loss most often occurred when the infection was acquired in the first weeks of pregnancy. Five of the pregnancy

Table 3
Pregnancy outcome and clinical symptoms of Lyme borreliosis analyzed separately with regard to the time of the initial visit

	Pregnancy loss	Other adverse outcome	Healthy neonate	Total
All patients ($N = 95$)				
Therapy	$p = 0.001$			
No	3 (30%)	3 (30%)	4 (40%)	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%)	3 (100%)	3
EM	7 (7.9%)	13 (14.6%)	69 (77.5%)	89
FP	0 (0%)	0 (0%)	3 (100%)	3
Patients visiting during pregnancy ($n = 75$)				
Therapy	$p = 0.001$			
No	1 (100%)	0 (0%)	0 (0%)	1
Oral	3 (30%)	1 (10%)	6 (60%)	10
Parenteral	1 (1.6%)	7 (10.9%)	56 (87.5%)	64
Clinical symptom	$p = 1$			
ACA	0 (0%)	0 (0%)	0 (0%)	0
EM	5 (6.9%)	8 (11.1%)	59 (81.9%)	72
FP	0 (0%)	0 (0%)	3 (100%)	3
Patients visiting after delivery ($n = 20$)				
Therapy	$p = 0.531$			
No	2 (22.2%)	3 (33.3%)	4 (44.4%)	9
Oral	0 (0%)	2 (22.2%)	7 (77.8%)	9
Parenteral	0 (0%)	0 (0%)	2 (100%)	2
Clinical symptom	$p = 0.657$			
ACA	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

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

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)	Trimester in which the infection started during pregnancy, 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

losses occurred in the 8th week of gestation and one in the 13th week; one stillbirth (at 22 weeks) occurred amongst our patients (Table 4). We have no information regarding any morphological exams done on these pregnancy losses.

Our patients come to us from all over Hungary. There was no opportunity for PCR or culture attempts on the placentas or on the fetuses. Borrelia immunoblot from the cord blood was performed for 74 patients, including seven cases with adverse outcomes. None of the tested newborns showed an IgM reaction. Moreover, we were unable to detect *Borrelia burgdorferi* IgM antibodies in any of the six infants with congenital anomalies (four of them were born to mothers infected in late pregnancy) or in 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.

4. Discussion

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

Our findings demonstrate a statistically significant association between untreated Lyme borreliosis and adverse pregnancy outcome. The association is also supported by the fact that a similar, though statistically non-significant, trend was found with slow responder mothers (those whose EM had not resolved by the time of first course antibiotic completion) 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. We think that our study is sufficiently heterogeneous and with a large number of mothers 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, the patient's 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. For 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 those with healthy offspring, but we cannot rule out that other factors present might have influenced neonatal outcome. We should stress that adverse pregnancy outcome is a combination of several perinatal and neonatal indicators with different degrees of severity.

It appears that a specific syndrome representing 'congenital Lyme borreliosis' is unlikely. However, spontaneous abortion, stillbirth, and preterm birth have frequently been identified in other published studies[1,2,4] and were also found in our series. The miscarriage rate in our cohort is much lower than the average in Hungary. Pregnancy loss was significantly more frequent among 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 when mice were challenged weeks before mating in comparison with 12% fetal deaths when the infection was introduced after mating.[25] Patients with late Lyme borreliosis, especially with ACA, always produce a strong antibody reaction against *B. burgdorferi*, while most 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 or culture in our study. Therefore, it cannot be concluded that the adverse outcomes were a result of a Borrelia invasion of the fetus or placenta. The adverse outcome may have been a consequence of damage to the placenta or a maternal reaction to the infection. There are animal studies that have demonstrated maternal–fetal transmission,[26] but others have not supported this conclusion.[25]

At our center we prefer parenteral antibiotic treatment for Lyme borreliosis during pregnancy, due to suggestions in some papers that oral penicillin treatment is coincidental with intrauterine embryonic, fetal, or newborn death.[2,24] During the last 17 years, intravenous ceftriaxone has been 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] amoxicillin has lower plasma concentrations and more rapid elimination during pregnancy than in the postpartum or non-pregnant situation. The pharmacokinetics of ceftriaxone, however, are not significantly influenced by pregnancy[28]. In addition, ceftriaxone in vitro is more effective against Borrelia than other β-lactams.[29,30]

Our present data do not conclusively support the superiority of high dose IV penicillin or parenterally administered ceftriaxone over the oral antibiotic treatment, since we could not show a

statistically significant difference between the two groups. 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. Similarly, we could not find an 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 should be conducted, enrolling sufficient numbers of women, in order to adequately address these research questions.

Conflict of interest

None of the authors reports a potential conflict of interest. The study was not supported financially by any source.

Ethics

This is a retrospective evaluation going back over 22 years; consequently, written informed consent was not sought from the patients. All examinations and interventions were 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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