LYME BORRELIOSIS DURING PREGNANCY

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ABSTRACT

Background and Patients

One of the authors (AL) presented a poster on 34 pregnancies of maternal Lyme borreliosis (Lb) in 1995. It was striking that untreated Lb associated with higher probability of adverse outcome but the number of patients were small and the statistical power was low (1). We have recently published a paper on 95 maternal Lb and the outcome of their pregnancies (2). Since the closure of the database for that manuscript the number of the pregnant women with Borrelia infection observed in our Centre increased to 124, and the statistical analysis strengthened our previous doubtful observations and reached significant results in important aspects by now. This series is the largest study to date on this topic.

Results

Treatment was administered parenterally to 87 (70%) women and orally to 25 (20.0%). Infection remained untreated in 12 (10%) pregnancies. Adverse outcomes were seen in 7/87 (8%), 9/25 (36%), 8/12 (67%), 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: 11.62, p<0.001). Mothers treated orally comparing to iv. treatment had an increased chance (OR: 6.28) to have an adverse outcome (p=0.001). In the adverse pregnancy outcome, the most impressive difference was between the untreated and parenterally treated women (OR: 21.44, p<0.001). The probability of adverse outcome increased by the exposition time (from the first maternal symptom to the treatment or delivery). When the exposition time has reached four months, the probability of adverse outcome increased by 33%. We had no chance to examine the bacterial invasion of the foetus. Loss of the pregnancy (N=9), small for gestational age or preterm birth (N=7) were the most prevalent adverse outcomes in our series. The other complications were heterogeneous.

Conclusion

Our results indicate that untreated or orally treated maternal Borrelia burgdorferi s.l. infection is associated with adverse outcomes. ‘Congenital Lyme disease’ similar to the Hutchinson’s triad in syphilis is unlikely.

Adverse outcome	Number of cases - frequency %		Start of infection in pregnancy weeks (average)	Average incidence in Hungary - %
Spontaneous abortion	8	6.4	1-5 (2)	14.8*
Stillbirth	1	0.8	5	0.51*
Premature birth	3	2.4	17-28 (21)	8.2-9.8**
Small for dates (i.u. dystrophy)	4	3.2	13-37 (26)	NA
Cavernous hemangioma	3	2.4	13-27 (21)	0.11**
Neonatal jaundice required exchange transfusion	2	1.6	13-38 (25)	NA
Dysplasia coxae	2	1.6	before conception; 18	0.21**
Pyloric stenosis	2	1.6	before conception; 14	0.02**
Papulovesicular eruption at birth	1	0.8	38	NA
Cerebral bleeding	1	0.8	4	NA
Muscular hypotonicity	1	0.8	4	NA
Hypospadias	1	0.8	27	0.21**
Skeletal anomaly	1	0.8	13	NA
Ectopic kidney	1	0.8	24	0.09-0.12***

Table 1

Adverse outcome in 24 of the 124 pregnancies of maternal Lyme borreliosis

Some infants were born with multiple anomalies. NA=not available. * Data are from 1996-2006. ** Data are from 1986-2006. *** Data are from 1992 and 2002.

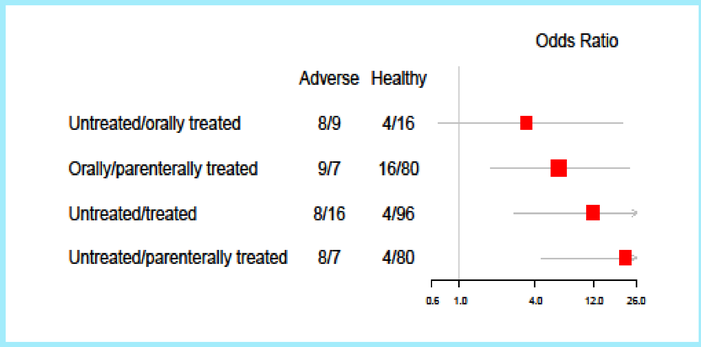

Figure 1.

Risk of adverse pregnancy outcome in various comparisons of treatment groups

The red boxes represent the odds ratio (OR), the horizontal grey line are the 95% confidence intervals of estimation. The vertical grey line means the OR=1, ie. there is no difference in the odds of the compared groups. If the confidence interval contains the value OR=1, then the estimation is not significant on the certain level (p<0.05). The size of the red boxes is proportional to the precision of estimation.

INTRODUCTION

Lb 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. With the exception of some publications, 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 Lb and, therefore, remained inconclusive with respect to risk for adverse pregnancy outcomes.

Epidemiological evaluation of treated and untreated patients is also complicated by the low rate of untreated cases present and identified in most populations. Almost every patient in the largest study until the present report on gestational Lb was treated with ceftriaxone. Many years ago, analysis of our recorded data suggested that untreated Lb 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.

The Center for Tick-borne Diseases, Budapest was opened in 1986 under the leadership of one of the authors (AL). Since then, almost 9000 erythema migrans (EM) patients were seen, including 124 cases in which Borrelia burgdorferi s.l. infection was clinically evident during pregnancy. Here we report our experience with these cases.

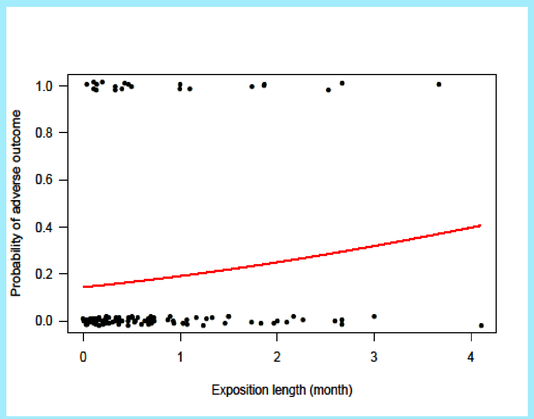

Figure 2

Probability of the adverse pregnancy outcome in maternal Lyme borreliosis and the Borrelia exposition length (month) of the fetus

The individual outcomes are represented as jittered dots around 0 (no adverse outcome) and 1 (adverse outcome).

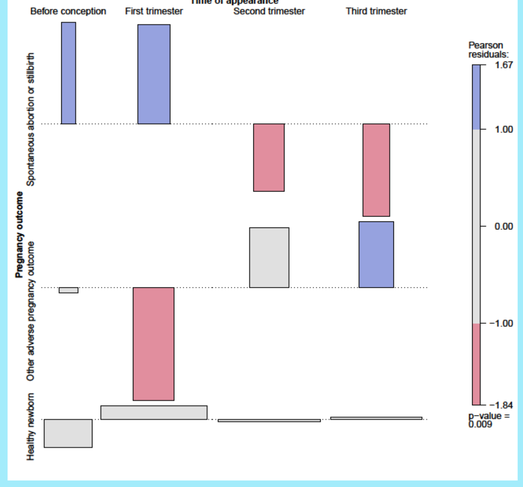

Figure 3

Association plot of pregnancy outcome and the time of appearance (trimester) of the symptom

The differences (Pearson's residuals) between the observed and expected frequencies of contingency table are presented with rectangles. Height and width of the bars are proportional to Pearson's residuals, and the expected counts, respectively. If the observed frequency of a cell is greater than the expected one, the box rises above the baseline, and falls below otherwise.

RESULTS

Almost every mothers showed the typical sign of Lb, i.e. erythema migrans. Three had acrodermatitis chronica atrophicans and four had facial palsy with intrathecal antibody production (3). We registered 31 adverse outcomes in 24 (19.3%) of the 124 offspring; these are listed in Table 1.

Treatment was administered parenterally to 87 (70%) women and orally to 25 (20.0%). Infection remained untreated in 12 (10%) pregnancies. Adverse outcomes were seen in 7/87 (8%), 9/25 (36%), 8/12 (67%), 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. Mothers treated orally comparing to iv. treatment had an increased chance to have an adverse outcome. In the adverse pregnancy outcome, the most impressive difference was between the untreated and parenterally treated women (Figure 1)

The probability of adverse outcome increased by the exposition time (from the first maternal symptom to the treatment or delivery). When the exposition time has reached four months, the probability of adverse outcome increased by 33% (Figure 2).

There was a higher risk of pregnancy loss if the infection was shortly before or after the conception, while other complication were more frequent when the infection happened during later in the pregnancy (Figure 3).

We had no chance to examine the bacterial invasion of the foetus.

CONCLUSION

Our findings demonstrate a statistically significant association between untreated Lyme borreliosis and adverse outcome of pregnancy. Many controversial papers have been published and we think that our study is the first in which sufficiently heterogeneous and large numbers of mothers were gathered for statistical evaluation.

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 and also in our series. Pregnancy loss was significantly more frequent amongst untreated patients than among the parenterally treated women in our study population.

During the last 18 years, intravenous ceftriaxone was preferred to treatment with oral amoxicillin in our practice. 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. In addition, ceftriaxone in vitro is more effective against Borrelia than other beta-lactams.

Our present data are definitively support the superiority of high dose iv. penicillin or parenterally administered ceftriaxone over the oral antibiotic treatment. 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.

Acknowledgements

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