Treatment of Erythema Migrans in Pregnancy

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The course of the illness and the outcome of pregnancy were investigated in a prospective study of 58 consecutively enrolled pregnant women with typical erythema migrans at the University Medical Centre of Ljubljana, Slovenia. Thirteen patients (22.4%) acquired borrelial infection in the first trimester of pregnancy, 27 (46.6%) in the second trimester, and 18 (31%) in the third trimester. All patients were treated for 14 days: 2 (3.4%) with phenoxymethylpenicillin (1 million IU thrice per day), 3 (5.2%) with benzylpenicillin (10 million units twice per day), and 53 (91.4%) with ceftriaxone (2 g daily). For 51 of the 58 women (87.9%), the pregnancies were normal and the infants were born at term, were clinically healthy, and had normal psychomotor development. Of the remaining 7 pregnancies, 1 ended with a missed abortion and 5 with preterm birth; 1 of the preterm babies had heart abnormalities. One child born at term was found to have urologic abnormalities at 7 months of age. A causal relationship between borrelial infection and fetal adverse effects has not been proven, and for at least some cases a reasonable explanation (not associated with Lyme borreliosis) was found.

Lyme borreliosis is a multisystem infectious disease caused by *Borrelia burgdorferi sensu lato* and transmitted by *Ixodes* species ticks. The illness proceeds in stages, with various clinical manifestations. Erythema migrans (EM), the pathognomonic skin lesion of the early localized infection, usually appears within 1 month at the site of the entrance of the causative agent in the skin and may be accompanied by flulike symptoms. Within days or weeks spirochetes may spread hematogenously or lymphogenously from the skin to other organs, leading to early disseminated infection with dermatologic, neurological, cardiac, arthritic, or musculoskeletal symptoms. Late infection may evolve a year or more after initial infection, with chronic manifestations involving the skin, joints, and nervous system [1, 2].

During gestation *B. burgdorferi* may spread transplacentally to the fetus, causing adverse outcome of pregnancy, including various congenital abnormalities, premature birth, and even fetal death [3–11]. The frequency of fetal involvement in women who acquire EM during pregnancy has not been accurately assessed.

For the past 5 years our attention has been focused on the possible association between *B. burgdorferi* infection during gestation and eventual adverse outcome of pregnancy. Herein we present the mode of treatment of pregnant women with EM in Slovenia—where Lyme borreliosis is endemic [12]—and the outcome of their pregnancies.

Patients and Methods

At the Lyme Borreliosis Outpatients’ Clinic of the Department of Infectious Diseases at the University Medical Centre in Ljubljana, Slovenia, 58 pregnant women with typical EM were registered and investigated from 1990 through 1994. Each patient was seen by at least one of the authors of this report. For diagnosis of EM, the criteria of the Centers for Disease Control and Prevention were used [13]. In short, patients with a lesion that began as a red macule and papule and expanded over a period of days to weeks to form a round or oval lesion with a diameter of at least 5 cm (often with central clearing) were included in the study. The years of patients’ first visits were as follows: 2 patients, 1990; 9 patients, 1991; 15 patients, 1992; 16 patients, 1993; and 16 patients, 1994. Each patient provided a medical history and underwent a physical examination, assays for borrelial antibodies, and other laboratory tests; data were collected by means of questionnaires.

**Clinical evaluation.** Patients were examined prior to the initiation of antibiotic treatment and 2 weeks, 2 months, 6 months, 12 months, and 18 months after the institution of therapy. For patients seen for the first time in 1994 the follow-up was shorter, but only patients whose pregnancies were completed by June 1995 were included in the present report. At follow-up visits after delivery, babies were examined as well (by a pediatrician).

**Laboratory evaluation.** The erythrocyte sedimentation rate, blood cell counts, serum electrolyte concentrations, and serum immunoglobulin levels were determined and a urine examination and liver function tests were performed at the first visit and 2 weeks later (with the exception of serum immunoglobulin measurements).

**Serology.** An immunofluorescence assay without absorption [14] was used to determine titers of IgM and IgG antibodies against *B. burgdorferi* prior to therapy and 2 months, 6 months,
Table 1. Symptoms associated with erythema migrans in 58 pregnant women studied at the University Medical Centre of Ljubljana, Slovenia (1990–1994).

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>No. (%)</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>15 (25.8)</td>
<td></td>
</tr>
<tr>
<td>Local only</td>
<td>26 (44.8)</td>
<td></td>
</tr>
<tr>
<td>Systemic only</td>
<td>4 (6.9)</td>
<td></td>
</tr>
<tr>
<td>Local and systemic</td>
<td>13 (22.4)</td>
<td></td>
</tr>
<tr>
<td>Local and/or systemic</td>
<td>43 (74.1)</td>
<td></td>
</tr>
<tr>
<td><strong>Episodes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itching</td>
<td>36 (62.1)</td>
<td></td>
</tr>
<tr>
<td>Burning</td>
<td>7 (12.1)</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>6 (10.3)</td>
<td></td>
</tr>
<tr>
<td>Systemic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue, malaise</td>
<td>9 (15.5)</td>
<td></td>
</tr>
<tr>
<td>Headaches</td>
<td>8 (13.8)</td>
<td></td>
</tr>
<tr>
<td>Arthralgias</td>
<td>9 (15.5)</td>
<td></td>
</tr>
<tr>
<td>Myalgias</td>
<td>2 (3.4)</td>
<td></td>
</tr>
</tbody>
</table>

* No. of episodes (percentage of patients \( n = 58 \)).

12 months, and 18 months later. A local isolate of *Borrelia afzelii* was used as an antigen. Antibody titers of 1:256 or higher were considered positive. Serological tests for syphilis (Venereal Disease Research Laboratory; fluorescent treponemal antibody, absorbed; and *Treponema pallidum* hemagglutination) were also done at the first visit.

**Special procedures.** Electrocardiography was performed at the first visit.

**Treatment.** Patients received phenoxymethylpenicillin (1 million IU t.i.d. for 14 days), benzylpenicillin (10 million IU b.i.d. for 14 days) or ceftriaxone (2 g daily for 14 days).

**Results.**

The ages of the 58 pregnant women with typical EM who were examined in the study ranged from 17 years to 42 years (median, 27 years). All of their medical histories were negative for chronic diseases, but two of the investigated patients had previously had EM. Thirty-five patients (60.3%) recalled incurring a tick bite at the site of an EM lesion. The median interval from the tick bite to onset of EM was 7 days, and the median duration of EM prior to the first visit was 8 days. One patient had two skin lesions, but all other patients had a solitary EM lesion. The diameter of the skin lesions varied from 5 cm to 60 cm (median, 10 cm). Forty-three patients (74.1%) had local and/or mild constitutional symptoms (table 1).

Thirteen women (22.4%) were found to have EM during the first trimester of pregnancy; three of them had noticed the first signs of borrelial infection before they became pregnant (5 weeks, 2 weeks, and 1 week before pregnancy, respectively). On 27 patients (46.6%) the skin lesions appeared in the second trimester, and on 18 patients (31.0%) they appeared in the third trimester.

Two patients (3.4%), both registered in 1990, were treated with phenoxymethylpenicillin (1 million IU t.i.d. for 14 days). The first three patients (5.2%) seen in 1991 received benzylpenicillin (10 million IU b.i.d. for 14 days). The other 53 patients (91.4%) were given ceftriaxone (2 g daily for 14 days). Aside from a mild allergic reaction to ceftriaxone in one patient, no significant adverse effects of therapy were noted.

Laboratory test values and electrocardiographic tracings were within normal ranges, with the exception of the erythrocyte sedimentation rate, which was elevated for several patients and was attributed to pregnancy. Only six patients (10.3%) had elevated titers of antibody to *B. burgdorferi* at the first visit. Three patients (5.2%) had elevated IgM antibody titers (up to 1:256) only at the first visit; at later follow-up visits the titers were within normal ranges. Two patients (3.4%) had elevated IgG antibody titers at the first visit, and these remained elevated during the entire observational period. In one patient (1.7%) the titers of IgM and IgG were elevated and remained so during the follow-up period, with no clinical sequelae. Serological tests for syphilis were negative for all the pregnant women at the first visit.

EM disappeared completely within a range of 2–100 days (median, 11 days) following the institution of treatment. During follow-up none of the 58 patients had major manifestations of Lyme borreliosis, as defined according to the criteria of Steere et al. [15].

For 51 of the 58 women (87.9%), the pregnancies were normal and the infants were born at term, were found to be clinically healthy, and had normal psychomotor development. Of the remaining 7 pregnancies, 1 ended with a missed abortion and 5 with preterm birth; 1 of the preterm babies had heart abnormalities. One child born at term was found to have urologic abnormalities at 7 months of age.

Of the 5 babies (8.6%) who were born preterm (1 at 14 weeks, 2 at 4 weeks, and 2 at 3 weeks preterm), 2 had complications soon after birth. The mother of the infant who was born 14 weeks preterm had noticed a lesion a few days after a tick bite at 19 weeks’ gestation. She did not have any systemic symptoms. Treatment with ceftriaxone was instituted 6 days after the appearance of EM. At the time at which the patient detected the skin lesion, her obstetrician found an insufficient cervix uteri. A cerclage was planned, but the mother delayed the intervention and at 26 weeks’ gestation she gave birth to an 840-g girl. Three days later, respiratory distress syndrome developed in the baby. After 2 months of intensive care she was able to leave the hospital, and she had normal psychophysical development thereafter. Several months later the mother was found to have a uterus septus. In her second pregnancy, labor was induced at 23 weeks’ gestation because an anomaly of the fetus was found.
The mother of one of the two infants born 4 weeks preterm recalled a tick bite at 15 weeks’ gestation. EM appeared 4 weeks following the bite, and 1 week later she began treatment with ceftriaxone. The skin lesion, which was accompanied by mild local itching and arthralgias, disappeared in 4 days. The pregnancy was defined as risky because of an insufficient cervix uteri, and the mother was counseled to rest. At 36 weeks’ gestation she gave birth to a boy weighing 2,940 g, who had respiratory distress within 1 hour and was admitted to the intensive care unit. Wet lung was noted, and on the second day pneumothorax and atelectasis developed also. At the end of the first week of life a systolic murmur was heard, and an echocardiogram showed an atrial and ventricular septum defect. The infant was able to leave the intensive care unit after 2 weeks. His later development was normal.

The remaining 3 preterm infants, 1 born 4 weeks and 2 born 3 weeks prematurely, were healthy at birth and developed normally. One of the mothers reported myalgias and fatigue at the time of the occurrence of EM; the other two were asymptomatic. All of them were treated with ceftriaxone.

In one child, bilateral stenosis of the ureter with hydronephrosis was found at 7 months of age. The 28-year-old mother had noticed a lesion (30 × 15 cm) on her flap at 29 weeks’ gestation. She did not remember being bitten by a tick at this site and had no additional symptoms. Four days later her physician prescribed cefadroxil (500 mg t.i.d. for 14 days). Since the skin lesion persisted, she was then treated with ceftriaxone (2 g daily), but treatment was discontinued after 13 days because of an allergic reaction. The EM lesion disappeared completely 24 days after the institution of therapy with ceftriaxone (i.e., 2 days after delivery of the baby). A normal-appearing boy was born at term, but 7 months later he was found to have urologic abnormalities.

The only patient who had a missed abortion was a 28-year-old woman who became pregnant for the fourth time in 1993. Her first pregnancy ended with an abortion in the first trimester; at this time uterus bicornis was found. Later she gave birth to two healthy children. At 6 weeks into her fourth pregnancy she discovered a ringlike lesion (8 × 5 cm) on her leg, but she did not remember incurring an insect bite. During the same period she experienced mild transitory headaches, arthralgias, myalgias, and fatigue, similar to those experienced by the other three members of her family. At 7 weeks’ gestation treatment with ceftriaxone (for 14 days) was initiated. At 9 weeks’ gestation a missed abortion was noted. All laboratory test values were within normal ranges, and serological tests for B. burgdorferi and lues were negative.

**Discussion**

Particularly in the last several years, the possible association between the occurrence of Lyme borreliosis during pregnancy and an adverse outcome of pregnancy has received substantial public and medical attention. Like other spirochetal diseases occurring during gestation, Lyme borreliosis may be a potential cause of damage to or even death of the fetus [16]. In early, localized infection B. burgdorferi may spread hematogenously or lymphogenously from the affected skin and involve almost any organ system of the body [2, 15]. When spirochetaemia occurs during pregnancy, the placenta may be involved and the fetus infected. Transplacental transmission of B. burgdorferi has been well documented [3–9] and may result in various forms of fetal involvement. Knowledge regarding adverse fetal outcome for pregnant women infected with B. burgdorferi is rather limited and is based primarily on the findings described in individual case reports. Among the infants of untreated women who had symptoms and/or signs of Lyme borreliosis during pregnancy, researchers have noted cardiovascular malformations, prematurity, stillbirth, and neonatal rash [3, 5, 10].

The fact that outcome of pregnancy has been adverse not only for untreated women but also for patients treated with an oral antibiotic has caused additional concerns. In cases in which patients were treated for EM acquired during pregnancy, intraterine fetal death, neonatal death, syndactyly, hydrocephalus with spina bifida, and cortical blindness have been reported [6, 8, 10, 11]. Recently, cheilognathopalatoschisis, cavernous hemangioma, and dysplasia coxae have also been associated with borrelian infection during pregnancy [17]. However, in several reports, only a temporal connection between borrelian infection and fetal involvement was presented, and no causal relationship was ascertained. In addition, in some untreated and antibiotically treated patients, spirochetes were identified microscopically; in some cases spirochetes also were cultured from multiple organs of infants on autopsy and/or from placenta, with no evidence of inflammation in the affected tissues [3–9].

Such findings further complicate proper interpretation of the significance of borrelian infection in pregnancy for the outcome of gestation. No uniform pattern of malformations associated with maternal B. burgdorferi infection has been found, and no data on the frequency with which fetal involvement is associated with distinct clinical manifestations of Lyme borreliosis in pregnant women have become available. Without such data regarding untreated patients, recommendations for "proper" treatment are merely arbitrary and the efficacy of therapy is difficult to assess. Because it would be unethical not to treat patients with Lyme borreliosis with antibiotics, we are probably far from answering at least some of the basic questions mentioned previously.

Treatment with antibiotics has been shown to be effective during all stages of Lyme borreliosis, particularly in early, localized infection [18]. Which antibiotic is the most efficacious has not yet been established [15, 19–22], and failures have been reported with all antibiotic regimens used [22–30]. Although EM disappears spontaneously, treatment with antibiotics is important because it reduces the duration of the cutaneous lesions and usually prevents further progression of the disease [2, 15, 19–21, 23, 31–33]. For direct spirochetal
involvement of the fetus to occur during pregnancy, dissemination of borreliae from the EM lesion to the placenta and their crossing of the placenta to the fetus are essential mechanisms. However, we often are not able to determine whether the dissemination of borreliae from the skin lesion has taken place because (1) clinical symptoms of such dissemination are not characteristic and may be absent; (2) laboratory findings, as a rule, are normal or not distinctive; and (3) even B. burgdorferi antibody titers may be negative [34, 35].

The first clinical proof of such dissemination may manifest itself days to months later with secondary skin lesions or involvement of the nervous system, the heart, a joint, or another organ system or organ (i.e., only as a consequence of previous clinically indistinctive or silent dissemination of borreliae from the skin). The causative agent of Lyme borreliosis may also persist for a long time in the skin or other tissues of untreated and even antibiotically treated patients, with the potential for dissemination [22, 23, 26–30, 35, 36].

These data suggest that the usual treatment of EM with oral antibiotics may not be adequate for some patients. It seems important to treat at least some groups of patients with EM as effectively as possible: particular attention and concern must be devoted to pregnant women. The optimal mode of treatment during pregnancy has not yet been established, and recommendations have evolved over time. As orally administered penicillin did not seem to be sufficient to prevent fetal involvement, it was not recommended [6]. Procaine has to be avoided, and tetracyclines are contraindicated. The majority of physicians nowadays use oral antibiotics such as amoxicillin or cefuroxime only for the mildest cases of early, localized infection and give high doses of iv penicillin, cefotaxime, or ceftriaxone when signs or symptoms of disseminated infection with B. burgdorferi are present [18, 37–42].

Only two of our patients, both seen at the beginning of our study in 1990, received an oral antibiotic. At that time we thought that the data on fetal involvement in pregnant women with Lyme borreliosis were worrisome enough to justify prompt and aggressive treatment with iv antibiotics, as recommended by some authors then and later on [5, 37, 39, 43]. Thus, the remaining 56 patients (96.6%) were treated intravenously, the majority of them (53) with ceftriaxone. With the exception of an allergic reaction in one patient treated with ceftriaxone, no significant adverse effects of therapy were noticed.

Fifty-one of 58 pregnancies (87.9%) were normal and resulted in healthy, full-term babies. Five babies (8.6%) were born preterm, but no causal association between the premature birth and B. burgdorferi infection was affirmed. Three of these newborns were asymptomatic, while two had symptoms associated with their immaturity that appeared soon after birth. An obvious explanation for these two preterm births was that the mothers had a uterus septus and an insufficient cervix uteri, respectively. In the remaining three cases, no reason for prematurity was found. According to data from the Institute of Public Health of the Republic of Slovenia, the overall incidence of preterm births in the period of 1990–1994 was 10.3%, and 8.9% of premature births occurred between the 33rd and 37th week of gestation [44]. The theoretical possibility that preterm deliveries are a consequence of treatment with ceftriaxone seems quite remote for two reasons. First, the majority of our pregnant women received treatment with antibiotics weeks to months before preterm delivery; second, ceftriaxone is not known to induce preterm birth. For antibiotics used in the present study, no embryotoxic, teratogenic, or mutagenic effects have been reported [45, 46].

The mother of the preterm infant with an anomaly of the heart (an atrial and ventricular septum defect) acquired EM in the second trimester of pregnancy, while the mother of the child with the anomaly of the urinary tract noticed the skin lesion in the third trimester of pregnancy. Interpreting these abnormalities as sequelae of borrelial infection would be questionable, since (at least for the newborn with congenital heart involvement, in whom the time of infection is well defined) the organogenesis of these two distinct organ systems in the fetus should have been complete by the time borrelial infection occurred. Data for 1994 reveal that 301 of 19,743 newborns (1.5%) in Slovenia were found to have congenital anomalies [44]. Findings in previous years were similar [44].

The occurrence of a missed abortion at 9 weeks’ gestation was temporally connected with EM, but we were not able to confirm a causal relationship between this adverse effect and borrelial infection; in fact, the abortion was probably associated with the anomalous uterus. In the 5-year period of 1990–1994, 2,862 missed abortions per 107,304 births (2.7%) were registered in Slovenia [47], while in our group the incidence was one per 57 births (1.8%).

Thus, in our group of pregnant women treated with parenteral antibiotics for EM, the occurrence of fetal adverse effects was rare. Even in these few cases a causal relationship with borrelial infection was not proved, and for at least some cases a reasonable explanation (not associated with Lyme borreliosis) was found. We cannot comment on the eventual impact of different Borrelia genospecies on the outcome of pregnancy because we did not define the etiology of EM lesions in mothers. We assume that the majority of these lesions were caused by B. afzelii, which has been a predominant skin isolate in cases of Lyme borreliosis in Europe [48, 49] and was recently found to account for 85% of 101 isolates from EM skin lesions in Slovenia [Strle et al., unpublished data].

Conclusions

We conclude that for pregnant women with EM who are treated with ceftriaxone (2 g iv for 14 days), the outcome of pregnancy is good. We were not able to determine whether this favorable outcome was a consequence of effective treatment or of the low rate of fetal infections due to B. burgdorferi sensu lato. Prompt, aggressive therapy with iv antibiotics during the
whole gestational period seems to be an effective and safe approach to the problem of Lyme borreliosis in pregnancy.

References


