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Pregnancy complicated with Lyme disease

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SUMMARY

A growing incidence of Lyme disease in pregnant women makes it necessary to implement adequate management in these cases. The fact that there are only few studies on this problem forces us to broaden our knowledge in this area on a constant basis. Lyme disease is caused by the *Borrelia burgdorferi sensu lato* genus. In Europe and in Poland, the most common are *Borrelia burgdorferi*, *garinii* and *afzelii* types. Their reservoirs are wild animals and rodents, and they are transmitted with ticks of the *Ixodes Ricinus* genus. Since Lyme disease is similar to other conditions, differential diagnosis may sometimes be challenging. The medical history collected from patients as well as the clinical picture with expanding rash and concomitant fatigue and flu-like symptoms should be the basis for the diagnosis. In later stages, neurological and cardiological symptoms are usually predominant. In Lyme disease, both guidelines and various authors recommend antibiotic therapy. This treatment can be safe both in pregnant and breast-feeding women. To date, there is no evidence that would clearly show a relationship between *Borrelia* invasion on the fetus and unfavorable pregnancy course or fetal complications in the form of defects.
The article presents diagnostic and therapeutic management in pregnant women with Lyme disease, and describes appropriate prophylaxis to be implemented in this group of patients.
Key words: pregnancy; Lyme disease; diagnosis; treatment

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INTRODUCTION

Within the past several years, Lyme disease has become a genuine problem for a large group of patients. New cases of women with pregnancies complicated by Lyme disease are being encountered constantly.

Lyme disease [1] is a multi-organ condition caused by spirochaetes and transmitted via ticks, the most common of which in Europe and Poland belong to the *Ixodes Ricinus* species, with its reservoir being mainly wild animals and rodents [2-4]. The greatest number of cases is noted in the spring and summer, usually in April and May, and more rarely in the fall (September, October). This is probably associated with undertaking physical and recreational activities in green areas, such as parks, forests, meadows etc. [2,4,5]. As for professional groups, foresters are at the greatest risk [6]. Arvid Afzelius, a Swede, was the first to describe the typical rash and associated it with a tick bite. Many years later, a German scholar, Albert Bannwarth, linked skin manifestations (erythema migrans) and neuroborreliosis with a tick bite. To date, neuroborreliosis has been referred to as Bannwarth's syndrome [7]. The term "Lyme disease" is used probably because of a dozen or so reports of borreliosis in children, all of which occurred in 1975 in the area of the town called Lyme in Connecticut, United States of America [1,8].

In Poland, the disease is called *borelioza* (borreliosis). The name is derived from Amedee Borrela, a French biologist. In 1983, after *Borrelia* was isolated from a tick by Willy Burgdorfer, the name *borrelia burgdorferi* was coined, apparently as a result of works on this problem conducted by both these researchers. The clinical course can be divided into stages based on the severity of symptoms [3]. Stage I is called early, and usually includes the typical expanding rash (*erythema migrans*). It is a skin lesion, in adults typically localized within the extremities and trunk of the body. It is sur-

rounded by a rim or ring, usually reaching up to 5 cm, and typically appears within 30 days of a tick bite. These skin lesions may be accompanied by flu-like symptoms in the form of weakness or fever [2-5]. Many cases may be asymptomatic [8]. Later, the bacteria spread via the vascular system. Cardiological and neurological signs and symptoms are predominant. Patients may report fever and weakness, typically paroxysmal in nature. Moreover, patients may develop facial palsy, usually bilaterally, and meningeal signs. A number of authors report polyneuropathy. These stages are also frequently associated with stage I, II and III atrioventricular heart block. Encephalitis is a relatively common sign as well. Inflammatory conditions develop within multiple joints. Authors also report a blue-reddish skin lesion, reaching the size of 5 cm, referred to as *Borrelia lymphocytoma*, that usually subsides spontaneously as adequate treatment is implemented [2,3,5]. Such a case has been reported in a pregnant woman, in whom the lesion regressed completely upon implementation of antibiotic therapy [9]. Stage II, called late Lyme disease, occurs several or a dozen or so months after a tick bite. Signs and symptoms may become chronic and include ataxia, dementia, nerve VII, VIII and optic nerve palsy. Moreover, patients may present with keratitis and iritis. This stage is also characterized by the occurrence of a severe complication in the form of encephalitis. Other relatively frequently reported signs are spastic paraparesis and arthritis. Another grave complication of this phase of the disease is *acrodermatitis chronica atrophicans* (blue-red skin discoloration) that, after many years, may lead to skin atrophy within the involved area [2,3,5]. The differential diagnosis should include diseases that may be manifested by some of the above mentioned most common signs and symptoms [3,10-12]. The diagnosis should be based on medical history, the presence of erythema and other accompanying symptoms, often resembling flu [2,5,13]. At this stage, it must also be determined, based on medical history, whether the current infection is not in fact a reactivation of a previous contact and tick bite (a reinfection) or an effect of the lack of treatment or its inefficacy [3,5,8]. According to guidelines and recommendations, adequate antibiotic therapy should be implemented promptly based on the medical history and clinical signs alone, often before ordering serological tests [3,5]. It is worth remembering that this therapy may cause a Jarisch-Herxheimer reaction, i.e. the occurrence of certain signs and symptoms, such as increased temperature, shivers and skin rashes, that tend to subside within a day [14].

LYME DISEASE IN PREGNANCY – A LITERATURE REVIEW

Butler draws attention to possible uterine contraction in the course of Lyme disease during pregnancy. The paper lists renal and hepatic dysfunction, hypotension, myocardial injury and neurological disorders ranging from seizures to stokes. This is presumably caused by substances released by spirochaetes, such as pyridase, nonendotoxins and lipoproteins. This may in turn activate individual cytokines as a result of the response to the inflammatory factor [14].

Another publication worth listing here is a paper by Hungarian authors who analyzed 95 pregnant patients with diagnosed Lyme borreliosis over the period of 22 years. The analysis involved the manner of antibiotic therapy and non-treated cases. The authors concluded that the risk of an unfavorable course of pregnancy increased in a statistically significant way in untreated mothers (OR=7.61). Although they described single cases of certain complications in the form of cavernous hemangioma detected in the fetal liver during an ultrasound scan, intrauterine death in week 20 of pregnancy, hypertension, jaundice and fetal cardiac defects [15], the authors did not observe any statistically significant positive correlation in their results that would provide unambiguous evidence for a teratogenic effect of the spirochaete on the fetus.

In 2007, American authors [16] analyzed the effect of the spirochaete on the negative course of pregnancy taking into account the similarity of the disease to other spirochaete-induced conditions. They reported a case of a pregnant woman with Lyme disease diagnosed in the third trimester. The patient underwent full treatment with oral amoxicillin. The authors observed no negative effect on the course of pregnancy and postnatal condition of the neonate [16].

In another study, published in 2011 [17], the authors described 7 patients with erythema migrans and Borrelia infection based on the clinical picture and blood tests. Ceftriaxone administered for 14 days brought complete remission of symptoms, and the course of pregnancy remained uncomplicated.

Yet another article, from 2014, described fetal cholecystolithiasis and polyhydramnios in an ultrasound scan. The case concerned a black patient with Lyme disease treated with ceftriaxone during pregnancy. A cesarean section was performed in week 36 of pregnancy. The abnormal ultrasound image of the gall bladder persisted in the child for over 2 years after birth. However, as the author states, 70% of cases with prenatally identified cholelithiasis will not be complicated [18].

Borrelia spirochaetes are capable of penetrating the placenta to the fetus with the maternal blood [4]. Some authors report the risk of certain developmental defects. This usually concerns first trimester infections and women who have not received proper pharmacological treatment. The same author also described a case of first trimester Lyme disease from 1985. She reported numerous cardiovascular defects in a pre-term neonate born in week 35 of gestation, who died. The post-mortem examination revealed the presence of a spirochaete-like morphology in various organs, but not in the fetal heart. The author also quotes a study conducted by Nadal et al. where 1,416 women were observed after childbirth in terms of, for instance, the presence of the infection-specific antibodies, which were demonstrated in merely 0.86% of the women, which cannot be considered statistically significant [4].

Based on the clinical picture and serological tests, Canadian authors [13] showed no negative effects of infection on obstetric outcomes in women with Lyme disease diagnosed before and during pregnancy. Moreover, the clinical signs present in most cases (erythema or flu-like symptoms) varied in duration, ranging from several to even 30 days after a tick bite. Due to possible adverse effects, such as enamel discoloration or skeletal problems, doxycycline is excluded from antibiotic therapy as a first-line drug [13].

An interesting study is that by Maraspin, who tested 105 pregnant women with erythema. She noted single cases of abnormal pregnancy (approximately 11%): miscarriage, premature birth, urinary tract defects and cardiac defects. All women participating in this study underwent antibiotic therapy with penicillin or ceftriaxone [4,17].

To date, despite a number of studies based on clinical, serological and epidemiological data, no causal relationship has been discovered between *Borrelia burgdorferi* infection and adverse obstetric outcomes. There are several works on various animal models that report potential transmission of such an infection, and the similarity of congenital syphilis induced by spirochaetes to Lyme disease has led to a conclusion that this transmission is likely, which is surely associated with impaired cell-mediated immunity due to infection [19,20]. The author of the same publication showed no transmission of spirochaetes to human milk [21].

There is agreement across all publications and recommendations in the world that adequate antibiotic therapy, based on defined clinical signs and available serological tests, is necessary [3,5,8].

DIAGNOSIS AND DIAGNOSTIC WORK-UP

An adequate diagnosis of Lyme disease should always be based on medical history and clinical signs. The latest guidelines concerning serology recommend a two-step diagnostic protocol that combines the detection of specific IgM or IgG antibodies with mutually supplementary methods, i.e. immunoenzymatic assay (ELISA, high sensitivity) and Western-Blot technique (high specificity) [3,5]. IgM antibodies tend to appear 3–4 weeks after infection. They may persist for many years, even with effective treatment. IgG antibodies, however, are usually typical of a late stage of the disease [3,5]. It must be underlined that assays can also be made with PCR (polymerase chain reaction) from skin tissue, rather than from serum as the method is capable of detecting the spirochaete's DNA. Because of the lack of standardization, this technique is not in common use [3,5,22]. If the patient present with erythema migrans, this sole sign is a sufficient diagnostic criterion [3].

TREATMENT

The authors of recommendations and various publications recommend antibiotic therapy, including amoxicillin (Tab. 1) [3,5,16,19]. This treatment can be safely implemented both in pregnant and breast-feeding women. Moreover, it is also admissible to use intravenous penicillin G or ceftriaxone [17,23]. In allergic patients, macrolide antibiotics may be ordered, such as azithromycin, which is, however, characterized by lower therapeutic efficacy. Treatment should last 14–28 days [3]. Due to potential adverse events, such as enamel discoloration and possible skeletal changes [13], doxycycline is not recommended [3]. Moreover, prophylactic

antibiotic therapy after a tick bite is not recommended either. The application of therapies lasting weeks or months is not justified as, to date, its efficacy has not been fully confirmed, either scientifically or clinically [3,5].

PREVENTION

As of today, there is no active prevention in the form of a vaccine [21]. When staying at endemic regions or using green areas, such as forests, parks, meadows or home gardens, one should wear adequate protective clothes and shoes, and implement hygienic measures involving careful control and washing of the whole body [24]. Moreover, when a tick is found on the body, one should carefully remove it and disinfect the bite site. If tick removal is difficult, one should promptly see a doctor or report to an adequate medical facility.

Tab. 1. Therapeutic management in various forms of Lyme disease* [3]

Clinical picture	Medicine	Dosage	Route	Therapy duration (days)
Tick bite	observation and education about potential symptoms@			
Multiple tick bites in the endemic region with the patient coming from a different region@	Doxycycline	1x200 mg	p.o.	1
Erythema migrans Borrelial lymphocytoma Cranial nerve palsy	Amoxicillin	3x500 mg (children: 50 mg/kg daily)	p.o.	14-21
	Doxycycline	2x100 mg or 1x200mg	p.o.	14-21
	Cefuroxime axetil	2x500 mg (children: 30 mg/kg daily)	p.o.	14-21
	Azithromycin*	1x 500 mg (children: 10 mg/kg daily)	p.o.	7-10
	Clarithromycin*	2x500 mg (children: 15 mg/kg daily)	p.o.	14-21
	Penicillin V	3x1000 mg	p.o.	14-21
Arthritis (onset)	Amoxicillin	3x500–1000 mg (children: 50 mg/kg daily)	p.o.	14-28
	Doxycycline	2x100 mg or 1x200mg	p.o.	14-28
	Cefuroxime axetil	x500 mg (children: 30 mg/kg daily)	p.o.	14-28
Neuroborreliosis (meningitis, encephalitis, radiculitis) Arthritis (relapse) Myocarditis#	Ceftriaxone	1x2,000 mg (children: 50–75 mg/kg daily)	i.v.	14-28
	Cefotaxime	3x2,000 mg (children: 150–200 mg/kg daily in 3–4 doses)	i.v.	14-28
	Penicillin G	3–4 IU every 4 hours (children: 0.2–0.4 MU/kg daily in 4–6 doses)	i.v.	14-28
Chronic atrophic dermatitis	Amoxicillin	3x500-1000 mg	p.o.	14-28
	Doxycycline	2x100 mg or 1x200mg	p.o.	14-28
	Ceftriaxone	1x2000 mg	i.v.	14-28
	Cefotaxime	3x2000 mg	i.v.	14-28
	Penicillin G	3–4 IU every 4 hours	i.v.	14-28
Antibiotic-resistant arthritis	Non-steroidal anti-inflammatory drugs or a different symptomatic therapy; a different cause of the condition should be considered			

@ A single doxycycline dose (200 mg p.o.) is indicated only after multiple tick bites at an endemic region in an adult patient coming from a different region.
* Azithromycin and clarithromycin are indicated only in cases of erythema migrans in patients with hypersensitivity to ß-lactam antibiotics.
\# Myocarditis may be treated for up to 21 days; in cases of rapid improvement, it is admissible to continue treatment with oral antibiotics (as in erythema migrans).

CONCLUSION

Based on statistical and epidemiological data, Lyme borreliosis may constitute a significant problem for a certain group of pregnant patients, which forces profound and broad consideration of this subject. Every year, there are approximately 40 new cases of Lyme disease. During pregnancy, the infection may spread through the placenta [6].

In pregnant women, obstetricians should implement perinatal care involving complete diagnostic and therapeutic management. After establishing the diagnosis based on currently available guidelines and recommendations, proper antibiotic therapy should be implemented promptly, and patients should be given access to specialist clinics (clinic of prenatal pathology, clinic of infectious diseases) in order to periodically monitor the fetal well-being in ultrasound scans and, at a proper time in pregnancy, in CTG, and should remain under constant care of their attending physicians. Despite the diagnostic and therapeutic progress observed in this field in the past several years, there is still no vaccine [21] that would help avoid infection or lower the risk of potential complications in the mother and fetus. A number of studies indicate that there is no clear and statistically significant evidence to corroborate the direct effect of this infection on congenital defects in the fetus or neonate [25]. Because of the dimension of this problem, a proper model of monitoring and follow-up should be developed for these patients, and an adequate multicenter study should be designed.

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