

# Listeriosis in Pregnancy: a Public Health Problem in Romania?

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## Abstract

*There is a lack of knowledge regarding the correct laboratory diagnosis and the public health importance of *Listeria monocytogenes* infections in pregnancy, in Romania. Although the number of reported listeriosis cases in Romania is very low; we consider it represents an important public health issue.*

*We presume that general knowledge regarding the laboratory diagnostic practices for *Listeria monocytogenes* infection in pregnant women, negatively influencing two main pillars of the medical system (curative and preventive). We decided on a current situation overview based on a case*

*study, our hypothesis being supported by an analysis of specialized literature.*

*The incidence listeriosis increased in the EU during the past decade, mortality rates remaining stable, but very high. Therefore there is an actual concern for improving detection and surveillance for listeriosis in Europe.*

*We need to underline the need for a more comprehensive assessment using public health tools, followed by a multidisciplinary project, implemented for the benefit of future mothers and children.*

**Keywords:** *listeriosis, diagnosis, public health, pregnancy*

## Background

Listeriosis is produced by *Listeria monocytogenes*, a bacteria carried by various animals and birds which can be found in soil, water, sewage etc. Humans acquire this pathogen by eating contaminated food<sup>(1-4)</sup>; it is then spread into the bloodstream and central nervous system.

In many countries listeriosis is deemed as a serious infection and an important public health problem as well. Newborns, people of old age, the immunosuppressed, and pregnant women have the highest risk for developing severe symptoms. During pregnancy, listeriosis often causes miscarriage, premature labor or even

stillbirth. The death rate in infected newborns can be as high as 20-40%<sup>(1-5)</sup>.

We consider this disease to be an important public health issue for Romania requiring an update on the diagnosis of infections with *Listeria monocytogenes* affecting pregnant women.

We based this paper on a real, suggestive patient case. It might be argued that listeriosis is not an important problem for curative medicine or for the public health sector, as shown by disease incidence data in our country. However this data is not nationwide available and this issue was insufficiently studied. Actual data is either unknown, or unreliable.

We think that, even if listeriosis incidence in pregnant women is as low as available data shows, the misery incurred even by a single mother/child due to any eventual inadequate medical care requires that this message needs to be transmitted, that adequate information should be known by the appropriate personnel, thus resulting in a responsible administration of medical care; every single case, albeit a mother, fetus or newborn should be a priority.

## Material and Methods

We started our study with an analysis of several cases of insufficiently substantiated use of laboratory diagnostic for monitoring pregnant women, focused on

the existence of any potential infectious pathogens (viral, bacterial or parasitic) possibly occurring in pregnancy. We then selected a single case to be further presented.

We analyzed the official position on laboratory diagnosing the infection with *L. monocytogenes* in Romania and in other European countries.

We have studied all data available in national and international medical literature.

## Results

### Case study

A couple of newlyweds reported to the obstetrician for a clinical evaluation of the pregnant wife. The doctor recommended a series of tests, including „Listeria serology.” The lab report noted positive serology for *Listeria* spp. (newlyweds do not recall the titer).

They returned to the doctor who, in view of the lab result, recommended a 3-week regimen with ampicillin “for preventing the transmission of listeriosis to the fetus” even if the mother had no signs or symptoms of the disease. The young mother started the medication according to prescribed dosage and schedule. After one month, at the next examination, she was advised to repeat the serology workup. Based on the results of the second lab report (“positive serology for *Listeria* spp.”) she was advised to continue the ampicillin medication; the patient disregarded the recommendation.

By the end of the pregnancy the patient was advised to repeat the serologic assessment twice, both results being positive for *Listeria* spp.

The mother gave birth to a healthy, full-term baby, nowadays preparing for kindergarten. At a routine check-up, the mother’s lab report still noted “positive serology for *Listeria* spp”.

### Listeriosis in Romania

There have been no reported listeriosis in 2003-2004 and 2006 in Romania; however two cases were reported in 2005, whilst between 1998 and 2002 only one case per year was reported<sup>(6)</sup>.

Adequate laboratory diagnostic is not implemented nationwide. Although irrelevant, serologic diagnostic is still recommended. Several times, positive serology results were (wrongly)

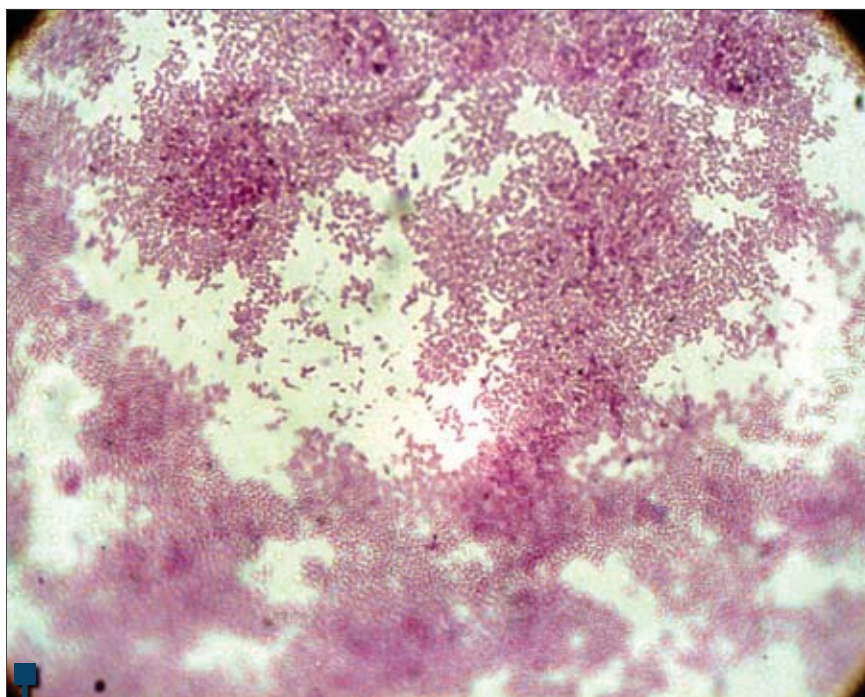


Figure 1. Microscopy aspect of *Listeria Monocytogenes*

thought to require antibiotic medication or even pregnancy termination.

### Listeriosis in USA and Europe

American public health authorities consider listeriosis as a rare illness with a potential for a severe outcome; they therefore decided to include listeriosis in the list of nationwide reported diseases starting in 2000. Between 2001 and 2005 the number of reported cases ranged from 613 (2001) to 896 (2005); the incidence in 2005 was 0.270/0000. Most cases were in people aged 60 years or more<sup>(6)</sup>. To diagnose and detect epidemic outbreaks in the US, the strains were initially isolated and cultured and then classified by molecular biology methods, as Pulsed-Field Gel Electrophoresis (PFGE).

Many studies were performed in Europe throughout the past decade, confirming most of the data already known and showing an increase in listeriosis incidence for several countries (e.g. Belgium, Denmark, England and Wales, Finland, Germany, Netherlands, Switzerland)<sup>(7-17)</sup>.

The highest rates were reported from countries with mandatory reporting of listeriosis cases and laboratory surveillance implemented. Unusually high mortality rates were registered in

Israel (fetal mortality rate: 45%) and Spain (average case fatality rate: 52.5%).

### Diagnosing Listeriosis

The National Center for Expertise in Medical Microbiology of the „Cantacuzino” National Institute stated that serologic tests are performed at clinicians’ request (knowing that possible false positive reactions can exist, being due to cross-reactivity to other gram-positive bacteria); bacteriological methods are required for a definitive diagnostic.

There is no routine screening test for listeriosis-susceptibility in pregnancy. Pregnant women should seek medical advice if they develop flu-like symptoms (i.e. fever, headache, nausea, vomiting, tiredness, and diarrhea)<sup>(1-4,18-19)</sup>.

The sole method for establishing and asserting the diagnostic of listeriosis is isolating *Listeria monocytogenes* from blood, cerebrospinal fluid, amniotic fluid, meconium, lochia, gastric washings or other samples; molecular biology techniques can be of help<sup>(1-4,20-21)</sup>.

If pregnant women have fever or stiff neck symptoms, they should request medical advice for follow-up. A sample of blood is of the utmost importance; three blood cultures over 24 hours are recommended.

Fetal (e.g. amniotic fluid, tissues) and maternal (e.g. blood, placenta, lochia) cultures should be obtained in every case of spontaneous abortion or stillbirth.

Cultures from sterile sites (e.g. blood) do not require special media. For possibly contaminated samples, special selective media have been developed<sup>(1-3)</sup>. Since *Listeria* spp. can grow at 0-4°C, the less expensive „cold enrichment” may be used as a selective cultivation method: the sample is cultivated on nonselective broth, refrigerated for 24-48 hours and then subcultured onto solid media.

Direct microscopy may reveal short gram-positive bacilli lying alone, in small clusters or in short chains.

The simplest presumptive identification for *L. monocytogenes* includes non-pigmented colonies (hemolytic on blood-agar), evenly-stained gram-positive & catalase-positive bacilli, with tumbling motility at room temperature.

Serological tests are unreliable. Antigenic cross-reactivity between *L. monocytogenes* and other gram-positive bacteria can occur. The relationship with other gram-positive genera (*Bacillus*, *Enterococcus*, *Aerococcus*, *Lactobacillus*, *Leuconostoc*, and *Staphylococcus*) was demonstrated by 16s rRNA sequence analysis. Cross-reactivity and similarities were demonstrated for antigens from different genera (*Streptococcus*, *Erysipelotrix*, *Lactobacillus*, *Bronchotrix*, and *Kurthia*). *Listeria monocytogenes* strains released antigen, cross-reacting with the *Streptococcus* group G antigen<sup>(22)</sup>, and the resulting monoclonal antibodies reacted with both *Listeria* and other genus extracts, particularly with *Streptococcus* and *Enterococcus*<sup>(23)</sup>. In addition, it was demonstrated that patients with a bacteriological diagnosis positive for *L. monocytogenes* did not show detectable antibody levels<sup>(3)</sup>, and since the antibodies do not have any protective role against *Listeria* spp., no prognostic statements could be formulated either in the presence or in the absence of antibodies.

We must underline that the diagnostic criteria for confirming listeriosis in the EU are as follows: any person meeting the laboratory criteria OR any mother with a laboratory confirmed *Listeria* infection in her fetus, stillborn or newborn<sup>(24)</sup>. The Commission Decision established the following two Laboratory Criteria, at least one which is required: (1) isolation

of *Listeria monocytogenes* from a normally sterile site, and (2) isolation of *Listeria monocytogenes* from a normally non-sterile site in a fetus (stillborn or newborn) or mother within the first 24 hours of birth. These criteria need to be used in all Member States.

Any fever episode during the pregnancy and any fever occurring during abortion or delivery (and disappearing afterwards) should be carefully and completely investigated (i.e. repeated blood cultures).

### Treatment

There are no controlled clinical trials to prove the efficacy of a particular medical drug against *L. monocytogenes*. Many antibiotics show in vitro activity, but the clinical usefulness is more relevant than in vitro antibiotic susceptibility testing. Like and example, bacteria is susceptible to cephalosporins but these are not clinically effective.

Ampicillin or penicillin (at least 2 weeks) is the drug of choice for treating confirmed listeriosis. In patients hypersensitive to penicillin, trimethoprim-

sulfamethoxazole should be preferred. Many authors recommend also adding aminoglycosides.

It is widely recommended to avoid cephalosporins, chloramphenicol, tetracycline, and erythromycin.

### Discussions

Listeriosis is a public health problem for the EU and USA. We deem listeriosis as a great concern for public health due to clinical severity and high case fatality. When comparing data for listeriosis in Romania with data reported by CDC and other EU Member States, we can presume a deficit in diagnosing and reporting listeriosis in Romania.

We hereby presented a case with a positive turnout, but sometimes antibiotic administration can be accompanied by side effects, hypersensitivity, or selection of antimicrobial antibiotic-resistant strains; all of these may require assessing the opportunity of „therapeutic” abortion.

Even if the case outcome is positive, negative stress is imposed on the mother (actually on both parents), in spite of the

Table 1

#### CDC recommendations for reducing the risk of Listeriosis

##### General recommendations:

- Thoroughly cook raw food from animal sources, such as beef, pork, or poultry.
- Wash raw vegetables thoroughly before eating.
- Keep uncooked meats separate from vegetables and from cooked foods and ready-to-eat foods.
- Avoid unpasteurized (raw) milk or foods made from unpasteurized milk.
- Wash hands, knives, and cutting boards after handling uncooked foods.
- Consume perishable and ready-to-eat foods as soon as possible

##### Recommendations for persons at high risk, such as pregnant women and persons with weakened immune systems, in addition to the recommendations listed above:

- Do not eat hot dogs, luncheon meats, or deli meats, unless they are reheated until steaming hot.
- Avoid getting fluid from hot dog packages on other foods, utensils, and food preparation surfaces, and wash hands after handling hot dogs, luncheon meats, and deli meats.
- Do not eat soft cheeses such as feta, Brie, and Camembert, blue-veined cheeses, or Mexican-style cheeses such as queso blanco, queso fresco, and Panela, unless they have labels that clearly state they are made from pasteurized milk.
- Do not eat refrigerated pâtés or meat spreads. Canned or shelf-stable pâtés and meat spreads may be eaten.
- Do not eat refrigerated smoked seafood, unless it is contained in a cooked dish, such as a casserole. Refrigerated smoked seafood, such as salmon, trout, whitefish, cod, tuna or mackerel, is most often labeled as “nova-style”, “lox”, “kippered”, “smoked”, or “jerky”. The fish is found in the refrigerator section or sold at deli counters of grocery stores and delicatessens. Canned or shelf-stable smoked seafood may be eaten.



problem “solving itself” through the birth of a healthy child.

Following the study of both medical literature data and our personal experience, we deem that the serologic assessment for anti-*Listeria* antibodies detection is not recommended as a follow-up method in pregnancy.

On the other hand, a possible infection with *L. monocytogenes* can pose serious problems, and preventing of such problems is mandatory. Clear guidelines are available<sup>(4)</sup> and they need to be known and followed.

The general guidelines recommended for listeriosis prevention are similar to those preventing other food-borne illnesses, such as salmonellosis. In addition, specific recommendations are available for those at high risk for listeriosis<sup>(4)</sup> (Table 1).

A weakness in our review is the unavailability of national data for comparisons. We can assume that the international literature data applies to our country (but we cannot extrapolate).

Our review should be credited for emphasizing the need for enhanced listeriosis surveillance as recommended by the European Centre for Prevention and Control (ECDC) in Stockholm, 2005. ECDC is an EU Agency meant to strengthen EU's defense against

infectious diseases. Strengthening surveillance in individual countries by harmonizing microbiological methods and providing epidemiologic investigation tools are key steps in lowering the listeriosis public health burden<sup>(26)</sup>.

We need a European *Listeria* surveillance network and Romania needs to be part of it. Clinicians, epidemiologists and microbiologists should collaborate and the importance of this collaboration should be emphasized.

We need future research for answering unsolved questions; we need training courses in *Listeria* spp. laboratory diagnosis and clinical and laboratory studies to identify real prevalence and incidence rates for this disease.

We are definitely interested in setting up and conducting a series of studies to find out what pregnant women know about fetus-transmissible infections; this data would be relevant to Romanian public health. We further plan to compare this data with other international studies, whose authors we have already contacted in this issue<sup>(25)</sup>.

Having established a database of documented cases, the experience gathered so far as well as future information, we would like to initiate a prevention and control project to be followed by measures applicable in our country; this project

would rejoin multidisciplinary teams of specialists (obstetricians, pediatricians, infectious disease specialists, general practitioners, microbiologists).

## Conclusions

1. Listeriosis represents an important public health problem at an international level and should be taken into consideration in our country as well.

2. Listeriosis is an infection that should be of great concern to public health due to its clinical severity and high mortality rate.

3. The positive diagnosis of *L. monocytogenes* infection during pregnancy is possible only by classical and modern bacteriological methods.

4. We do not recommend monitoring listeriosis during pregnancy by the so-called “serologic diagnosis”.

5. A study to assess the statistical significance regarding what not only pregnant women but also what the medical staff know with reference to communicable infections during pregnancy, methods on prevention and control of spread, is needed.

6. We consider the setup and implementation of such a multidisciplinary project with regards to communicable infections during pregnancy for the state of public health in Romania. ■

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