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Bacterial Infections (H Bach, Section Editor)

Listeriosis in Pregnancy

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Abstract

Purpose of this review Optimal management of listeriosis is critical due to the potential for adverse obstetric and neonatal outcomes. The aim of this paper is to present recent scientific developments regarding listeriosis in pregnancy, including presentation, diagnosis, management, and prevention.

Recent findings Pregnant individuals can be approximately 13–100 times more susceptible to this pathogen, which is concerning due to the potential for obstetric, fetal, and neonatal complications. Close to 25% of pregnancies complicated by listeriosis result in adverse consequences, including preterm labor and fetal death. About 30% of pregnant individuals are asymptomatic, which further complicates diagnosis and, therefore, medical management. Novel vaccines, drugs, drug targets, and an epidemiological surveillance system could aid in disease prevention and treatment, and the emergence of new probiotics appears promising.

Summary Pregnant individuals should be educated on the risks of listeriosis. Also, clinicians should consider the challenges associated with the diagnosis of listeriosis: the pregnant individual can be asymptomatic, and cultures can be falsely negative for *Listeria monocytogenes*. Optimal

management of listeriosis in pregnancy is dependent upon utilizing education, prevention measures, maintaining a high index of suspicion for disease, and prompt clinical management.

Introduction

Listeriosis is caused by *Listeria monocytogenes*, a Gram-positive bacterium that is resistant to cold refrigeration storage temperatures [1] and is transmitted through the consumption of contaminated food [2, 3••]. There has been a continued rise in invasive listeriosis cases, with 1876 confirmed cases reported by European Union countries in 2020 and 1600 annual cases in the USA, as estimated by the Center for Disease Control and Prevention (CDC) [4, 5]. Though it is common to be in contact with *L. monocytogenes*-contaminated products, microbiologically confirmed disease is rare [2], and the respective incidences for the USA and Europe are 0.28 and 0.6 per 100,000 individuals [2]. Nevertheless, listeriosis is the 3rd most common leading cause of death due to foodborne illness in the USA [6, 7].

Pregnant individuals are especially vulnerable to invasive listeriosis, with 25% of pregnancies complicated by listeriosis having poor obstetric and neonatal outcomes, including preterm birth, fetal loss, and behavioral and neurological sequelae after neonatal infection [7, 8]. Therefore, it is necessary for healthcare workers to familiarize themselves with the clinical presentation of *L. monocytogenes* infection for more effective prevention. This review aims to present recent scientific findings regarding listeriosis in pregnancy, including prevention, presentation, diagnosis, and management.

Risk factors associated with listeriosis

The risk of listeriosis in pregnancy is approximately 13–100 times higher than in non-pregnant individuals [1], with recent estimates indicating that 9–50% of listeriosis cases worldwide affect pregnant individuals [3••]. The risk of *Listeria* acquisition increases in pregnant individuals [9]. Listeriosis is tightly connected to immunosuppression and a highly vulnerable group, with physiologic changes in the immune response, is pregnant individuals [10•]. In pregnancy, the increased susceptibility to invasive listeriosis is thought to be due to increased progesterone levels. Elevated progesterone levels are crucial to enhance implantation and sustain the pregnancy, but many factors it regulates can also result in immunomodulation [11]. For example, increased progesterone is associated with indoleamine 2,3-dioxygenase 1(IDO1) expression, interleukin 10 (IL-10) production, and T-helper cell 2 (Th2) cytokine release by the pregnant individual [12].Additionally, increased progesterone levels are linked to the downregulation of Th1 and Th17 in the embryo [12].

Socioeconomic factors impact the susceptibility to invasive listeriosis. Women living in low-to-middle-income areas are at an increased risk for *Listeria* infection. A universal review based on nine systematic reviews, including listeriosis-infected pregnant mothers and neonates cross-culturally, reported that the listeriosis infection rate was higher in less affluent areas [8]. The explanation for the link between listeriosis and lower socioeconomic status could be decreased level of quality checks and looser hygiene policies that characterize small local businesses from where people in these areas are more

likely to obtain their food supplies [8]. Interestingly, despite the correlation described above, some evidence contradicts this association between listeriosis and lower socioeconomic status. Recently, listeriosis outbreaks have been more frequently identified in higher-income and developed countries. However, this has been attributed to more easily accessible diagnostic means rather than an increased listeriosis risk [3••].

Notably, *L. monocytogenes* may disrupt the breast milk microbiome. Severe acute malnutrition (SAM) affects children ages 0–5 years old in low-to-middle-income countries. This public health problem can be linked to several factors, including inadequate maturation of the gut microbiome, malabsorption, and insufficient food consumption [13••]. For example, a study detected an increased presence of *L. monocytogenes* in the breastmilk samples cultured from women living in Mali in areas endemic for SAM when comparing it to the breastmilk samples of women living in France [14]. Another case–control study involved the evaluation of samples from lactating Senegalese mothers [13••]. Using 16S amplicon and qPCR sequencing, the investigators found an association between infected breast milk and children with SAM. Moreover, children with SAM appeared more likely to have previously received *L. monocytogenes*-infected milk from their mothers, which seemed linked to reduced lactic acid bacteria and disruption of the microbiome in their gut [13••].

Listeriosis can affect all racial and ethnic groups; however, some racial and ethnic groups have been overrepresented among cases of perinatal listeriosis. For example, surveillance data from the US population reported an increased risk of invasive listeriosis among pregnant compared to non-pregnant women and in Hispanic compared to non-Hispanic women, which was independent of whether they were pregnant [15]. It has been hypothesized that this may be secondary to certain cultural dietary choices, such as the consumption of soft cheeses made with unpasteurized milk [9, 16, 17]; however, further studies are needed to better define subpopulations at increased risk for invasive and perinatal listeriosis and the factors that may lead to this increased risk.

Data on the suggested seasonal distribution of listeriosis are contradictory. Recent studies have demonstrated a seasonal variation of *Listeria* infection. Research in China and Taiwan indicated that 50% of the listeriosis cases identified presented during the summer months. These findings were explained by the increased chances of consuming insufficiently refrigerated pre-cooked food that is more likely to be infected by this bacterium during this specific period [3••]. However, according to a study evaluating long-term data from New Zealand, there appears to be no seasonal link and most cases were sporadic [18]. Consequently, environmental modifications due to seasonal change can occasionally be positively correlated with listeriosis. However, this relationship is not definitive and does not apply to every infectious outbreak.

The use of long-term gastric acid medical control with H2-antagonists and proton-pump inhibitors may also increase the risk of *Listeria* infection. *L. monocytogenes* is relatively resistant to the acidic environment of the stomach and, therefore, is more likely to infect people receiving medicinal gastric acid suppression, which weakens the acidity-based protective barrier to infectious pathogens [19]. Finally, the risk is even higher for immunologically vulnerable pregnant individuals, including individuals living with HIV in middle-income countries. For example, research following the 2017 *L. monocytogenes*

outbreak in South Africa demonstrated that 38% of the listeriosis cases in people living with HIV were in pregnant individuals [20].

Transmission

The vast majority of listeriosis outbreaks are linked to consuming food products that were consumed without the food receiving prior antibacterial treatment such as thermic treatment to eliminate microbial load or were refrigerated over extended periods [19]. Once ingested, *L. monocytogenes* enters the body's gastrointestinal tract and has the potential to cross the intestinal epithelium, infecting the mesenteric lymph nodes and finally entering the bloodstream [6].

Even though pathogens are meant to be cleared by the liver, this is only sometimes entirely efficient, especially in immunocompromised patients [19]. Uncleared *L. monocytogenes* bacteria can reproduce in hepatocytes. Polymorphonuclear cell activity, as a response to the pathogen, results in hepatocyte lysis [21]. This causes a bacterial release in the bloodstream, leading to a secondary bacteremia [8, 21]. Moreover, the fecal carriage has also been noted; *L. monocytogenes* has been identified in 5% of human stool [2]. However, there are no documented cases of invasive listeriosis associated with fecal carriage [19].

Of note is that neonates may become infected transplacentally, leading to early-onset *Listeria* infection [21]. Transmission can also be perinatal and postnatal. This occurs through interaction with the vaginal canal and contaminated maternal amniotic fluid during birth, and both perinatal and postnatal transmission are highly associated with late-onset *Listeria* infection [22]. Perinatal and postnatal transmission are highly associated with late-onset *Listeria* infection [8, 21, 22].

Pathophysiology

L. monocytogenes is a non-spore-forming intracellular facultative anaerobic bacterium. Its intracellular nature makes its diagnosis difficult as it can easily conceal itself among host cells. Once inside the cell, it has the capacity to utilize actin filaments using the host cell cytoskeleton, forming an "actin tail" and allowing bacterial intercellular transmission [6]. Figure 1 illustrates the intracellular life cycle of *L. monocytogenes* in non-phagocytic cells and cell-to-cell spreading.

Interestingly, *L. monocytogenes* is highly resistant to humoral immune defenses and the host's phagocytotic vesicles [21]. It also can avoid the T-cell-mediated immune barrier and neutrophils, antibodies, and complement reactions through its intracellular transmission. Moreover, *L. monocytogenes* can overcome this immune barrier and stimulate the NF-κβ pathway and type I interferon responses in the cytoplasm [26]. This also applies to environmental

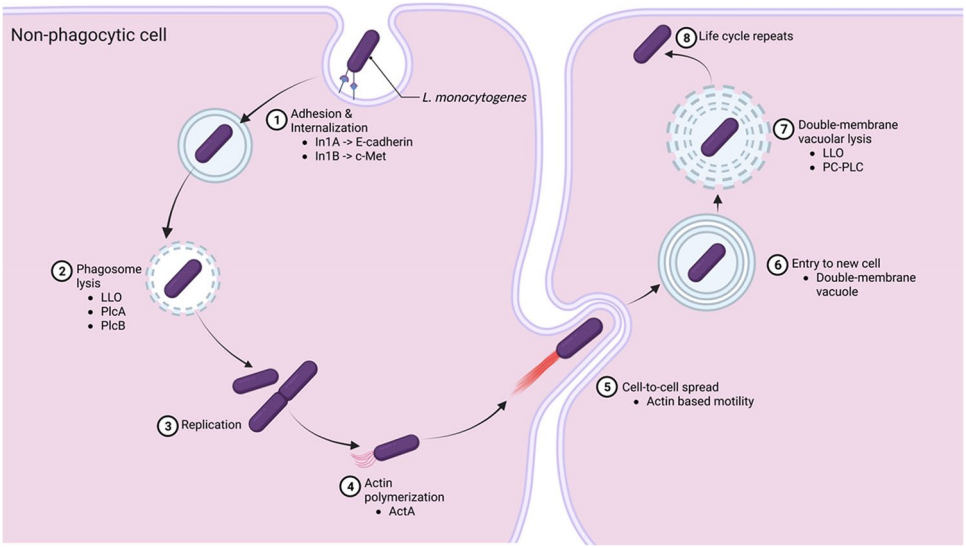

Fig. 1 Cellular invasion *by L. monocytogenes* is initiated by adherence to the cellular epithelium. It is followed by subsequent internalization controlled mainly by Internalin A and B via binding to E-cadherin and c-Met receptor tyrosine kinase. The vacuole formed is then lysed by listeriolysin O (LLO) protein, allowing bacterial replication within the cell cytoplasm. Actin polymerization mediated by actin assembly-inducing protein (ActA) follows, promoting *L. monocytogenes* motility and cell-to-cell spread. Further endocytosis occurs, leading to the invasion of a new cell in the form of a double membrane vacuole. Finally, lysis by LLO, phospholipase A (PlcA), and PlcB proceeds, and the cycle repeats itself. The figure was adapted on from the article by Radoshevich and Cossant [23], Portnoy et al. [24], and Bonazzi et al. [25]. The figure was created with BioRender.com

factors since, compared to other bacteria, it can grow at lower temperatures, from 0 to 45 °C, and thrive even at refrigeration conditions [8].

Over a dozen different serological types of *L. monocytogenes* have been identified. Serotype 4b appears to be the most virulent serotype and the one that is most likely to affect individuals during their pregnancy. However, type 1/2b is the most frequently identified in the food products [6]. This is important since transmission occurs through food consumption, and an inoculum of 10^4–10^6 organisms/g of contaminated food ingested can result in symptomatic and detectable listeriosis. However, the bacterial load required is decreased in high-risk groups [6], and transmission can also occur through direct skin contact with livestock and their products of conception during the birthing process [21].

Clinical presentation and complications in pregnant individuals

Clinical presentation of listeriosis in pregnancy is highly variable. About 30% of infected pregnant individuals are typically asymptomatic, and only 36% of infected females have detectable growth of *L. monocytogenes* on the

blood culture [1]. The incubation period lasts 1–2 weeks but may present after 90 days [21]. Non-invasive listeriosis may present with gastrointestinal symptoms, including nausea, vomiting, diarrhea, and fever [21]. Symptoms can arise as early as 11 h after infection in the form of bacterial gastroenteritis [21]. Listeriosis can also present with symptoms of head/joint aches, sore throat, and muscular discomfort and can even cause pyelonephritis in pregnant individuals [19].

When the infection spreads to the circulatory system, it causes septicemia and can lead to rigors, tachycardia, and multiple organ failure [19]. Additionally, neurological symptoms known as neurolisteriosis can arise as *L. monocytogenes* has the ability to cross the blood–brain barrier [27]. However, in healthy pregnant individuals, neurolisteriosis rarely occurs, and pregnancy is not considered a risk factor for this form of listeriosis [19, 28]. Finally, *L. monocytogenes* lymphadenitis is an infrequent but highly concerning manifestation of infection. It can occur in cases of severe invasive listeriosis and is strongly linked to the cancer status of patients, and is associated with poor prognosis [29]. There have been no reported cases of *L. monocytogenes* lymphadenitis associated with pregnancy.

Clinical presentation and complications to the fetus

The large-impact MONALISA cohort study in France reported that 24% of 101 patients with maternal-neonatal listeriosis experienced fetal loss, while preterm labor or complications occurred in 65% of the cases [10•]. Notably, the fetal loss rate associated with listeriosis has remained high over the past decade. US population data extracted from 153 pregnancy cases showed that 34% of cases with relevant data resulted in the death of the fetus/neonate [9]. Similar results were reported from New Zealand, where an observational study of 147 pregnancy-related listeriosis cases demonstrated a 34% rate of fetal loss [18].

Moreover, even if the fetal loss is prevented, other severe complications may still occur. These include pre-term labor, stillbirth, miscarriage, sepsis, and meningitis of the newborn [1, 8, 30•]. Neonatal listeriosis can be present in two forms: early-onset and late-onset. Early-onset neonatal listeriosis occurs 0–5 days after birth and generally results from chorioamnionitis and presents with septicemia and respiratory symptoms [31]. Late-onset neonatal listeriosis presents on the day of life 5–7 and typically presents as meningitis [31].

Notably, neonatal disease manifestations are associated with the mode of *Listeria* transmission (transplacentally, via the intestinal barrier, or by contact with infected body fluids in the birth canal leading to perinatal infection). The early-onset disease is often associated with a symptomatic pregnant patient, can result in pre-term birth, and usually occurs through transplacental transmission via the hematogenous route. Late-onset listeriosis occurs following infection of the neonate via the birth canal during a vaginal delivery [31].

Diagnosis

The gold standard for diagnosis of listeriosis is bacterial culture. These can be cultures of the blood, placenta, cerebrospinal fluid, stool, vagina, amniotic, or even synovial fluid [21]. The bacterium presents as single Gram-positive rods with measurements of 0.4–0.5 × 0.5–2.0 μm or in the form of chains [21]. However, *L. monocytogenes* may have variable Gram staining patterns and appearance, commonly leading to misdiagnosis as other pathogens [30•]. In pregnant individuals presenting with gastrointestinal or flu-like symptoms, often with a normal temperature and a suspicion of contact with an infective source, blood cultures should be obtained [8].

The gold standard method of neonatal diagnosis, though, is placental cultures and should be performed in addition to maternal blood cultures [28]. Moreover, blood and CSF cultures are often required to establish the diagnosis in neonates. Other blood tests can be useful in supporting the diagnosis of *Listeria* infection in neonates, which can present with anemia, thrombocytopenia, coagulopathy, and elevated transaminases [30•]. Central nervous system imaging could indicate intraparenchymal hemorrhage related to the infection and, thus, provide additional information to support the diagnosis [30•].

Enzyme immunoassays and polymerase chain reaction (PCR) tests can also be performed [8]. In neonates, diagnosis can be confirmed through PCR testing of swabs from the ear, umbilical, and oropharyngeal surfaces. Enzyme-linked immunosorbent assays (ELISA) are sometimes utilized as they can identify listeriolysin-O antibodies [32], but their ability to discern current versus prior infection is less reliable [8].

Management and pharmacological approach

Generally, if the pregnant individual was exposed to a contaminated product that appeared associated with listeriosis cases but is asymptomatic, medical treatment is usually not required, apart from monitoring for signs and symptoms over a period of 2 months [8]. In the presence of symptoms and fever, blood cultures, and if applicable placental cultures, should be obtained, and intravenous (IV) ampicillin can be initiated [33]. In cases of invasive listeriosis and meningitis, according to the guidelines from the European Society of Clinical Microbiology and Infectious Diseases, gentamicin can be co-administered for 2–5 days [34]. Women with a life-threatening penicillin allergy may use IV trimethoprim-sulfamethoxazole [6], while meropenem is another alternative option [35]. Of note, penicillin and ampicillin resistance requires monitoring [1], and aminoglycosides are associated with complications including nephrotoxicity and ototoxicity [34, 36].

Prevention

Currently, listeriosis prevention relies on precautionary dietary modifications and the application of safe food handling [37]. Education regarding listeriosis, as well as establishing optimal public health surveillance and infection tracing, is important [8]. For example, medical guidance on which types of food to avoid, as well as advice on avoiding contact with silage and sheep at lambing time, could prove helpful. Moreover, dietary advice on safer eating habits, such as avoiding pre-cooked meals and eating out less frequently to have more control over food handling, should also be considered [38].

Listeriosis prevention and management guidelines have been provided only by a few countries, including Ireland, the USA, Canada, and Australia [8]. Further development of these at the international level could provide a more robust strategy for disease prevention. Table 1 summarizes preventative measures that can be utilized to reduce the mortality and morbidity associated with pregnancy-related listeriosis.

Novel discoveries

Vaccines are a highly effective way of minimizing infection transmission and the number of hospitalizations. Currently, there is no approved vaccine against listeriosis. Most studies exploring the development of vaccination strategies against *L. monocytogenes* are animal studies and could be divided into 3 different subtypes: live attenuated vaccines, subunit vaccines, and vector vaccines [26].

Two novel vaccines are currently under development. The first is a triple-virulence-genes deletion vaccine (NTSNΔ*actA/plcB/orfX)* against *L. monocytogenes* serotype 4b [26]. The results from a study in 6-week-old female mice showed that the vaccine is potentially safe as the vaccine was eliminated by the mice on day 7 without any histopathological changes in the liver and spleen for 23 days [26]. Additionally, there was a greater increase in anti-listeriolysin-O (LLO) antibodies and a stronger strong Th1 type immune response than the control with 100% protection against serotypes 4b and 1/2b in vaccinated mice [26]. Another potential vaccine

Table 1. Suggested measures to prevent *Listeria* infection transmission and infection

By healthcare workers	By national public health services
• Medical education for pregnant individuals on listeriosis, its risk factors, transmission route, and its potential complications on both the mother/fetus • Information on which food products to avoid/be cautious with • Guidance on safe food handling and storage methods	• Focused and precise international clinical guidelines by relevant public health/medical societies • Utilizing new and increasing existing listeriosis surveillance and infection tracing

against listeriosis involves the use of a LLO subunit vaccine, combined with adjuvant cholera toxin [39••]. This virulent, pore-forming LLO toxin is the main activator of the immune reaction cascade to *L. monocytogenes*. By creating a gene-edited new form of the LLO toxin, Th1, Th2, and Th17 immune responses were elicited by mice involved in the study [39••]. Even though these vaccines are still in the experimental stages of their development and sufficient safety needs to be ensured, especially in pregnant individuals, they are a promising intervention to mitigate the risk of listeriosis.

Bacterial probiotic strains edited by bioengineering could be an interesting tool for managing listeriosis spread. Drolia et al. used a mouse model to study *Lactobacillus* strains edited to contain the *Listeria* Adhesion Protein (LAP) on their surface. The investigators found that this modification could protect mice from listeriosis through competitive inhibition [37]. Probiotic use also appears to be linked to a stimulated immune system and decreases the effects of *L. monocytogenes* on the function and efficiency of the intestinal barrier [40]. Another use of probiotics could be to ensure food preservation, which is directly linked to listeriosis since *L. monocytogenes* thrives in the circumstances associated with poor food maintenance.

Listeriosis outbreaks are often associated with increased consumption of pre-made/partially cooked meals. The probiotics industry has not had any major applications in the food market. However, bacteriocins, which are antimicrobial peptides that have either bacteriostatic or bactericidal functions, could be very useful in the infection control [41]. These peptides, produced by lactic acid bacteria, can be applied during or after food production, enhancing food preservation and preventing contamination. Otherwise, bacteriocin-secreting bacteria could be used during or after production for protection cultures or in the form of probiotics. Such measures could all be applied to listeriosis management and significantly impact infection control.

Novel drug discoveries, as well as the identification of alternative target sides for medications and other therapeutics, have been under investigation recently. CRS0540 is a thiadiazole urea compound that attacks bacterial PolC, a DNA polymerase that is used for bacterial replication. According to data originating from pharmacokinetic research on rodents, this agent could provide a new option for fighting against *L. monocytogenes*, as it appeared to be a strongly bactericidal [42]. The bacterial transcriptional activator PrfA may also provide a druggable target, as PrfA is a key regulator of the *L. monocytogenes* virulence [43]. Inhibition of PrfA resulted in *L. monocytogenes* bacteria becoming trapped within vacuoles and eliminated via the lysosomal degradation [43].

In addition to novel vaccines and treatments, close epidemiological monitoring of the disease is needed. For example, using a novel tracing system called LmTraceMap could prove helpful [44]. LmTraceMap is an online platform that enhances listeriosis surveillance by allowing research teams to rapidly compare patient whole genome sequencing results to results originating from other infective sources at an international level [44].

Conclusions

Listeriosis can have devastating consequences, especially in the context of pregnancy. The current lack of awareness of the potential risks, and the challenging diagnosis, given the often-asymptomatic nature of the disease, can result in significant morbidity and mortality. Mitigation of the consequences of this potentially devastating infection requires the education of pregnant people as well as their communities on the risks of listeriosis, as well as the development of universal guidelines on prevention, diagnosis, and management. Collaboration between the individual healthcare provider and broader public health services is imperative in achieving this goal.

Compliance with Ethical Standards

Conflict of Interest
The authors report no conflict report conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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