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Pathogenicity and Spontaneous Abortion Caused by *Listeria monocytogenes*: a brief report

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Abstract

Listeria monocytogenes, as one of the foodborne pathogens, is a causative agent of listeriosis. *Listeria* is ubiquitous in the environment and can produce biofilms in the food production environment and thus contaminate ready-to-eat (RTE) products, which are typically consumed raw or without further processing. *L. monocytogenes* is an adaptable environmental bacterium. One of the most important characteristics of *L. monocytogenes* is its cold tolerance and resistance to high salt concentrations and low pH. On the other hand, this bacterium is an important pathogen in pregnant women, neonates, elderly individuals, immunocompromised individuals and patients with cancer. Spontaneous abortion is the loss of a fetus before the 20th week of pregnancy, when occurring naturally without any surgical or phar¬maceutical intervention. Based on previous studies, it appears that *L. monocytogenes* incidence is high among pregnant women. It can be concluded that, pregnant women and their health care providers should be informed about listeriosis during pregnancy.

Key words: *Listeria monocytogenes*, Pathogenicity, Abortion

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Introduction

The organism now called *Listeria monocytogenes* was called *Bacterium monocytogenes* and was first described by Murray based on cases of sudden death in six young rabbits. Then, thanks to the efforts of the English surgeon and founder of disinfection, Joseph Lister, he changed the genus to *Listeria* (Murray et al., 1926, Harvay, 1940, Fauci et al., 2008). Due to the proliferation of monocytes in infected experimental animals, the name *monocytogenes* was chosen for this species (Nowrozi, 1996). *L. monocytogenes* is a Gram-positive, non-spore forming, short rod, non-encapsulated, catalase-positive, oxidase-negative, facultative anaerobic, with a diameter of 0.4 to 0.5 micrometers and a length of 0.5 to 2 micrometers with a rounded end. It grows well at a temperature of 37°C and a pH equal to 6-9 (Cliver, 1990, Tabouret et al., 2003). It is a facultative anaerobic intracellular pathogen that spreads throughout the environment and has been isolated from soil, feed, water, feces, animals and humans. Although most bacteria do not grow or grow poorly below 4°C, *L. monocytogenes* survives at refrigerator temperatures. Therefore, *L. monocytogenes* is an important foodborne pathogen in refrigerated prepared foods (Ramaswamy et al., 2007, Salyers & Whitt, 2002). Since 1980, many cases of *L. monocytogenes* infection have been reported as epidemics or sporadic infections caused by consumption of contaminated food (Iwamoto et al., 2010).

Food poisoning is a significant health concern for patients and populations worldwide. The etiologies of foodborne illness are varied, and the clinical presentations are diverse. The presentation patterns can aid in diagnosing and managing these diseases (Adam et al., 2022). Centers for Disease Control and Prevention (CDC) estimates that *Listeria* is the third leading cause of death from foodborne illness in the United States in 2023. *Listeria* can also cause an intestinal illness that is usually mild. When *Listeria* spread beyond the intestines, we call the infection invasive (CDC, 2023a). Listeriosis, a serious infection usually caused by eating food contaminated with the bacterium *L. monocytogenes*. This agent is an important pathogen in pregnant women, neonates, elderly individuals, immunocompromised individuals and patients with cancer. Listeriosis in pregnant women cause mild illness in mothers but can be devastating to the fetus and leading to a clinical syndrome known as granulomatosis infantiseptica and death (Pourkaveh et al., 2016). The presence of older patients, primary bacteremia, central nervous system involvement, non-hematological malignancies, alcoholism, chronic kidney disease, cardiovascular disease, and pulmonary disease should alert physicians to the higher risk of mortality (Huang et al., 2023). One of the most important characteristics of *L. monocytogenes* is its cold tolerance and resistance to high salt concentrations and low pH (Vazquez-Boland et al., 2001). This bacterium can grow well at the temperature of the refrigerator and is able to tolerate a concentration of 2.5% salt at a temperature of 4 °C for 4 months. Therefore, it can easily be transferred to humans through food stored in the refrigerator and cause food poisoning (Bollag & Edelstein, 1991).

L. monocytogenes is an adaptable environmental bacterium (Ramaswamy et al., 2007). A previous study demonstrated that different doses of environmental stresses including heat stress, acid stress, alkaline stress, oxidative stress, ethanol stress, and osmotic stress have lethal or sub-lethal roles in the survival of these bacteria and lead to different changes in its characteristics. The phenotypical and biochemical characteristics of them changed when exposed to each stress (Kazemi & Faezi-Ghasemi, 2015a). Adaptation to some stresses including hydrogen peroxide and heat increase resistance to antibiotics. Stresses such as ethanol, hydrochloric acid and sodium chloride act in adverse. Exposing to some sub-lethal stresses increased cell survival when lethal doses of the same stress such as acid, ethanol and sodium chloride were used. But when we treating the cells to sublethal doses of H_2O_2 and heat the cell survival decreased (Kazemi & Faezi-Ghasemi, 2015b).

Pathogenicity mechanisms

The disease caused by this bacterium was called "listeriosis". It is also a cause of men-

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ingitis, encephalitis, septicemia, endocarditis, abortion, abscesses and local wounds in humans (Bortolussi et al.,1985, Gilchrist,1988). In addition to humans, it can also cause diseases such as spontaneous abortion, meningitis and listeriosis in animals. Listeriosis in sheep is called "circling disease". The gastrointestinal tract is the main entry point for *Listeria* (Baron & Finegold, 1990).

L. monocytogenes induces cell death in vitro and in vivo in various cell types including hepatocytes (Rogers et al., 1996), lymphocytes (Merrick et al., 1997), and dendritic cells (Guzman et al., 1996).

L. monocytogenes is a facultative intracellular pathogen whose virulence depends on several factors, including host immunity, size of inoculum, strain-specific pathogenic factors, and coordinated expression of a number of specific proteins (Baron & Finegold, 1990, Esvan et al., 2000). Entry, reproduction, and pathogenesis of *L. monocytogenes* are described below (Figure 1):

Adhesion in *Listeria* is done by proteins such as FbpA and LapB (Stavru et al., 2011).

This bacterium has internalin proteins (InlA and InlB) on the surface of its cell wall, which react with a receptor called E-cadherin on the surface of epithelial cells and lead the phagocytosis of the microorganism into the epithelial cells (Werbrouck et al., 2006).

After phagocytosis, the bacterium is enclosed inside the phagolysosome, where it is activated due to the low pH and produces listeriolysin O (LLO) (encoded by the hly gene) (Rahimi et al., 2008). LLO is an important virulence factor. This protein is a cytolysin/hemoglobin similar to streptolysin and performs its action by destroying cell membranes (Ekhtiari, et al., 2011). In other words, it lyses the phagolysozyme membrane and allows *Listeria* to move through the phagolysosome towards the cytoplasm of the epithelial cell (Rahimi et al., 2008). In addition, two other main factors also play a role in the virulence of this bacterium, which allow it to escape from the vacuole/phagosome. These two factors are; Phospholipase A (encoded by plcA gene) – Phospholipase B (encoded by plcB gene) (Schmid et al., 2005, Zhang et al., 2003).

After leaving the phagolysosome, the bacterium in the cytosol begins to express several genes, including hpt and lPL, in order to adapt to the environment (Stavru et al., 2011).

In addition, the bacterium in the cytosol begins to polymerize actin on its surface with the help of the ActA protein. It has been shown that ActA is not only necessary but also sufficient to cause movement in bacteria in the absence of other bacterial factors (Zigmond, 2004).

Actin polymerization causes the microorganism to be pushed forward towards the membrane of eukaryotic cells (Grundling et al., 2004).

And finally, by creating pressure on the host cell membrane, it causes the formation of long protrusions called "cracks". The cracks are ingested in the adjacent cells, macrophages and hepatocytes, and the *Listeria* in them are released in the adjacent cells and the cycle begins again. In this way, *L. monocytogenes* can move from one cell to another cell without being exposed to antibody, complement and polymorphonuclear cells (Rahimi et al., 2008). Spreading from one cell to another is done by a cellular mechanism called "parasitophagy" (Robbims et al., 1999).

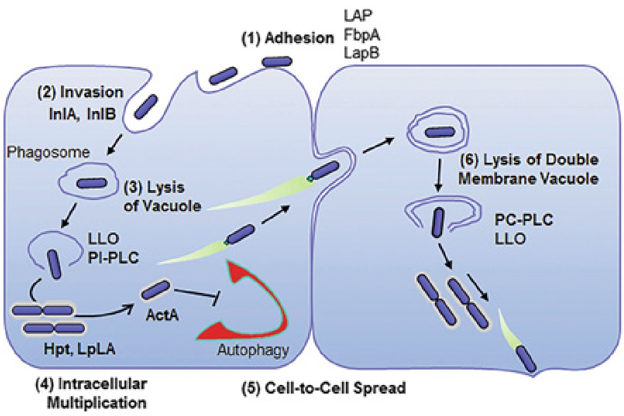

Figure 1. Entry, reproduction and pathogenesis of *L. monocytogenes* (*Listeria monocytogenes*)

Spontaneous abortion

A variety of pathogens, including bacteria, viruses, and protozoa, can cause abortions in humans and animals. However, little is known about the mechanisms of infectious abortion (Tachibana et al., 2011).

Spontaneous abortion is the loss of a fetus before the 20th week of pregnancy when it occurs naturally without surgery or treatment. On the other hand, listeriosis is caused by *L.* monocytogenes, one of the foodborne pathogens. Transmission of *L. monocytogenes* to pregnant women presents as self-limiting flu-like symptoms that can cause miscarriage, stillbirth, or premature birth of infected infants (Pourkaveh et al., 2016).

During pregnancy, there is a natural suppression of the generalized adaptive immune system, characterized by significantly weakened cell-mediated immunity and a reduced T helper 1 (Th-1) response, to prevent maternal fetal rejection. Unfortunately, this immunosuppressive state can lead to increased susceptibility of the mother to certain infectious agents (Mor & Cardenas, 2010). Indeed, the placenta provides a protective niche for the growth of *L. monocytogenes* and can cross the intestinal, blood-brain and placental barriers, causing gastroenteritis, meningoencephalitis and maternal-fetal infections, respectively (Barikbin et al., 2016). On the other hand, *L. monocytogenes* has the ability to evade the killing mechanisms of phagocytic host cells and spread to placental tissues without exposure to antibodies, neutrophils or antibiotics in the extracellular fluid. Bacterial colonization of placental trophoblast cells through production of IFN-γ can cause abortion (Abram et al., 2002).

The CDC only tracks invasive *Listeria*. Invasive disease in pregnant women is usually mild. However, invasive disease during pregnancy usually results in miscarriage, stillbirth, premature birth, or life-threatening infection in the newborn. Infection during pregnancy causes fetal loss in about 20 percent of cases and neonatal death in about 3 percent of cases. Other people with invasive disease—mostly adults age 65 and older with weakened immune systems—usually have inflammation of the bloodstream (sepsis) or inflammation of the brain (meningitis or encephalitis). *Listeria* can sometimes infect other parts of the body. For invasive diseases not related to pregnancy, most people end up in hospital (about 87% of cases) and about one in six dies (CDC, 2023a). Every year, 4/100,000 pregnant people in the U.S. get sick with *Listeria*. But it can harm for baby. Sadly, 1/4 pregnant people who get this illness lose their pregnancy or their baby shortly after birth. This is because bacteria can spread and harm your baby during pregnancy, even if you don't feel very sick (CDC, 2023b). Additionally, pregnant women are said to be responsible for 27 percent of all *Listeria* infections (Goldstein & Overturf., 2003). Because *Listeria* infection can have serious consequences in causing spontaneous abortion and infant mortality, it is very important that obstetricians, midwives, and pregnancy care providers know about *L. monocytogenes* transmission, prevention, and associated risk factors.

Although listeriosis is rare, the fatality rate can be as high as 30% (Ramaswamy et al., 2007). Infection in pregnant women is important for two reasons. First, the placenta is a suitable niche for the growth of *L.* monocytogenes. The incidence of listeriosis in the general population is 0.7/100,000, but in pregnant women the incidence is 12/100,000 (i.e., a 17-fold increase) (Kaur et al., 2007).

A variable prevalence of *L. monocytogenes* has been reported in several countries. The prevalence of *L. monocytogenes* (9%) in Iran (Lotfollahi et al., 2019) was higher than previous reports of isolation of *L. monocytogenes* in three of 100 in Delhi, India (Bhujwala et al., 1973), four of 305 in Punjab and Uttar Pradesh, northern India (Kaur et al., 2007), and one of 958 in Belgrade, Serbia (Stepanovih et al., 2007). The difference reported between studies may be due to differences in the study population, including race, culture, geographic region, diet, and laboratory diagnostic methods.

Ahmadi et al., (2022) reported that the frequency of *L. monocytogenes* infection was 4.109 (3.66%) observed among women with spontaneous abortion, 2.109 (1.83%) among women with normal delivery, 3.100 (3%) in fertile women and 0.99 (0%) among infertile women (Ahmadi et al., 2022).

Lotfollahi et al., (2019) isolated 3 (16.66%), 0 (0%), 1 (4%), 3 (12%) and 2 (8%) out of 9 isolates of *L. monocytogenes* from placental tissue, blood, urine, vaginal and rectal swabs. Resistance to penicillin G (77.8%) was the highest. However, the highest sensitivity was to trimethopyrim, norfloxacin and erythromycin (100%) (Lotfollahi et al., 2019). Because of high incidence rate of *L.* monocytogenes, diagnosis procedures for detection of *L. monocytogenes* and on time treatment is recommended. Additionally, because of high resistance rate of bacteria to antibiotic, antibacterial susceptibility before initiation of treatment is recommended especially in women with history of abortions or bad obstetric history. Pourkaveh et al., (2016) showed that identifying the risk factor of *L. monocytogenes* during pregnancy and considering it in pregnancy information and counseling can be crucial to reduce the prevalence of this bacterium and thus its side effects during pregnancy (Pourkaveh et al., 2016).

Conclusion

The prevalence of *L. monocytogenes* appears to be high among pregnant women; therefore, pregnant women and their health care providers should be informed about listeriosis during pregnancy. Healthcare providers for pregnant women, such as midwives and birth attendants, should be trusted sources of information for pregnant women and provide them with accurate advice about the risks associated with listeriosis. Most cases of listeriosis during pregnancy could be prevented not only by avoiding eating certain foods and avoiding contact with certain animals, but also by proper food preparation. In addition, it is recommended to raise awareness among people, including pregnant women, about not consuming unpasteurized dairy products, in order to significantly reduce listeriosis and its spread by health and treatment centers and gynecologists.

Conflict of interest

No conflict of interest declared.

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