

# Listeriosis in Pregnancy: A Deadly and Under Diagnosed Gastrointestinal Infection

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## ABSTRACT

Human listeriosis, a dreaded gastrointestinal disease of the West has surfaced in the last two decades in India, and there have been a series of reports on sporadic cases. The causative organism, *Listeria monocytogenes* is an intracellular Gram-positive bacillus ubiquitous in soil and vegetation. It is responsible for cases and outbreaks of febrile gastrointestinal disease in otherwise healthy people and invasive listeriosis, which usually affects pregnant women, newborns & the elderly. Immunocompromised individuals and pregnant women have been identified as major risk factors for listeriosis. It is about 20 times more common in pregnant women than in the general population. It causes mild illness in mothers, but can be devastating to the fetus, in some cases leading to severe disease or fetal death. It may cause abortion, premature labour, fetal death or neonatal morbidity in the form of septicemia and meningitis. This review is an attempt to sensitize clinicians especially obstetricians to include listeriosis as a differential diagnosis in patients with high suspicion and institute early antimicrobial therapy. Also there is need to press upon proper counseling of pregnant women for preventive measures against this deadly infection.

**Keywords:** Listeriosis, *Listeria monocytogenes*, pregnancy, neonates

## INTRODUCTION

Listeriosis is a gastrointestinal infection caused by *Listeria monocytogenes*, a Gram-positive, facultative, intracellular and foodborne pathogen. *Listeria* was first described in 1926 by Murray *et al* who discovered it while investigating an epidemic among laboratory rabbits and guinea pigs.<sup>1</sup> *Listeria* is ubiquitous in the environment and can be isolated from wild and domestic animals, birds, insects, soil, wastewater, processed foods, raw meat and the feces of animals and humans. In addition to being present in the environment, *L. monocytogenes* can live in the gastrointestinal tract of humans, animals and birds for long periods of dormancy. Annual incidence of listeriosis ranges between 1 – 10/million population.<sup>2</sup> Centers for Disease Control and Prevention (CDC) estimates that approximately 1600 illnesses and 260 deaths due to listeriosis occur annually

in the United States.<sup>3</sup> Pregnant women may be able to reduce risk of listerial infection by following dietary guidelines recommended by CDC<sup>4</sup>. The largest listeriosis outbreak in U.S. history occurred in 2011, when 147 illnesses, 33 deaths, and 1 miscarriage occurred among residents of 28 states; the outbreak was associated with consumption of cantaloupe from a single farm.<sup>5</sup> In India, human listeriosis cases have emerged to be evident and there have been a series of reports to substantiate this.<sup>6-8</sup> About one-third of listeriosis cases happen during pregnancy. Incidence of listeriosis in general population is 0.7/100,000 whereas the incidence in pregnant women is 12/100,000 i.e. 17 fold increase.<sup>9</sup>

## PATHOGENESIS

*L. monocytogenes* has 13 serotypes; serotypes 1/2a, 1/2 and 4b have been involved in the majority of reported human listeriosis cases.<sup>10</sup> Several population type including pregnant women, immune-compromised individuals and the elderly are particularly at risk for listeriosis. *Listeria* is a unique pathogen because it has an intracellular life cycle. Once contaminated food has been ingested, *Listeria* can be phagocytosed by intestinal macrophages and can enter the host without disrupting the integrity of the gastrointestinal tract. Once

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the organism has reached the host cytoplasm, it rapidly divides and pushes up against the cell membrane; it can then be ingested by adjacent cells. Through this series of steps, *Listeria* can multiply and spread without being exposed to antibodies, neutrophils or antibiotics in the extracellular fluid. This explains why maternal listerial illness can be mild or even asymptomatic<sup>4</sup>. The body's defense against *L. monocytogenes* depends on 'cell-mediated immunity' (CMI). Pregnant women naturally have a depressed CMI system due to increased level of progesterones,<sup>11,12</sup> making pregnant women particularly susceptible to infections by intracellular microorganisms like *L. monocytogenes*. In addition, the systems of fetuses and newborns are very immature and therefore are extremely susceptible to intracellular pathogens. *L. monocytogenes* has the unique ability to induce its own entry into host cells, such as macrophages, epithelial cells and endothelial cells of the gastrointestinal tract.<sup>13</sup> After ingestion, those cells surviving the low pH in the stomach pass through to the small intestine—the first site where invasion occurs—disseminate from the mesenteric lymph nodes to the spleen and the liver and from there *L. monocytogenes* can reach the brain or the placenta<sup>14</sup> causing, respectively, infections of the central nervous system (CNS) mostly in immunocompromised patients and intrauterine/cervical infections in pregnant women.<sup>15</sup>

*L. monocytogenes* uses various proteins including some internalins to adhere and to invade the host cells. Once in the intracellular phagocytic vacuole, bacteria secrete listeriolysins and phospholipases that allow it to lyse the vacuolar membrane and avoid intracellular killing. Upon being released into the cytoplasm, *L. monocytogenes* can multiply and induce the formation of actin filaments which will allow it to move in the cytoplasm until it reaches the plasma membrane. Subsequently, adjacent cells are invaded through plasma membrane protrusions and cell-to-cell spread occurs. Through this cycle *L. monocytogenes* can move from one host cell to another cell without being in the extracellular environment, thus escaping from the human T-cell immune system and invading other tissues and organs.<sup>16,17</sup>

### Listeriosis during pregnancy

Infection by *L. monocytogenes* during pregnancy may

result in serious outcomes including miscarriage, stillbirth, chorioamnionitis, preterm delivery and maternal and neonatal sepsis.<sup>18,19</sup> There is an increased susceptibility for listeriosis in late pregnancy. A third of the listeriosis cases affect pregnant women mostly in the third trimester of pregnancy rarely in the second and only exceptionally occurs in the first trimester.<sup>11,20</sup> Interestingly, it has been observed that women with multi-fetal gestation were at a fourfold risk of infection.<sup>21</sup> Listeriosis during early gestations generally has a poorer prognosis for fetuses as opposed to later gestations and commonly results in miscarriage or stillbirth.<sup>18,22</sup>

Listeriosis in pregnant women may be asymptomatic or cause a febrile illness that may be confused for influenza, pyelonephritis or meningitis. Moreover, pregnant women may present with nonspecific clinical symptoms (e.g., flu-like symptoms, backache, headache, vomiting/diarrhea, muscle pains and sore throat).<sup>18,19,23</sup> It is important to point out that listeriosis is not often diagnosed in pregnancy due to the microbiological diagnostic techniques being difficult and also due to the histological alterations in the placenta being similar to other diseases, hindering, therefore, a definitive assessment of the importance of listeriosis in pregnancy health.<sup>24</sup> The diagnosis is usually not apparent unless blood cultures are reported as positive.

Two distinct infection forms are described in the newborns. Transmission to neonates can occur transplacentally and during delivery. The vertical cell-to-cell transmission is frequent since *L. monocytogenes* shows uterus and placenta tropism leading to early-onset listeriosis also known as granulomatosis infantiseptica.<sup>20</sup> This infection, generally occurs at a mean age of 36 hours after birth<sup>25</sup> and probably due to aspiration of infected amniotic liquid, is characterized by clinical features like septicemia (81–88%), respiratory distress or pneumonia (38%) and meningitis (24%).<sup>26,27</sup> The formation and dissemination of abscesses and granulomas in multiple organs may occur.<sup>28</sup> The mortality rate for infants born alive approaches 20% and the frequency of abortion and stillbirth increases the overall mortality rate to more than 50%.<sup>29</sup>

Transmission during delivery leads to late-onset neonatal listeriosis presenting with symptoms such as meningitis or meningoencephalitis together with septicemia, occurring 2 or 3 weeks after delivery.<sup>30</sup> The

mortality rate associated with late-onset disease is 10%<sup>23</sup>, but as commented by DeWaal *et al*<sup>31</sup> and Buzby<sup>32</sup> a high rate of surviving babies develop severe and chronic neurological complications for example delayed mental development and blindness.

### Diagnosis and management

The diagnosis of listeriosis depends upon high degree of suspicion in pregnant women with fever or flu-like illness and confirmation of the same with microbiological findings and blood culture.<sup>6,33</sup> For this purpose, pregnant women should report any disease symptom, because listeriosis can be apparently harmless for the pregnant woman but can severely infect the fetus.<sup>31,34,35</sup> In early-onset neonatal infection, *L. monocytogenes* can be isolated from blood, CSF, superficial swabs, placenta or skin biopsy of a rash. Once diagnosed, listeriosis often requires antimicrobial therapy. The treatment of choice consists of a beta-lactam antibiotic, usually ampicillin, alone or in combination with an aminoglycoside, classically gentamicin. Second-line agents in case of allergy to beta-lactams or in certain disease states include trimethoprim/sulfamethoxazole, erythromycin, vancomycin and the fluoroquinolones.<sup>36</sup> Resistance of clinical isolates of *L. monocytogenes* to these antibiotics is low.<sup>37</sup>

### Prevention

Due to the high mortality rate of listeriosis among neonates, it is necessary to reduce its incidence in pregnant women. For that purpose, it is important to identify strategies based on risk assessment from food production to consumption.<sup>20,38</sup> *Listeria spp.* can be transmitted to pregnant women via food. It has been found in a variety of foods at all stages of preparation, from raw to well-cooked left-overs and will still grow on food that is stored in a refrigerator. Pregnant women should avoid soft cheeses, unpasteurized milk and refrigerated ready-to-eat food that is not freshly prepared, should peel or wash raw fruit and vegetables to remove soil. Hand washing is important. There is no vaccine for listeriosis at present. There is need for campaigns about food safety education targeted towards doctors especially obstetricians so that they can proactively counsel pregnant women to change their beliefs and attitudes during pregnancy regarding their food habits. Finally, we wish to emphasize the

importance of considering listeriosis as a differential diagnosis in pregnant women with high degree of clinical suspicion.

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