Maternal-Neonatal Listeriosis Sequelae

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Date: 2018-10-26T00:00:00+00:00

Abstract

Listeriosis (Lm disease) is a zoonotic disease caused by infection with *Listeria monocytogenes* (Lm). It occurs sporadically in healthy individuals with relatively mild symptoms; however, in high-risk populations (such as the elderly, neonates, immunocompromised individuals, etc.), it is often difficult to control and has an extremely poor clinical prognosis with very high mortality rates. Among high-risk groups, pregnant women and neonates are the most susceptible. The clinical manifestations of listeriosis are severe but nonspecific, easily confused with other diseases, posing significant challenges for clinical diagnosis and treatment. This article systematically reviews and analyzes the clinical characteristics, diagnosis, and prevention and treatment of maternal-neonatal *Listeria* infection by integrating multiple case reports and retrospective studies.

Full Text

Preamble

Maternal and Neonatal Listeriosis

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Abstract

Listeriosis is a zoonotic disease caused by *Listeria monocytogenes* (Lm). While it occurs sporadically in healthy individuals with relatively mild symptoms, it often becomes difficult to control in high-risk populations (such as the elderly, newborns, and immunocompromised patients) and results in devastating clinical outcomes with extremely high mortality rates. Among high-risk groups, pregnant women and neonates are the most susceptible. The clinical manifestations of listeriosis are severe yet nonspecific, easily confused with other diseases,

posing significant challenges for clinical diagnosis and treatment. This article provides a systematic review and analysis of the clinical characteristics, diagnosis, prevention, and treatment of maternal and neonatal *Listeria* infection based on multiple case reports and retrospective studies.

Keywords: *Listeria monocytogenes*; pregnancy outcome; neonatal; sepsis

1.1 Pathogenic Characteristics and Susceptible Populations of Lm

Listeria monocytogenes is a Gram-positive, non-spore-forming anaerobic bacterium that is widely distributed in the environment. It exhibits acid and salt tolerance, can survive for months in dry conditions, and continues to proliferate at low temperatures (4°C). These characteristics provide numerous opportunities for contamination during food production and processing, making it a significant foodborne pathogen [5-8]. Within the host, Lm primarily resides as an intracellular parasite, and clearance of the pathogen depends mainly on Th1-mediated cellular immunity [9]. Listeriosis cases are typically sporadic. In healthy populations, the disease occurs occasionally with mild, often self-limiting symptoms that are frequently overlooked. However, in high-risk groups such as neonates, pregnant women, the elderly, and immunocompromised individuals, it often leads to severe infection with low incidence but extremely high mortality rates [3,8,10,11]. Pregnant women show significantly higher susceptibility to Lm than other at-risk groups. Studies indicate that after consuming Lm-contaminated food, pregnant women have an 18-fold higher risk of developing the disease compared to the general population, accounting for 27% of all listeriosis cases [5,8,12,13].

1.2 Transmission Routes of Lm

As a foodborne pathogen, the primary transmission route of Lm is oral ingestion. It can also enter the body through the eyes and broken skin or mucous membranes, with sexual contact being another possible transmission route. Clinical studies have shown that in maternal-neonatal cases, pregnant women are mainly infected through oral transmission, while neonates acquire the infection primarily through vertical transmission via the placenta, intrauterine infection, or passage through the birth canal during delivery [6,14].

2.1 Immunological Basis of Listeriosis in Pregnant Women

Listeriosis can occur at any stage of pregnancy, but the majority of cases (approximately 70%) occur in the third trimester, with the second trimester being the next most common. This predilection is believed to be associated with maternal immunosuppression during late pregnancy [8,15,16]. During pregnancy, to prevent rejection of the semi-allogeneic fetus and protect both mother and fetus

from infection, the maternal immune response shifts toward humoral immunity, with cell-mediated immunity gradually transitioning from a Th1-dominant to a Th2-dominant pattern. This immunological shift facilitates Lm invasion [15,17].

2.2 Clinical Manifestations of Listeriosis in Pregnant Women

The median incubation period of Lm in pregnant women is approximately 27.5 days (range 17-67 days). Infected pregnant women typically present with non-specific flu-like symptoms such as fever, chills, myalgia, irregular abdominal pain, and gastrointestinal symptoms [18]. Among these, fever (38-39°C), abdominal pain, and diarrhea are the most common manifestations [7,8,15,16]. These clinical presentations are generally mild, and many pregnant women remain asymptomatic, leading to delayed medical consultation. Statistics show that approximately 29% of infected pregnant women exhibit no clinical symptoms. Maternal symptoms generally precede fetal symptoms by 1-14 days [3].

3 Clinical Characteristics of Fetal Lm Infection

3.1 Routes of Fetal Lm Infection

Although pregnant women exhibit mild symptoms, the fetus suffers severe consequences [3,7,15]. Researchers have compared serotypes, PFGE patterns, and MLST types between maternal and neonatal isolates in maternal-neonatal listeriosis cases, confirming that both share the same clonal strain and verifying that vertical transmission is the primary route of mother-to-child transmission [9,15]. Lm possesses multiple virulence factors, adhesion proteins, and internalins that enable rapid bloodstream invasion and successful penetration of both the blood-brain and placental barriers. Furthermore, due to the immature immune system of the fetus, Lm cannot be effectively cleared once it enters the fetal circulation. Combined with the bacterium' s adaptive and evasion capabilities, Lm can proliferate further within the fetus, causing devastating damage to both the fetus and neonate [6,7,13].

3.2 Outcomes of Fetal Lm Infection

Pregnancies complicated by Lm infection typically end in miscarriage, preterm delivery, or stillbirth [8,19]. The fetal outcome varies depending on the gestational stage at infection: first-trimester infections mainly result in spontaneous abortion, second-trimester infections primarily cause intrauterine fetal death, and third-trimester infections predominantly lead to preterm delivery, fetal distress, abnormal fetal heart rate monitoring, or other severe neonatal diseases [3,16,20]. Globally, the rates of fetal death and miscarriage in maternal-neonatal listeriosis cases remain high (approximately 20-29%). The mortality rate among infected fetuses reaches 14.3%, which is 13 times higher than the overall fetal mortality rate [6,7,13,16]. Among surviving neonates, approximately two-thirds are preterm infants [6].

3.3.1 Gestational Age

Gestational age is a crucial predictor of fetal viability [3,8]. Multiple studies have identified 24 weeks as a critical threshold; fetuses younger than 24 weeks have relatively lower survival rates, while survival probability gradually increases beyond this point. Each additional week of gestation increases fetal survival probability by approximately 33% [8]. The survival capacity of third-trimester fetuses is, on average, 22 times that of second-trimester fetuses [8]. Generally, the greater the gestational age at maternal disease onset, the higher the likelihood of delivering a live infant; fetuses beyond 36 weeks of gestation can typically be delivered successfully [16].

3.3.2 Severity of Maternal Infection

The severity of fetal damage from Lm varies with the presence or absence of maternal symptoms [8]. Studies have shown that pregnant women with clinical symptoms are more likely to experience stillbirth and spontaneous abortion. Maternal fever during pregnancy also significantly impacts fetal viability [3,8]. However, other research indicates that the presence of maternal symptoms may lead to early disease detection, enabling prompt maternal treatment and early delivery, which may actually reduce neonatal disease burden and result in less severe or even completely healthy fetal outcomes [8,21]. Therefore, this predictive method is not reliable.

3.3.3 Maternal Bacterial Detection Sites

Studies have demonstrated that compared to other body fluid cultures, positive blood cultures in pregnant women are associated with higher rates of fetal miscarriage or death (59.5% vs. 17.8%). However, in cases of miscarriage or fetal death, 34.2% had negative maternal cultures and other negative tests, indicating that the relationship between fetal outcome and maternal bacterial detection sites requires further investigation [16].

3.3.4 Singleton vs. Multiple Pregnancies

Multiple pregnancies exhibit greater susceptibility to Lm than singleton pregnancies, and the proportion of multiple gestations in maternal-neonatal listeriosis cases has been increasing in recent years. This may be because multiple pregnancies are more prone to preterm delivery and other complications, or because they receive more clinical attention and have more opportunities for pathogen culture, artificially inflating the statistical proportion of multiple gestation cases [16]. The relationship between these factors also requires further exploration.

4.1 Immunological Basis of Neonatal Listeriosis

The neonatal immune system primarily relies on Th2-mediated cellular immunity, which prevents Th1-mediated inflammatory responses against fetal anti-

gens and reduces the risk of spontaneous abortion or preterm delivery [22,23]. However, neonates also exhibit lower expression of various cytokines, collectins, and pattern recognition receptors (TLRs) compared to adults, creating favorable conditions for Lm proliferation and dissemination [6,24].

4.2 Epidemiological Characteristics of Neonatal Listeriosis

International data indicate that the incidence of listeriosis is approximately 0.3-0.4 per 100,000 population. The incidence of Lm infection in pregnant women is 0.12‰, with rates of preterm delivery and miscarriage caused by listeriosis at 2.4‰ each. The incidence of neonatal listeriosis is approximately 0.52‰, though this may vary by region [3,7,25]. These incidence rates are based on cases with positive Lm cultures from blood, cerebrospinal fluid, or fetal appendages; however, cases without cultures or with false-negative results are not included, suggesting that the actual incidence may be underestimated [15].

Overall, the most significant factors affecting clinical manifestations of the disease are the presence of maternal symptoms during pregnancy, treatment status, and placental pathology. The severity of clinical manifestations does not directly correlate with disease prognosis. Although geographic and racial factors influence disease incidence, they have minimal impact on clinical presentation [8,16].

4.3 Classification of Neonatal Listeriosis

Neonatal Lm infection manifests primarily as neonatal death and neonatal listeriosis. Neonatal listeriosis is classified based on onset time into early-onset and late-onset disease [3,6,26]. Early-onset disease occurs from birth to 7 days postpartum, primarily resulting from transplacental infection and manifesting as sepsis symptoms. Late-onset disease occurs from 7 to 60 days postpartum, mainly presenting as meningitis. In addition to transplacental infection, neonates can also acquire the disease by aspirating infected amniotic fluid during delivery [6,13,15]. Neither form has specific manifestations that distinguish them from sepsis caused by other bacteria, and they are often confused with diseases caused by pathogens such as Group B *Streptococcus* and *Neisseria meningitidis* [6].

4.4.1 Early-Onset Neonatal Listeriosis

The predominant Lm serotypes causing early-onset neonatal listeriosis are 1/2a and 1/2b, which account for most neonatal cases. The average time of symptom onset is 1.5 days after birth, with most affected infants being preterm. Clinical manifestations include asphyxia, respiratory distress, fever, hypotonia, circulatory dysfunction, poor responsiveness, and other sepsis symptoms, which may be accompanied by acute respiratory distress and pneumonia. This form is primarily caused by mother-to-child transmission and intrauterine infection, with Lm first infecting the placenta, causing inflammatory changes, and subsequently infecting the fetus [6,7,13].

4.4.2 Late-Onset Neonatal Listeriosis

Late-onset listeriosis typically occurs in full-term infants with uncomplicated deliveries and is less common than early-onset disease. The main pathogenic serotype is 4b. The mothers of affected infants usually show no clinical symptoms during pregnancy. The average time of disease onset is 14.3 days after birth, with the vast majority of late-onset cases presenting as meningitis. Cerebrospinal fluid shows typical meningitis changes (increased cell count and protein, decreased glucose and chloride), often accompanied by fever, irritability, anorexia, diarrhea, and lethargy. Lm can cross the blood-brain barrier to cause meningoencephalitis and brainstem encephalitis. Approximately 30-50% of surviving infants suffer severe neurological sequelae [6,7,13].

Studies show that even with timely and effective treatment, neonatal mortality remains as high as 30%. However, late-onset cases have significantly better prognoses than early-onset cases after prompt treatment. Neonatal listeriosis often leaves varying degrees of sequelae. Some neonates show no clinical symptoms, with diagnosis only made through placental biopsy revealing acute suppurative chorioamnionitis and other signs of infection, with Lm detectable in placental tissue or amniotic fluid. These cases are also classified as neonatal listeriosis, with mild clinical manifestations, high survival rates, and relatively the best prognosis.

5 Pathogen Diagnostic Methods for Maternal-Neonatal Listeriosis

For neonates infected with Lm through mother-to-child transmission, the mortality rate reaches 100% without timely treatment, and remains as high as 30% even with effective therapy, making diagnosis and treatment crucial for disease control. Given the nonspecific clinical manifestations of maternal-neonatal listeriosis, pathogen isolation and culture combined with placental pathology currently represent the gold standard for diagnosis [3,8,13].

Diagnosis of maternal listeriosis typically involves culturing maternal peripheral blood [27]. Additionally, cerebrospinal fluid, amniotic fluid, placental smears, uterine swabs, or cervical smears can be used for culture. Neonates born to culture-positive mothers are automatically classified as infected. The positive rate of blood and cerebrospinal fluid cultures reaches 60-75%. When mothers are asymptomatic and culture-negative, neonatal listeriosis can be confirmed by culturing umbilical cord blood, cerebrospinal fluid, meconium, or umbilical swabs [3,6,9,13,16].

It is particularly important to note that maternal samples should be cultured at the time of fever onset, as listeriosis in mothers is often self-limiting and frequently cleared by the maternal immune system. Furthermore, culture results become unreliable after antibiotic administration [8]. For high-risk neonates with negative cultures, placental pathology should be performed promptly. If

significant inflammatory changes are observed in the placenta, neonatal infection markers should be monitored, as placental inflammation reflects the likelihood of neonatal disease [28,29].

Rapid advances in detection technologies for this pathogen have been made in recent years [30]. The clinical testing procedure involves initial isolation and culture from blood, cerebrospinal fluid, umbilical cord blood, or placental swabs, followed by confirmation of Lm through biochemical reaction tests and hemolysis assays. Subsequent serotyping, MLST typing, and virulence factor analysis provide better understanding of Lm pathogenicity [31]. For serotyping, Lm is classified into 16 serotypes based on somatic O and flagellar H antigens. The primary serotypes causing human disease have been identified as 4b, followed by 1/2a and 1/2b [20,32], which together account for 90% of all listeriosis cases [6,9,13,16]. Specific markers for Lm, including unique genomic sequences and specific virulence gene sequences, have been identified, making PCR detection methods increasingly important for clinical diagnosis [7,33]. Specific virulence factors such as hly, InlA, actA, and plcB can be detected in nearly all infected infants. Many scholars consider InlA an important molecular marker for assessing pathogen virulence, as strains expressing InlA are over 1,000 times more virulent than those that do not [5,13,34]. Analysis of *Listeria monocytogenes* virulence factors can clarify strain pathogenicity and guide clinical treatment intensity to improve neonatal survival rates. Therefore, detection of these virulence factors may become a new direction in diagnostic testing.

6 Prevention and Treatment of Maternal-Neonatal Listeriosis

Early monitoring and effective treatment play crucial roles in improving patient survival and prognosis [35,36]. Lm is sensitive to multiple antibiotics but naturally resistant to cephalosporins. The first-line treatment regimen for listeriosis typically combines ampicillin with gentamicin, while trimethoprim-sulfamethoxazole, vancomycin, and erythromycin serve as second-line agents for Lm bacteremia and maternal listeriosis. Patients allergic to ampicillin or gentamicin can be switched to trimethoprim-sulfamethoxazole or erythromycin [6,13,15].

6.1 Treatment of Pregnant Women

Pharmacological treatment for pregnant women focuses primarily on maternal therapy. Antibiotics should be administered as early as possible, with empirical antibiotic use initiated even before culture results are available. Early effective antibiotic treatment can significantly reduce mortality and improve prognosis [3,13,37,38]. Prompt antibiotic administration and pregnancy termination at disease onset can minimize the risk of neonatal infection. Early antibiotic use can eliminate the pathogen promptly, and timely pregnancy termination not only reduces the risk of vertical transmission but also allows rapid restoration

of the maternal immune system [5,9]. The typical duration of antibiotic therapy is two weeks or from disease onset until delivery, which can be appropriately extended in severe cases [6]. Except for rare cases of maternal meningitis requiring postpartum antibiotic continuation, most mothers do not need further medication as the disease often resolves spontaneously with immune system recovery.

Since some pregnant patients exhibit very mild or even no symptoms during pregnancy, the condition is easily overlooked. When pregnant women have relevant dietary histories or develop unexplained fever, abdominal pain, abnormal fetal heart rate monitoring, or preterm labor, clinicians should consider the possibility of listeriosis, closely monitor disease progression, and administer prophylactic antibiotic therapy [39]. During treatment, fetal heart rate monitoring and amniotic fluid status should be closely observed. If abnormalities occur, timely intervention and appropriate pregnancy termination should be implemented, with prophylactic or therapeutic antibiotics administered to newborns after birth [7].

6.2 Fetal Treatment

For fetal treatment, maternal antibiotic therapy generally effectively controls fetal infection. For high-risk infants, in addition to timely delivery through pregnancy termination, intrauterine or intra-amniotic prophylactic antibiotic injection can be administered to minimize infection risk and extend gestational age as much as possible to improve fetal survival rates [15].

6.3 Neonatal Treatment

Neonatal treatment requires careful consideration of both drug selection and dosage [6,7]. The optimal regimen for early-onset disease is parenteral ampicillin/amoxicillin (100-300 mg/kg daily) or parenteral penicillin G (24 million units/day) for two weeks. International literature recommends combining either of these with gentamicin (1.7 mg/kg every 8 hours, maximum dose 2 mg/kg, for up to 7 days). For late-onset disease, the optimal regimen is parenteral ampicillin/amoxicillin (100-300 mg/kg daily) or parenteral penicillin G (24 million units/day) for at least three weeks, combined with gentamicin (1.7 mg/kg every 8 hours, maximum dose 2 mg/kg, for up to 7 days) [6,7]. The average hospital stay for neonatal patients is 14 days (range 4-50) [6,16]. Skin testing should be performed before drug administration to prevent allergic reactions in neonates. When switching medications, it is important to note that trimethoprim-sulfamethoxazole cannot be used in infants younger than 6 weeks [6,16]. Additionally, neonatal infection markers and vital signs should be monitored closely, and neonatal care should strictly adhere to disinfection protocols to prevent cross-infection.

Lm infection can cause not only miscarriage, stillbirth, and preterm delivery in pregnant women but also neonatal respiratory distress syndrome, asphyxia, and

sepsis, with high fatality rates. Even with timely and effective treatment, the risk of other diseases due to immature organ development increases, potentially leading to sequelae in physical, motor, intellectual, and psychological development. Therefore, children treated for listeriosis should receive regular follow-up after discharge to reduce the occurrence of sequelae.

6.4 Prevention of Listeriosis

Clinically, physicians' understanding of Lm etiology and infection characteristics should be enhanced. When pregnant women show signs of infection, particularly fever, abdominal pain, or diarrhea during pregnancy, specimens should be collected promptly for pathogen detection and early, adequate antibiotic therapy administered. For high-risk neonates, regardless of clinical symptoms, infection-related signs and symptoms should be monitored with relevant laboratory tests. Once infection symptoms or abnormal biochemical indicators are detected, listeriosis should be suspected and anti-infective treatment initiated promptly [16]. For neonates born to mothers with confirmed Lm infection, prophylactic anti-infective treatment should be administered even in the absence of clinical symptoms and signs.

As Lm is a foodborne pathogen, infected pregnant women often have histories of consuming contaminated foods during pregnancy, highlighting the importance of strengthening health education and dietary guidance for pregnant women in the third trimester [3]. Lm can only be killed by high-temperature cooking and can survive in raw or undercooked foods [40]. Therefore, pregnant women should be advised to avoid cold and raw foods, refrain from consuming items stored long-term in refrigerators, separate raw and cooked foods, wash hands and bathe frequently, avoid unpasteurized dairy products and cheeses, and wash meat and vegetables separately during food preparation. Additionally, the significant increase in listeriosis incidence during summer reminds us to maintain food hygiene, avoid overnight leftovers, pay attention to kitchen utensil cleanliness, and reduce bacterial proliferation and pathogenic potential [6,9,15].

Globally, listeriosis incidence shows substantial regional variation, with higher rates among ethnic minorities, likely related to differences in regional dietary cultures [3,8]. Lm contamination is particularly severe in cooked foods, ready-to-eat products, and raw vegetables, suggesting that health departments should strengthen management of food production processes and implement Lm testing before food products reach the market and consumers to reduce disease incidence at its source [9,16].

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Note: Figure translations are in progress. See original paper for figures.