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Do We Really Need to Worry About Listeria in Newborn Infants?

Ifeanyichukwu O. Okike, MD, MRCPCH, Ronald F. Lamont, MB ChB, MD, FRCOG, †‡ and Paul Trafford Heath, MB BS, FRACP, FRCPC**

Listeria monocytogenes is a Gram-positive motile bacterium that causes infections mainly at the extreme ends of life (newborns and the elderly) in the immunocompromised and in pregnant women. Clinical presentation in pregnant mothers is often nonspecific, but disease may lead to stillbirths or early or late neonatal infections. Early presentation in neonates is most common (62%) and case fatality rates range from 14% to 56%.^{1,2} There are few studies that address long-term outcomes, but 1 study of 13 babies with *L. monocytogenes* meningitis in the 1980s revealed that 3 (23%) had moderate to severe disability at 10-year follow-up. Transmission to pregnant women is generally from contaminated foods, thus the best means of prevention is by through control of *L. monocytogenes* in the

food processing environment by appropriate regulation as well as education of pregnant women. Appropriate antibiotic therapy for management of *L. monocytogenes* infections must include a penicillin and for this reason guidelines for empiric antibiotic therapy for babies with possible sepsis or meningitis generally include a penicillin or ampicillin. However, a recent audit of UK neonatal units revealed that 19% and 10%, respectively, failed to include adequate antibiotic cover for *L. monocytogenes* meningitis and sepsis in their empiric antibiotic policies. This is a concern if invasive neonatal listeriosis is to be treated optimally. Some clinicians argue that *L. monocytogenes* is not common or serious enough to warrant the widespread use of such empiric antibiotics. In order to address this we conducted a review of the published literature from the last 20 years, focusing on cases of listeria infection in neonates and in pregnancy.

4 per million population. Between 2003 and 2007, a marked decrease in pregnancy-associated listeriosis was reported in the United States; in contrast, an increase in cases has been observed in England and Wales (110 cases annually between 1990 and 1999 versus 191 cases between 2001 and 2009).³

PREGNANCY-ASSOCIATED LISTERIOSIS

Listeriosis is 18 times more common in pregnant (12/100,000) than nonpregnant women (0.7/100,000), and overall 16–27% of all infections with *L. monocytogenes* occur in pregnancy.^{1,4} This is assumed to reflect the deficiency of cell-mediated immunity, recognized particularly in the 3rd trimester. In a series of 191 cases, 32% of women had symptoms of a “flu-like” illness, 65% had a fever and other symptoms included backache (22%), headache (11%), vomiting and diarrhea (7%), muscle pains (4%) and sore throat (4%). Approximately 29% of the women, however, were asymptomatic.⁵

EPIDEMIOLOGY

Over the last 20 years, listeriosis has become a notifiable disease in many countries. Overall, it is a rare infection; in Europe, rates vary between 0.1 and 11.3 per million population, with approximately 20% involving neonates. The reported incidence of neonatal listeriosis in the United Kingdom (5/100,000 live births) is higher than in the Netherlands (1.3/100,000) and lower than in the United States (8.6/100,000). In 1997, listeriosis was estimated to be responsible for 500 deaths annually in the United States, and in 2000, the prevalence was estimated to be

Outcomes of *L. monocytogenes* Infection in Pregnancy

Although listeriosis during pregnancy is usually mild in the mother, it is severe and sometimes fatal for the fetus. The prognosis for fetuses that are affected early in pregnancy is poorer than those born at later gestations. In 2 large series, the outcomes from *L. monocytogenes* infection in pregnancy included spontaneous abortion (10–20%), preterm birth (50%) and intrauterine fetal death (11%). At birth, 34% of the babies had

From the *Paediatric Infectious Diseases Research Group, Clinical Sciences, St George's, University of London, London; †Division of Surgery, University College London at Northwick Park Institute of Medical Research, Harrow, United Kingdom; and ‡University of Southern Denmark, Odense, Denmark.

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Address for correspondence: Ifeanyichukwu O. Okike, MD, MRCPCH, Clinical Sciences and Vaccine Institute, St George's, University of London, Jenner Wing, Level 2, Room 2.215D, London SW17 0RE, United Kingdom. E-mail: iokike@sgul.ac.uk.

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signs of fetal distress and 75% developed meconium staining of the amniotic fluid, particularly those who were born preterm.

NEONATAL LISTERIOSIS

L. monocytogenes was responsible for 6% of all sepsis presenting in the first 48 hours of life in a network of English neonatal units and for 4% of early onset neonatal meningitis in Australasia. Indeed, the majority of neonatal cases present in the first 7 days of life yet in many guidelines an appropriate antibiotic to cover listeria is recommended for up to 3 months of age. Knowledge of the age of reported cases is therefore essential in developing evidence-based guidelines. In England and Wales, for example, there were no cases of *L. monocytogenes* bacteraemia reported in children beyond 1 month of age between 1998 and 2007. Similarly, Greenhow et al reported that there was no case of *L. monocytogenes* out of 247 positive blood cultures in babies from 1 week to 3 months of age between 2005 and 2007 in the United States and in Israel between 2005 to 2009, and there was no case of *L. monocytogenes* infection identified out of 149 serious bacterial infections in hospitalized febrile infants aged 0–90 days.

A summary of relevant articles from the last 20 years, published in English (or with abstracts in English), with ≥ 5 cases of pregnancy-associated or neonatal *L. monocytogenes* infection and timing of onset (early/late stated) or where listeria infection is mentioned in infants 0–3 months, is presented in the Supplemental Digital Content, <http://links.lww.com/INF/B444>. Of 456 cases where the timing is stated, 342 (75%) were early onset (occurring < 7 days of age) and 114 (25%) were late onset and presented < 28 days of age.^{6–8} However, 5 infants (3 from France and 2 from the United States) were between 1 and 3 months of age. Similarly, in 2 series of *L. monocytogenes* meningitis from England and Wales, 2 cases occurred in infants older than 28 days of age.

Presentation in Neonates

The clinical manifestations of neonatal listeriosis are similar to those of other serious bacterial infections, such as group B Streptococcus. Early onset infection (< 7 days of life) accounts for the majority of cases (62%) and presents with bacteraemia (37%), meningitis (33%), pneumonia (6%) and other (focal) infections (15%).¹ Case fatality rates for EO infection range from 14% to 56%.^{1,2} Infants

with EO *L. monocytogenes* infection are frequently born preterm and in the presence of maternal chorioamnionitis. Babies with infection after the first week of life are typically born to asymptomatic mothers at full term and are well at birth. The mean age of onset of illness is 14 days,⁹ clinical features may be nonspecific and presentation with meningitis (67–93%) is more common than septicemia (17–95%). The case fatality rate is around 25%.

TREATMENT OF PERINATAL LISTERIOSIS

As with other serious bacterial infections, early identification and initiation of therapy in pregnant women can be expected to result in a more favorable neonatal outcome. There are no randomized controlled trials that address the type and duration of antibiotic therapy. Susceptibility to ampicillin and penicillin is well established, although these antibiotics have relatively weak bactericidal activity. An aminoglycoside can be added for synergy, a phenomenon supported by *in vitro* studies and partially replicated in animal models. It is important to note, however, that *L. monocytogenes* may survive intracellularly where gentamicin penetration is poor. Cotrimaxazole and erythromycin are alternatives in cases of penicillin allergy, although the former is contraindicated in pregnancy. Cephalosporins are not active against *L. monocytogenes*. The recommended duration of IV amoxicillin or ampicillin is 2–3 weeks. A recent report revealed a slow increase in aminopenicillin MICs over time (up to 2 ug/mL), highlighting the need for continued microbiological surveillance.¹⁰

DO WE REALLY NEED TO WORRY ABOUT LISTERIA IN NEWBORN INFANTS?

Yes, *L. monocytogenes* infection in neonates is a serious concern. Although not common, in many countries it is still recognized as a cause of severe neonatal infection. It is also indistinguishable at presentation from other causes of neonatal sepsis and is a particularly important cause of meningitis. Accordingly, empirical antibiotic policies for sepsis and meningitis in the first month of life should include an antibiotic, which is active against this pathogen. *L. monocytogenes* is rare in infants after the first month of life, although still capable of

causing meningitis; empiric cover is therefore less important.

PRACTICAL RECOMMENDATIONS

- Educate pregnant women to avoid food known to be associated with *L. monocytogenes* infection.
- Investigate pregnant women with fever and flu-like symptoms and consider early treatment with amoxicillin/ampicillin.
- Investigate babies at risk of infection and start empirical antibiotics as per local epidemiology; ensure that the antibiotics provide cover for *L. monocytogenes*.
- Further research should be focused on strategies to improve prevention, early detection and management of *L. monocytogenes* infection in the neonate.

Link to CDC recommendation for *L. monocytogenes* prevention: Available at: <http://www.cdc.gov/listeria/prevention.html>. Accessed October 3, 2012.

REFERENCES

1. Jackson KA, Iwamoto M, Swerdlow D. Pregnancy-associated listeriosis. *Epidemiol Infect.* 2010;138:1503–1509.
2. Antal EA, Högåsen HR, Sandvik L, et al. Listeriosis in Norway 1977–2003. *Scand J Infect Dis.* 2007;39:398–404.
3. Gillespie IA, McLauchlin J, Little CL, et al. Disease presentation in relation to infection foci for non-pregnancy-associated human listeriosis in England and Wales, 2001 to 2007. *J Clin Microbiol.* 2009;47:3301–3307.
4. Janakiraman V. Listeriosis in pregnancy: diagnosis, treatment, and prevention. *Rev Obstet Gynecol.* 2008;1:179–185.
5. Mylonakis E, Paliou M, Hohmann EL, et al. Listeriosis during pregnancy: a case series and review of 222 cases. *Medicine (Baltimore).* 2002;81:260–269.
6. Siegman-Igra Y, Levin R, Weinberger M, et al. Listeria monocytogenes infection in Israel and review of cases worldwide. *Emerging Infect Dis.* 2002;8:305–310.
7. McLauchlin J. Human listeriosis in Britain, 1967–85, a summary of 722 cases. 2. Listeriosis in non-pregnant individuals, a changing pattern of infection and seasonal incidence. *Epidemiol Infect.* 1990;104:191–201.
8. Jiao Y, Zhang W, Ma J, et al. Early onset of neonatal listeriosis. *Pediatr Int.* 2011;53:1034–1037.
9. Posfay-Barbe KM, Wald ER. Listeriosis. *Semin Fetal Neonatal Med.* 2009;14:228–233.
10. Morvan A, Moubareck C, Leclercq A, et al. Antimicrobial resistance of *Listeria monocytogenes* strains isolated from humans in France. *Antimicrob Agents Chemother.* 2010;54:2728–2731.