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Human listeriosis in Britain, 1967–85, a summary of 722 cases

1. Listeriosis during pregnancy and in the newborn

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SUMMARY

Clinical information was collected on 722 cases of *Listeria monocytogenes* infections in humans occurring in Britain between 1967 and 1985: 248 cases (34%) were associated with pregnancy (maternal, foetal, and neonatal), and comprised 9 cases (4%) of maternal bacteraemia without infection of the foetus; 42 cases (19%) of intra-uterine deaths; 118 cases (54%) of neonatal infection diagnosed within 2 days post-partum; and 50 cases (23%) of neonatal infection diagnosed as ill after 2 days post-partum. An overall mortality of 50% was recorded.

The cases unassociated with pregnancy are described elsewhere (see accompanying paper).

INTRODUCTION

Listeriosis has attracted much recent attention following an apparent increase in incidence in both domestic animals [1, 2] and man [3–6], and a series outbreaks in humans associated with food [7–10]. However, comparatively few data are available concerning human listeriosis in Britain. In this paper are summarized data concerning 248 cases of listeriosis associated either with pregnancy or which occurred in newborns.

METHODS

A case of listeriosis was defined as any episode of disease in an individual where a strain of *L. monocytogenes* was either isolated from a normally sterile anatomical site or was suspected by the clinician as causing disease. From 1981, a short questionnaire was used to obtain information on each patient.

Cases were categorized into two groups: those occurring during pregnancy, the intra-uterine, perinatal and neonatal periods (Group 1); and cases in non-pregnant individuals >12 months of age (Group 2). The categorization of group 1 cases was based on The International Classification of Disease, Injuries and Causes of Death, 1975 [11], and includes: *intra-uterine death*, an infant not born alive; *abortion*, foetal death occurring up to the 28th week of gestation; *stillbirth*, foetal death occurring after the 28th week of gestation; *perinatal deaths*, stillbirths and deaths

within the first week after delivery; *neonatal deaths*, deaths in the first 28 days after delivery. A mother and either her infant, or twin infant siblings were defined as a single case. A preterm or premature infant is defined as an infant born prior to the 38th week of gestation [12].

Neonatal cases were subdivided in a similar way to that previously described [13, 14] into the following categories: *early onset disease*, diagnosed as ill within the first 2 days after delivery; *intermediate onset*, diagnosed as ill between 3 and 5 days after delivery; *late onset disease*, diagnosed as ill after 5 days. Neonatal cases were further subdivided by the site of infection into: *central nervous system* (*CNS*) *infections*, where *L. monocytogenes* was isolated from cerebrospinal fluid (CSF), brain tissue, or a diagnosis of meningitis was made; *other systemic infections*, where *L. monocytogenes* was isolated from the blood, internal organs or cavities, but not from the central nervous system; and *superficial infections*, where *L. monocytogenes* was isolated only from skin, eye, ear, throat, rectum, umbilicus, nasopharynx, gastric aspirate or nasopharyngeal tubes. The term *sepsis neonatorum* is used to denote systemic bacterial infection in the neonate where *L. monocytogenes* was isolated from either blood, CSF and/or other internal sites [15]. The involvement of the respiratory tract was inferred by the isolation of *L. monocytogenes* from upper or lower respiratory tract specimens, and/or where a clinical diagnosis of respiratory distress, asphyxia, pneumonia, chest infection, cyanosis, apnoea, respiratory failure or breathing problems were made.

Between 1967 and 1985, strains from 786 cases of human listeriosis were sent to the Division of Microbiological Reagents and Quality Control (DMRQC) Colindale (previously the Standards Laboratory for Serological Reagents). By the end of 1985, strains from 722 cases remained viable, and all were identified as *Listeria monocytogenes sensu stricto* [4]. Of these cases, 248 (34%) occurred in group 1 (i.e. associated with pregnancy, in the unborn or in newborns). Data from these cases form the basis of this study.

RESULTS

The overall male-to-female ratio in infants was 1·1 : 1 (85 males and 77 females). None of the cases in this group involved successive pregnancies in the same individual. Twin infant siblings were involved in three instances: in one case a bacteraemic episode occurred in a pregnant woman and neither infant was infected; in the remaining two, both infant siblings were infected (early onset neonatal infection). Congenital abnormalities unrelated to listeriosis were reported in one infant with Down's syndrome.

The numbers of cases and time of onset of illness in infants by days post partum are shown in Fig. 1, and comprised: 9 maternal infections without involvement of the foetus, 42 intra-uterine deaths, 118 early onset neonatal cases, 8 intermediate onset neonatal cases and 42 late onset neonatal cases (a further 29 neonatal cases occurred where details of the time of onset of infection was not obtained). Each of these categories will now be considered.

Maternal infection with L. monocytogenes *during pregnancy without evidence of infection of the infant*

Eight cases of maternal influenza-like illness took place during pregnancy where *L. monocytogenes* was isolated from maternal blood cultures, and where the foetus

Table 1. *Neonatal listeriosis: numbers of cases and site of infection in the neonate, and maternal infection*

Onset of infection in the neonate (days post partum)	No. of cases		
	Early (0–2)	Intermediate (3–5)	Late (>5)
Total no. of cases	118	8	42
Sepsis neonatorum (%)	91/113 (81%)	6/8 (75%)	38/40 (95%)
Site of infection in neonate (%)			
Central nervous system	28 (24%)*	2 (25%)	39 (93%)
Other systemic†	63 (53%)*	4 (50%)	1 (2%)
Superficial	22 (19%)*	2 (25%)	2 (5%)
Involvement of the respiratory tract of neonate	52 (44%)	1 (13%)	3 (7%)
Neonatal mortality rate Total died/total outcome known (%)	40/104 (38%)	1/6 (20%)	6/23 (25%)
No. of cases premature‡/ total gestation known (%)	57/87 (66%)	3/5 (60%)	3/16 (19%)
Maternal fever	60 (51%)	2 (25%)	2 (5%)
Isolation of *L. monocytogenes* from maternal sites	52 (44%)	0 (0%)	0 (0%)

* Five of the early onset cases could not be categorized due to insufficient information.

† Other systemic infection, isolation of *L. monocytogenes* from blood or other internal organ or cavity, but not the central nervous system.

‡ Prematurity, birth <38 weeks gestation.

was either uninfected or not reported to be infected. The pyrexial episodes when *L. monocytogenes* was isolated from blood cultures occurred in 1 case immediately after delivery, and in the remaining 7 during pregnancy. In one case, healthy twin infant siblings were born following caesarian section of a 38-week pregnant woman (following a 10-day history of influenza like illness). No information was available on the remaining 7 infants.

One further case of unknown outcome occurred in which a 31-year-old woman in the 36th week of pregnancy developed meningoencephalitis, and *L. monocytogenes* was isolated from the CSF.

Intra-uterine deaths

The 42 cases of intra-uterine death comprised; 31 abortions, 9 stillbirths, and 2 cases of unknown duration of pregnancy. Amongst the cases involving abortion, 10 occurred between the 12th and 20th week of gestation, 18 between the 21st and 28th week, and in 3 cases the duration of pregnancy was not stated. *L. monocytogenes* was isolated from foetal tissue in 26 cases, and placental and/or amniotic tissue in 17 cases.

Maternal fever either prior to, or just after delivery was reported in 32 cases (76%). *L. monocytogenes* was isolated from maternal sites in 22 cases; blood (18 cases), blood and high vaginal swabs (1 case), and high vaginal swabs only (3 cases). In 10 of the abortions, *L. monocytogenes* was isolated solely from maternal blood cultures.

Table 2. *Possible maternal predisposition to listeriosis in 11 of the 248 cases involving pregnancy*

Predisposition	No. of cases
Diabetes	2
Renal transplant	2
Epileptic	1
'Arthritic' (plus anti-inflammatory drugs)	1
Systemic lupus erythematosus	1
Placental abscess	1
Hepatitis B surface antigen positive	1
Mumps infection during pregnancy	1
Rubella infection during pregnancy	1

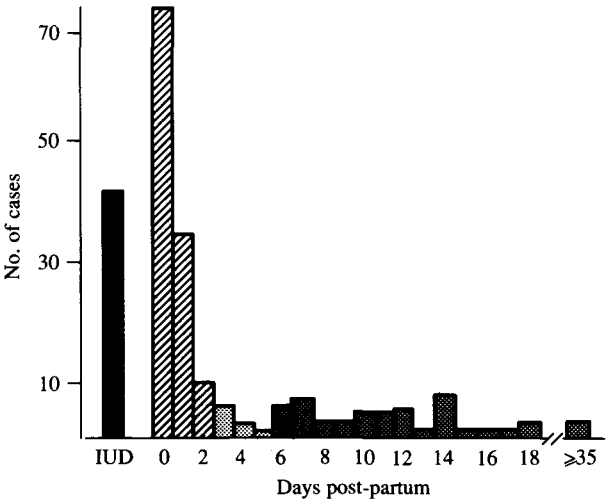

Fig. 1. Onset of illness (time of diagnosis) in days post partum in 210 cases of listeriosis in the neonate and foetus. ■, IUD (intra-uterine death); ▨, early onset; ▩, intermediate onset; ■, late onset.

Early, intermediate and late onset disease in the neonate

A summary of 168 neonatal cases is shown in Table 1; 80% (135/168) had sepsis neonatorum, with similar proportions occurring in each of the onset of infection categories. Early onset infection accounted for 70% (118/168) of the cases and a range of affected sites was recorded; however in the late onset group, more than 90% (39/42 cases) had central nervous system infection (Table 1). Involvement of the respiratory tract in the neonate together with prematurity, maternal fever and isolation of *L. monocytogenes* from maternal sites was a common feature of the early but not the late or intermediate onset categories (Table 1).

The overall neonatal mortality rate was 35% (47 of 133 neonates died), and differed with time of onset of infection (Table 1), the poorest prognosis occurred in the early onset group. The highest mortality rates were found in those infants born earliest in gestation (early onset group only): i.e. 50% (23/46) of those born up to 36 weeks gestation died, compared with 17% (5/29) of those after 36 weeks.

Within the early onset group, those neonates colonized at different sites varied

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in both the proportion of premature births and in mortality rates. Prematurity and fatality were most common in the central nervous system infection group, and least in the superficial infection group. The proportion of premature births were; 78% (14/18), 65% (31/48) and 47% (8/17) for the CNS, other systemic and superficial infection groups respectively; the mortality rates were; 65% (13/20), 36% (20/56) and 20% (4/20) respectively.

Maternal infection and risk factors

Maternal fever and the isolation of *L. monocytogenes* from maternal sites was common in the early onset neonatal group (Table 1), but less frequent than in the intra-uterine death group (previously described). These features were rare in mothers in the late and intermediate onset groups (Table 1). Prior to the introduction of the questionnaire information was not specifically sought concerning the absence of a pyrexial influenza like illness in the mother. In cases occurring after 1981 however, maternal influenza-like illness was absent in 32% (29/91 mothers) of cases involving an intra-uterine death or early onset neonatal infection.

Within all these cases associated with pregnancy, maternal risk factors (in addition to obstetric factors) were uncommon, where underlying disease which may predispose to infection occurred in only 4·5% (11/247) cases (Table 2).

DISCUSSION

This (together with the accompanying paper) is the first summary of a large series of human listeriosis cases in Britain. This study is biased and limited in that cases are included only where strains of *L. monocytogenes* were sent to DMRQC, which may comprise less than 50% of the total number of cases occurring in Britain (D. M. Campbell, Communicable Disease (Scotland) Unit, Ruchill Hospital, Glasgow, personal communication). However, the cases described here comprise a relatively large series over an extended period, and may constitute a sufficiently representative sample to contribute to an understanding of listeriosis in Britain.

Amongst the infants infected, 76% died *in utero*, or presented with early onset neonatal infection. The remaining 24% (Fig. 1) comprised the intermediate and late onset neonatal infections, a similar proportion to the 24% and 36% described by Humbert and co-workers [16] and Larsson and co-workers [17]. A higher proportion of the neonates were found in the late onset category, with 52% (21/40) ill after the 5th day post partum as described by Albritton and colleagues [18].

In cases of foetal death, severe overwhelming multi-system involvement occurred here as described elsewhere [19, 20]. Cases of listeriosis have been identified in the first and second trimesters (this study [16, 21]), hence listeriosis occurs throughout pregnancy, and should not be regarded as a disease exclusively of the third trimester. Increasing attention given to abortions, stillbirths and perinatal deaths in Britain may explain the higher proportion of these in this study than those described elsewhere [16, 19, 22]. In some of the cases involving abortion in this series however, the true cause of foetal loss is unknown since *L.*

monocytogenes was isolated from maternal blood cultures only. The presence of *L. monocytogenes* in the maternal blood stream may be the result of, and not necessarily the cause of, the foetal death. However, early foetal loss is rarely as fully investigated as those later in gestation [23, 24] and this clearly is an area for further study.

Neonatal sepsis shows two patterns of disease, that of 'early onset infection' (within the first few days after birth) and 'late onset infection' (after the 5th day after birth) [14]. The early onset infections are acquired from the maternal sources *in utero*. However late onset infections occur in the previously apparently healthy neonate and is acquired either from maternal sites (including those outside the birth canal), or the postnatal environment (e.g. other human contacts, contaminated equipment or materials). Early onset neonatal infections, follow complications during pregnancy and delivery, present as fulminant multisystem infection (frequently with pneumonia) and have a mortality rate of between 15 and 50%. Late onset infections less often follow complications during pregnancy and delivery, present as more slowly progressive infection (where meningitis is frequent) and show mortality rates of between 10 and 20% [14]. From the data presented here (and by other studies), *L. monocytogenes* is clearly responsible for both early and late onset neonatal infections.

In this study, maternal listeriosis frequently presented as a non-specific influenza-like illness either during pregnancy or immediately after delivery in mothers of uninfected infants, intra-uterine deaths or early onset neonatal cases (Table 1). However, in 32% of the mothers whose infants were in the early onset and intra-uterine death categories, a pyrexial illness was not reported: a similar value to that of 13% and 45% reported by Humbert and co-workers [16] and Relier [19]. This may reflect the lack of symptoms suggestive of infection in these mothers (hence the lack of medical investigation), rather than exposure to *L. monocytogenes per se*. The onset of labour was frequently premature in the early and not the late onset neonatal cases (Table 1). *L. monocytogenes* was frequently isolated from the maternal blood cultures in the cases of intra-uterine deaths, and from the maternal genital tract in the early onset neonatal infections (Table 1). The cultures isolated from maternal sites and corresponding infants were indistinguishable by phage typing [25]. Thus *L. monocytogenes* is acquired from maternal sites in the cases of intra-uterine death and early onset neonatal infection.

Mothers whose infants were categorized into the late and intermediate onset groups generally did not have influenza-like illnesses, nor was *L. monocytogenes* cultured from maternal sites (Table 1). McLauchlin [4] reported that cross-infection in 12 instances occurred by contact between early onset and late onset neonatal cases in this series. Amongst the intermediate and late onset cases, 24% were due to cross-infection, and for every ten early onset cases a late onset case resulted. The source of infection for the remaining 76% of neonates in the late and intermediate onset categories is unknown, but could include maternal sites (including those outside the genital tract), or the post-natal environment.

Meningitis was a common feature in over 90% of the late onset neonatal cases (Table 1). In the early onset cases however, non-meningitic systemic infection

occurred most frequently (58% of cases), with only 24% involving the central nervous system (Table 1). The respiratory tract was frequently involved in the early, but not the late and intermediate onset neonatal groups.

The early onset neonatal cases showed a spectrum of disease, categorized here as CNS involvement, systemic infection without CNS involvement, and infection at superficial sites only. This categorization may be somewhat artificial and biased by the open ended nature of the questionnaire used. However, since both gestational age and mortality rates differed between these three groups, these may represent real differences (possibly due to gestational age at primary exposure to *L. monocytogenes* or the route of infection).

The mortality rates in this study (38% for the early onset group and 25% for the late onset group, Table 1) are at the upper end of the range described by Klein and Marcy [14] for early and late onset neonatal infection. The overall mortality rate for this study was 36%, which is similar to the 34% reported by Humbert and colleagues [16]. The infants born prematurely had an overall mortality rate of 50%, compared with a 17% rate in the full term group. Lower mortality rates in a similar early onset group of neonates were reported by Relier [19], with 34% in the premature group and none of 26 patients in a full term group. The better prognosis in the series described by Relier [19] may reflect a greater familiarity together with a more rapid recognition of the disease since all the cases described occurred in a single hospital. Robertson and co-workers [26] and Fleming and co-workers [8] remarked that, in common with other serious infectious diseases of the very young, early diagnosis together with appropriate management can markedly modify the poor prognosis of neonatal listeriosis.

Possible maternal risk factors leading to infection were not identified here, and the incidence of severe underlying illness was very low (Table 2), unlike the non-pregnant individuals (see accompanying paper). There is evidence from experimental infection in animals to support the view that pregnancy itself may be a risk factor in the acquisition of infection [27–30], but it is not known what contribution this may make in human listeriosis. However, the pregnant woman is more intensively medically investigated than the general population, and the incidence of listeriosis as a mild subclinical infection in the otherwise healthy and non-pregnant individuals is unknown. Maternal infection (bacteraemia) can occur without subsequent infection of the foetus, even if the mother is not treated with antimicrobial agents. If listeriosis is identified (i.e. by isolation of *L. monocytogenes* from maternal blood or amniotic fluid), treatment with antimicrobial agents can result in remission of maternal symptoms and subsequent delivery of an uninfected infant [9, 31–34]. The maternal immune system is manifestly capable of dealing with the listerial challenge and serious maternal disease rarely occurs. Only one case of serious systemic disease (meningoencephalitis) in a pregnant woman occurred in this series, and the rarity of such infection has been noted by others [16, 33, 35]. The reasons why central nervous system infections occur very rarely in pregnant women, but in 57% of the cases not associated with pregnancy (see accompanying paper) are not known.

Recurrent listeriosis in the same woman during different pregnancies did not occur in this study. This has been reported elsewhere [36], but is extremely rare

and did not occur in other large series of patients [16, 17, 37]. However, recurrent episodes of listeriosis do occur in non-pregnant individuals [38], thus chronic infection or long term carriage may take place.

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