

Perinatal listeriosis patients at a maternity hospital in Beijing, China, during 2013 – 2018

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Abstract

Background: Listeriosis is a rare but severe foodborne infectious disease. Perinatal listeriosis is extremely prone to causing septicaemia, central nervous system (CNS) infection, and serious adverse pregnancy outcomes (abortion and neonate death). This research reports perinatal listeriosis cases over the course of six years at Beijing Obstetrics and Gynecology Hospital (BOGH), which is the largest maternity hospital in China.

Methods: We retrospectively searched all the laboratory confirmed pregnancy-associated listeriosis cases during Jan 1, 2013 to Dec 31, 2018. The clinical manifestations, laboratory results, perinatal complications and outcomes (follow-up for half a year after birth) were investigated.

Results: In BOGH, 12 perinatal listeriosis cases were diagnosed based on *Listeria monocytogenes* positive culture, including 10 single pregnancies and 2 twin pregnancies, and the incidence of which is 13.7/100,000 deliveries. Among those cases, four pregnant women and four newborns had septicaemia, and two of the neonatal septicaemia also got CNS infection. All the maternal patients recovered. For the fourteen offsprings, there were 8 newborns and 6 aborted fetuses, with two newborns died and 6 survived among the 8 newborns, and none of survivors had sequelae. The fetoneonatal fatality ratio is 57.1%.

Conclusions: Perinatal listeriosis is associated with high mortality, which has become a public health concern. Subsequently, further researches about perinatal listeriosis among a wider range of population are needed to strengthen the epidemiological understanding of listeriosis in China.

1. Background

Listeria monocytogenes (*L. monocytogenes*) is a facultative anaerobic Gram-positive bacterium that causes severe foodborne illnesses carrying substantial mortality (20% to 30%) [1]. This pathogen, a ubiquitous bacterium in nature, can be isolated from soil, stream water, vegetables, fruits, raw meat, milk products, the ready-to-eat products, and even processed foods stored at refrigerator, because *Listeria* can survive and grow at a wide range of pH and temperatures, and high salt concentrations [2-4].

L. monocytogenes is mainly transmitted through the consumption of contaminated food. After crossing the intestinal mucosal barrier, *L. monocytogenes* can spread through blood, and shows a preference for central nervous system (CNS) and the placenta [5]. The increased progesterone during pregnancy weakens the cellular immunity, which makes the expectant mothers particularly susceptible to microorganisms like *L. monocytogenes* [6,7]. The infection risk of pregnant women is 12- to 20- times higher than that of the general population [8,9]. It is reported that incidence of pregnancy-related listeriosis was about 4.3-25 cases per 100,000 births [10-13]. As shown in systematic reviews, the pregnancy-associated cases accounted for 20.7%-43% of all listeriosis cases worldwide [14,15]. In China, human listeriosis surveillance system was established in 2013. But as yet, listeriosis is not a notifiable disease in China. Two recent reports showed that in China, 41.1%-52% of clinical cases were perinatal listeriosis, which means the burden of pregnancy-related listeriosis in the country is not light [16,17]. Pregnant women infected with *L. monocytogenes* is usually asymptomatic or with nonspecific clinical symptoms such as gastrointestinal and flu-like symptoms. However, perinatal listeriosis patients often have adverse pregnant outcomes, including fetal loss, preterm birth and neonatal listeriosis.

This report retrospectively reviews all the laboratory-confirmed pregnancy-associated listeriosis cases at Beijing obstetrics and gynecology hospital (BOGH) during January 2013 to December 2018, which is a high-level maternal

and child health care hospital with 660 beds in Beijing, China[1]. Further, we detail the clinical characteristics and outcomes of these *L. monocytogenes* infected perinatal patients.

2. Methods

The number of births in BOGH exceeds 14,000 every year. We retrospectively analyze the clinical data of all the laboratory-confirmed pregnancy-associated *L. monocytogenes* infections during January 1, 2013 to December 31, 2018, based on a list generated from the department of Disease Prevention and Control and Nosocomial Infection of BOGH. The clinical information of all patients are stored in the electronic database since 2013.

Pregnancy-associated listeriosis cases includes illness with an onset during pregnancy or within the first 2 weeks of the postpartum period and illness in the neonate between birth and 4 weeks^[18]. All the confirmed cases were based on the isolation of *L. monocytogenes* from a normally sterile site (eg, blood or cerebrospinal fluid (CSF)) or products of conception (eg, placental or fetal tissue), with the presence of compatible clinical symptoms. A perinatal listeriosis case was defined based on isolation of *L. monocytogenes* from a clinical sterile sample of pregnant woman or foetus, stillborn, and newborn aged < 4 weeks^[9]. Confirmed cases with isolation of *L. monocytogenes* from both mother and neonate were counted as single cases. Neonatal cases were divided to early onset (diagnosed between birth and day 6) and late onset (diagnosed between 7 and 28 days)^[18,19]. *L. monocytogenes* CNS infection were diagnosed in the case that *L. monocytogenes* was isolated from a patient's CSF or when a patient had neurological symptoms (altered consciousness, seizures, nuchal rigidity, or focal neurological symptoms, and an increased white blood cell (WBC) count in the CSF) and blood cultured *L. monocytogenes*. When the patient did not meet the criteria of CNS infection diagnosis but *L. monocytogenes* was cultured from the blood, this patient was considered to have septicaemia^[20].

The culturing, isolation and identification of *L. monocytogenes* rely on the traditional blood agar plating followed by automated biochemical confirmation (bioMérieux VITEK 2 COMPACT, France) with visible colonies^[20].

We define 'stillbirth' as death in the fetus between 24 and 41 weeks of gestation, and a fetus loss before 24 weeks is defined as an inevitable miscarriage. Furthermore, we calculate the overall fatality of pregnancy-associated listeriosis, including miscarriages, stillbirths and newborn deaths.

We used descriptive statistics in this study. Where appropriate, data were expressed as mean \pm SD (standard deviation).

3. Results

3.1 Annual and seasonal number of perinatal listeriosis cases in the considered period

We identified 12 cases of pregnancy-associated listeriosis from the overall 87,644 deliveries, and the incidence was 13.7/100,000 births. In detail, the annual and seasonal number of pregnancy-associated listeriosis cases were shown in Fig. 1a and Fig. 1b, respectively. We found ten cases (10/12 83.33%) occurred during summer and fall months (i.e. June to November) during 2013 to 2018.

3.2 Characteristics of pregnancy-associated listeriosis cases

The characteristics of the pregnancy-associated cases are summarized in Table 1. There were 12 maternal, and 14 neonatal infections with *L. monocytogenes*.

3.3 Clinical characteristics of maternal listeriosis cases

The median age of these women was 29 years (range, 25–41 years). The clinical characteristics of 12 maternal listeriosis patients are described in Table 2. Among them, 10 were singleton pregnancy and 2 were twin pregnancy (i.e. Case 2 and 9). Six cases were infected with *L. monocytogenes* in the middle trimester pregnancy (between 14 and 27 weeks) and the other six in the third trimester pregnancy (between 28 and 41 weeks), and their median gestation was 29.3 weeks (range, 20.0–38.1 weeks). 11 of 12 maternal listeriosis patients had prenatal fever (38–39.3°C), and 3 of 12 had Flu-like symptoms. Five patients had gastrointestinal symptoms (diarrhea and abdominal pain). Various obstetrical symptoms were presented among the 12 pregnant women, including decreased fetal movement (n = 5), intrauterine fetal death (n = 2), premature rupture of the membranes (PROM, n = 2), and vaginal bleeding (n = 1). All the symptomatic women received antibiotic therapy, and eight patients received only cephalosporin antibiotics at their beginnings.

Several adverse complications were presented during their pregnant periods. Among the 12 maternal patients, apart from one normal labor, five pregnant women progressed to fetal loss and six result in premature deliveries. Three pregnant women had postpartum hemorrhage, five progressed to amniotic fluid contamination, and three received induce labor. Four cases carried out Caesarean section (C-section) due to the abnormal fetal heart rates. No mother had CNS infection because there were neither neurological symptoms nor positive cultured *L. monocytogenes* from CSF. One third (4/12) had septicaemia. All the maternal patients finally recovered after delivery with no sequelae.

3.4 Clinical characteristics and outcomes of the offsprings

The clinical characteristics and outcomes of all the 14 offsprings born from the 12 maternal listeriosis patients are summarized in Table 3, and we found no late-onset cases of newborn-infant listeriosis. Among the offsprings, 9 out of 14 (64.29%) were girls. The median birth weight is 1,305g (range, 380–3,565g). Except two inevitable miscarriages and four fetal stillbirths, eight babies were presented with fetal distress. Four newborns received intubation. 6 out of 14 babies were confirmed *L. monocytogenes* infection based on microbiological methods (laryngeal swab: 2; blood + laryngeal swab: 2; blood + CSF + laryngeal swab: 2). Two neonates were diagnosed with CNS infection and four had septicaemia. Six infants survived, and two newborns were dead within 2 days after birth. None of the survivors had neurological sequelae through a six-month follow-up.

4. Discussion And Conclusions

The incidence of perinatal listeriosis in BOGH was 13.7/100,000 deliveries, which was consistent with the reports [10–13]. In our study, half of the pregnancy-associated listeriosis cases (6/12, Case 2, 3, 5, 8, 10, and 12) suffered from listeriosis in the middle trimester pregnancy, and all of their 7 offsprings were dead. While among the other six perinatal cases (Case 1, 4, 6, 7, 9, and 11; 7 newborns in total), except that the infant of Case 1 (31.3 week) deceased day 2 after birth, the remaining 6 livebirths survived without sequelae (including 4 septicaemia newborns and 2 of them also had CNS infection). This was consistent with the reports [13, 21] that the prognosis of neonate from maternal listeriosis patients occurring during late pregnancy were quite excellent even the infants were infected with *L. monocytogenes*, while the outcomes of perinatal cases infected before 28 weeks were very bad. The overall cases-fatality rate of the offsprings was 57.1%, which was close to 32.68%–50.7% reported in the two recent systematic reviews in the mainland of China [16, 22]. From these numbers, the fetoneonatal listeriosis mortality rate

in China was very high, which was in contrast to the low child mortality estimated by de Noordhout CM and colleagues^[14] during 2010.

We found that 66.67% (8/12) of maternal patients had received only cephalosporins antibiotics at their beginnings since cephalosporins are the preferred empirical therapy for the obstetric infections with nonspecific clinical symptoms in China. However, *L. monocytogenes* strains were susceptible to most antibiotics (e.g. ampicillin and penicillin G (PNG)) while not sensitive to cephalosporins^[23-26]. Delayed diagnosis and inappropriate antibiotic administration could decrease the probability of a favorable outcome among *L. monocytogenes* affection cases^[21, 27]. In China, there are still no national guidelines for the treatment of listeriosis. According to Hof et al^[24], when listeriosis is a likely diagnosis, the use of ampicillin, PNG, or vancomycin provides empiric coverage for *L. monocytogenes*. But empiric therapy for bacterial meningitis with ampicillin may not be necessary for children beyond the neonatal period^[28]. Ampicillin or PNG, with or without aminoglycoside or gentamicin, is recommended for all forms of listeriosis. Trimethoprim-sulfamethoxazole can be used as an alternative treatment. Two to three weeks of therapy is sufficient for most forms of listeriosis. Rhombencephalitis with abscess formation in the CNS may require 4-week therapy^[27, 29]. However, researchers recently found high resistant levels of *L. monocytogenes* to many antibiotics (ampicillin, PNG, tetracycline, cefotaxime, etc.) among the clinical and food isolates, which was considered as a serious problem for the treatment of listeriosis^[30, 31].

Listeriosis is a typical foodborne disease which means food contamination is the major source of infection. Data from Beijing centers for disease control and prevention (CDC) showed that among the 12 maternal patients, only Case 5 had positive cultured *L. monocytogenes* in the samples obtained from her kitchen and had the same strain with the patient. While various food sources of *L. monocytogenes* made it difficult to trace the pathogens and identify the food source.

The inspection reports^[32, 33] showed the average prevalence of *L. monocytogenes* in Chinese food products was about 4.42%^[32], and in the retail markets of Beijing 15.20% of the raw pork was contaminated^[33]. That is, food safety of *L. monocytogenes* contamination is still a problem in China. Besides, processed food stored and pasteurized dairy products in the refrigerator are also vulnerable to recontamination because that *L. monocytogene* can grow very well at 4°C^[34, 35]. There are no diet guidelines for the prevention of *L. monocytogenes* infection in China. Therefore, improving the awareness of food safety among the people at higher risk of *L. monocytogenes* infection, especially the pregnant women and immune compromised population, can facilitate prevention. Due to that doctors are the most credible source of health information for patients, campaigns among doctors about healthy diet habits education (such as, refusing to direct eat pasteurized dairy products and cooked food stored in the refrigerator without reheating, reducing the frequency of eating out eat out less often, etc.) are recommended for pregnant women.

There are several limitations in this study. First, it is a retrospective research over a protracted timespan of six years that there is no fresh sample available for further research, such as microbial typing. Second, the lack of epidemiological investigations is also a limitation of the study which does not allow to identify the food source and make clear recommendations. Third, it consists of a relatively small sample size in this study. Big data investigation of pregnancy-associated listeriosis is conducive to further understanding the demographic distribution in China.

Declarations

Ethics approval and consent to participate

The raw data is not publicly available, but as the medical staff at the hospital we have access to it. The need for ethics approval of our study was deemed unnecessary according to the national regulation –“The Regulations of Ethical Reviews of Biomedical Research Involving Human Subjects (2016)”^[1] issued by National Health and Family Planning Commission of the People's Republic of China. And the need for ethics approval was waived by the Ethics Committee of Capital Medical University Beijing Obstetrics and Gynecology Hospital. The data used in this study was anonymised before its use.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable.

Authors' contributions

CH Yin and RX Liu conceived and designed the study. CY Li, RX Liu, HH Zeng, X Ding, Y Chen, XW Liu, L Zhou, X Wang, SS Hu, YM Cheng, Z Cao collected the data. CY Li, RX Liu finished literature search, data interpretation, and writing. All the authors critically reviewed this report and approved the final version.

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Abbreviations

CNS: central nervous system; BOGH: Beijing Obstetrics and Gynecology Hospital; *L. monocytogenes*: *Listeria monocytogenes*; CSF: cerebrospinal fluid; WBC: white blood cell; PNG: penicillin-G; SLE: systemic lupus erythematosus; GDM: gestational diabetes mellitus; C-section: Caesarean section; PROM: premature rupture of the membranes; NA: not available; SpO₂: oxygen saturation from pulse oximetry; SOB: shortness of breath; DIC: disseminated intravascular coagulation; NRDS: neonatal respiratory distress syndrome; max, maximum; min, minimum; SD, standard deviation.

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Tables

Table 1 Characteristics of 12 pregnancy-associated listeriosis cases

Group	Neonatal	Maternal
Total	12	14
Median age (min, max), y	29 (25, 41)	NA
Median gestation (min, max), wk	29.0 (20.0, 38.1)	29.0 (20.0, 38.1)
Underlying disease		
GDM	2 (16.67)	
SLE	1 (8.33)	
Clinical manifestations		
Fever	11 (91.67)	
Gastrointestinal symptoms	5 (41.67)	
Flu-like symptoms	3 (25)	
Laboratory findings		
Peripheral WBC, mean \pm SD, $10^9/L$	21.13 \pm 6.55	
Neutrophils, %, median (min, max)	82.55 (74.3, 92.6)	
Mononuclear, mean \pm SD, $10^9/L$	0.98 \pm 0.34	
Mortality	0	8 (57.1)

Data are presented as No. (%) unless otherwise specified.

Abbreviations: max, maximum; min, minimum; NA, not applicable; GDM, gestational diabetes mellitus; SLE, systemic lupus erythematosus; WBC, white blood cell; SD, standard deviation.

Table 2 Clinical characteristics of 12 maternal listeriosis cases

No	Gestation (wk)	Obstetrical manifestations	Culture sites				Initial antibiotic	Switched antibiotic	Maternal complications and outcomes
			Maternal blood	Placental tissue	Cervical secretion	Others			
1	31.3	decreased fetal movement 3d; fetal distress; Tmax:39.3°C	(-)	(+)	/	/	metronidazole + amoxicillin 4d	No	premature delivery; C-section; severe meconium stained amniotic fluid; recovered
2	24.4	decreased fetal movement 3d; lower abdominal pain; twin pregnancy; PROM; Tmax:38.5°C	(-)	(+)	(+)	/	cefuroxime 3d	No	stillbirth; recovered
3	20.0	abdominal pain; fetal movement disappear 3d; chill; Tmax:38.7°C	(-)	(+)	(-)	hydrothorax, ascite, amniotic fluid (+)	amoxicillin 3d	No	inevitable miscarriage; induced labor; recovered
4	34.3	decreased fetal movement 1d; uterine contraction; fetal distress; headache; Tmax:38.8°C	(-)	(+)	(-)	/	cefmetazole 1d	moxifloxacin 6d	premature delivery; severe meconium stained amniotic fluid; recovered
5	26.0	lower abdominal pain 17h; PROM; fetal distress; septicaemia; Tmax:39°C	(+)	(+)	(-)	/	cefuroxime 3d	metronidazole 3d	stillbirth; induced labor; recovered
6	36.1	decreased fetal movement 2d; fetal distress; polyhydramnios; Tmax:38°C	(-)	(+)	/	/	cefuroxime 3d	No	premature delivery; C-section; severe meconium stained amniotic fluid; recovered
7	38.1	fetal distress; Tmax:39.2°C	(-)	(+)	/	/	metronidazole + ceftriaxone 4d	No	normal labor; postpartum hemorrhage; C-section; severe meconium stained amniotic fluid; recovered
8	21.7	fever15d; intrauterine fetal death1d; lower abdominal pain; headache; Tmax:39.1°C	(-)	(+)	(-)	/	cefuroxime 8d + cefdinir 5d	moxifloxacin 6d	inevitable miscarriage; induced labor; recovered
9	35.6	fetal distress; threatened prematurity; twin pregnancy; septicaemia; Tmax:38.4°C	(+)	(-)	/	/	ceftriaxone 5d	No	premature delivery; postpartum hemorrhage; recovered
10	24.9	fever7d; fetal distress; abdominal pain; septicaemia; Tmax:39.3°C	(+)	(+)	(-)	/	ceftriaxone 7d	PNG 4d	stillbirth; recovered
11	35.4	fetal distress; decreased fetal movement 1d; afebrile	(-)	(+)	/	/	cefuroxime 3d	No	premature delivery; recovered

12	27.3	fever 2w; prematurity; vaginal bleeding; uterine contraction; septicaemia; Tmax:39°C	(+)	(+)	(-)	/	clindamycin + ceftriaxone 2d	azithromycin + PNG 7d	premature delivery; postpartum hemorrhage; C-section; mild meconium stained amniotic fluid; recovered
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Abbreviations: Tmax, maximal temperature; GDM, gestational diabetes mellitus; ; SLE, systemic lupus erythematosus; PROM, premature rupture of the membranes; C-section, cesarean section; PNG, penicillin-G.

Table 3 Clinical characteristics and outcomes of all the 14 offsprings

No.	Birth weight (g)	Presentation	Culture sites			Amniotic fluid contamination	Initial antibiotic	Switched antibiotic	Intubation	Complications	Outcomes	
			Feto-neonatal blood	CSF	Laryngeal swab							
1	1610	fetal distress; apgar 6; SpO2 92% on ambient air; rash	(-)	/	(+)	Yes	NA	NA	Yes	preterm birth; neonatal asphyxia; pneumonia; hypoglycemia, DIC; septic shock; renal failure; hyperlactacidemia; metabolic acidosis	deceased day 2; infant listeriosis	
2.1 & 2.2	740/560	fetal distress; decreased fetal movement	/	/	/	No	/	/	/	stillbirth; induced labor	death	
3	440	fetal distress; decreased fetal movement	/	/	(+)	No	/	/	/	inevitable miscarriage; induced labor	infant listeriosis	
4	2275	fetal distress; apgar 9; SOB; SpO2 80% on ambient air; rash	(+)	(+)	(+)	Yes	NA	NA	Yes	septicaemia; preterm birth; CNS infection; meningitis; intrauterine infection; low birth weight; hypoglycemia; DIC; sepsis; thrombocytopenia; myocardial infarction	survived; infant listeriosis	
5	1000	fetal distress	/	/	/	No	/	/	/	stillbirth	Death	
6	2565	fetal distress; apgar 10; SpO2 95% on ambient air	(+)	/	(+)	Yes	cefotaxime + PNG 5d	meropenem + PNG 9d	No	septicaemia; preterm birth; intrauterine infection	survived; infant listeriosis	
7	3565	fetal distress; apgar 8; SpO2 88% on ambient air; meconium aspiration	(+)	/	(+)	Yes	piperacillin 3d	ceftazidime + vancomycin 12d	Yes	septicaemia; intrauterine infection; pneumonia; hyperlactacidemia; neonatal encephalopathy; anemia; myocardial infarction; thrombocytopenia	survived; infant listeriosis	
8	380	intrauterine fetal death	/	/	/	No	/	/	/	inevitable miscarriage	induced labor	
9.1	2730	fetal distress; apgar 8; SOB; SpO2 92% on ambient air	(-)	(-)	(-)	No	cefepime PNG 10d	+	No	No	preterm birth; pneumonia; patent foramen ovale	survived
9.2	2285	fetal distress; apgar 7; SOB; SpO2 90% on ambient air	(+)	(+)	(+)	No	meropenem PNG 19d	+	No	No	preterm birth; septicaemia; low birth weight; CNS infection; meningitis; liver function lesion, pneumonia; metabolic acidosis; hypoglycemia; anemia, neutropenia; patent foramen ovale; patent ductus arteriosus	survived; infant listeriosis
10	620	fetal distress	/	/	/	No	/	/	/	stillbirth	death	
11	2810	fetal distress; apgar 10; SpO2 96% on ambient air; cyanosis	(-)	/	(-)	No	PNG+latamoxef 7d	cefepime 7d	No	No	preterm birth; pneumonia; neonatal infection; hypocalcemia; neonatal jaundice; patent foramen ovale; hydronephrosis	survived
12	820	fetal distress; apgar 8; SpO2 94% on ambient air	/	/	(-)	Yes	/	/	Yes	extremely low birth weight; preterm birth; hyperlactacidemia; NRDS	deceased day 1	

Abbreviations: NA, not available; C-section, cesarean section; SpO2, oxygen saturation from pulse oximetry; SOB, shortness of

Figures

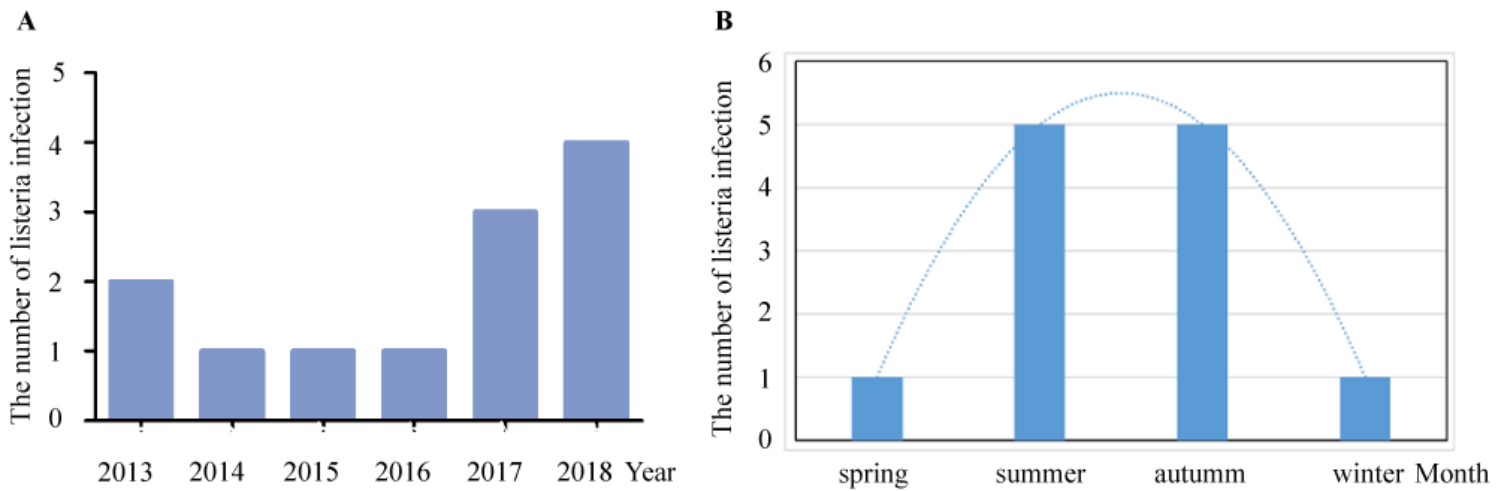


Figure 1

The annual and seasonal number of pregnancy-associated listeriosis cases during 2013 to 2018. (a) Annual number of perinatal listeriosis infections. (b) Seasonal number of perinatal listeriosis cases. Spring (March, April, May), summer (June, July, August), fall (September, October, November), and winter (December, January and February).