

# Perinatal listeriosis patients at a maternity hospital in Beijing, China

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## Research article

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# Abstract

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

**Methods:** Beijing Obstetrics and Gynecology Hospital (BOGH) is the largest maternal and child health care hospital in China. We retrospectively searched all the laboratory confirmed 12 pregnancy-associated listeriosis cases during Jan 1, 2013 to Dec 31, 2018. The clinical manifestations, laboratory results, perinatal complications and outcomes were investigated.

**Results:** In BOGH, 12 perinatal listeriosis cases were diagnosed based on *Listeria* positive culture, including 10 single pregnancies and 2 twin pregnancies, and the incidence of which is 13.7/100,000 deliveries (12/87,644). Among those cases, four pregnant women and four newborns had septicaemia, and two of the neonatal septicaemia also got CNS (central nervous system) 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% (8/14).

**Conclusions:** Perinatal listeriosis is associated with high morbidity and mortality. It has been confirmed that many factors contribute to the high mortality, such as high proportion of second trimester onset, empiric antibiotics with low pathogenic bacterium effective coverage.

## 1. Background

*Listeria monocytogenes* (*L. monocytogenes*) is an aerobic and facultatively 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, and even processed foods stored at refrigerator, because *Listeria* can survive difficult circumstances, such as a wide pH range, high salt concentrations and low temperature [2–4].

*Listeria* can be transmitted through the consumption of contaminated food. After crossing the intestinal mucosal barrier, *Listeria* 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 *Listeria* [6, 7]. The infection risk of pregnant women is at least 18 times higher than that of the general population [2, 8]. It is reported that incidence of pregnancy-related listeriosis was about 1.3–25.2 cases per 100,000 births [9–13]. As shown in systematic reviews, the pregnancy-associated cases accounted for 20.7%–43% of all listeriosis cases worldwide [14, 15]. Pregnant women infected with *Listeria* is usually asymptomatic or with nonspecific clinical symptoms such as 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. Further, we detail the

clinical characteristics and outcomes of these listeria infected perinatal patients.

## 2. Methods

BOGH is a high-level maternal and child health care special hospital with 660 beds in Beijing, China. 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.

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<sup>[16]</sup>. 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 sample of pregnant woman or foetus, stillborn, and newborn aged < 4 weeks<sup>[9]</sup>. Confirmed cases with isolation of *Listeria* 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)<sup>[16, 17]</sup>.

*Listeria* CNS infection were diagnosed in the case that *Listeria* 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 *Listeria*. When the patient did not meet the criteria of CNS infection diagnosis but *Listeria* was cultured from the blood, this patient was considered to have septicaemia<sup>[18]</sup>.

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.

## 3. Results

### 3.1 Annual and seasonal number of perinatal listeriosis cases

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).

#### 3.2 Laboratory characteristics of maternal listeriosis cases

The laboratory characteristics of the maternal listeriosis patients was shown in Table 1. The peripheral WBC count of all the 12 maternal cases increased significantly ( $14.56-39.92 \times 10^9/L$ ), accompanied by notable elevated percent of neutrophile granulocyte (74.3–92.6%), and 83.33% patients (10/12) had elevated level of mononuclear ( $0.79-1.79 \times 10^9/L$ ). All mothers had culture-proven *Listeria* infection (only placental tissue: 6;

placental tissue + blood: 3; placental tissue + cervical secretion: 1; only blood: 1; placental tissue + Amniotic fluid + hydrothorax + ascite: 1).

Table 1  
Laboratory characteristics of 12 maternal Listeria cases

No.	Laboratory findings			Culture sites					
	WBC 10 <sup>9</sup> /L	Neutrophils %	Monocyte 10 <sup>9</sup> /L	Maternal blood	CSF	Placental tissue	Cervical secretion	Amniotic fluid	Others
1	20.63	74.3	0.79	(-)	/	(+)	/	/	/
2	24.89	89.2	0.83	(-)	/	(+)	(+)	/	/
3	16.15	82.7	0.99	(-)	/	(+)	(-)	(+)	hydrothorax & ascite (+)
4	22.16	88.6	0.88	(-)	/	(+)	(-)	/	/
5	20.39	82.4	1.46	(+)	/	(+)	(-)	/	/
6	19.36	78.4	0.89	(-)	/	(+)	/	/	/
7	17.47	92.6	0.93	(-)	/	(+)	/	/	/
8	39.92	87.2	1.79	(-)	/	(+)	(-)	/	/
9	17.08	80.3	0.61	(+)	/	(-)	/	/	/
10	19.77	81.7	0.81	(+)	/	(+)	(-)	/	/
11	14.56	84.3	0.66	(-)	/	(+)	/	/	/
12	21.19	81.1	1.08	(+)	/	(+)	(-)	/	/

Abbreviations: WBC, peripheral white blood cell count; CSF, cerebrospinal fluid.

### 3.3 Clinical characteristics of maternal listeriosis cases

The median age of these women was 29 (the range is 25–41). 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 Listeria 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 (the range is 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. None had diarrhea, which was the most common gastrointestinal symptoms. Various obstetrical symptoms were presented among the 12 pregnant women, including decreased fetal movement (5 cases), intrauterine fetal death (2 cases), premature rupture of the membranes (PROM, 2 cases), and vaginal bleeding (1 case). All the symptomatic women received antibiotic therapy (only cephalosporin antibiotic: 4; metronidazole + amoxicillin: 1; amoxicillin: 1; cephalosporin + metronidazole: 2; cephalosporin + moxifloxacin: 2; cephalosporin + penicillin-G (PNG): 1; clindamycin + ceftriaxone + cefuroxime + azithromycin + PNG: 1). Three cases had underlying diseases (systemic lupus erythematosus (SLE): 1; gestational diabetes mellitus (GDM): 2). 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. Four pregnant women had postpartum hemorrhage (i.e. the blood loss exceeded 500 ml within 24 hours after childbirth), 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 mothers had CNS infection because there were neither neurological symptoms nor positive cultured Listeria 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 characteristics and outcomes of all the 14 offsprings born from the 12 maternal listeriosis patients were described 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. Most of the infant and fetus had low birth weights (the median weight is 1,305 g and the range is 380–3,565 g). 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 *Listeria* 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. The overall fetoneonatal fatality ratio is 57.1% (8/14).

## 4. Discussion

The incidence of perinatal listeriosis in BOGH was 13.7/100,000 deliveries, which was consistent with the reports (their overall range is 1.3–25.2/100,000 births) <sup>[9–13]</sup>. All the 12 pregnancy-associated listeriosis cases were non-clustered. Most of the cases (10/12) occurred during summer and fall months, which was also consistent with the reports <sup>[19–21]</sup>, and Stefanie Evans Gilbreth et al. <sup>[22]</sup> had proved that the recovery of *L. monocytogenes* was significant in the summer months since high temperature environments could promote the *Listeria* reproduction.

In our study, half of the pregnancy-associated listeriosis cases (6/12, Case 2, 3, 5, 8, 10, and 12) were infected with listeriosis in the middle trimester pregnancy (between 14 and 27 weeks), 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). Similarly, Sisó C et al. <sup>[23]</sup>, based on 25-years investigation on listeriosis pregnancy, found that those perinatal listeriosis cases occurring before 28 weeks had poorer outcomes than during late pregnancy. 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 <sup>[21, 24]</sup>. 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 <sup>[14]</sup> during 2010. This was because that the monitoring system for *Listeria* infection in China hadn't be established until 2013, and the listeriosis cases before 2013 were not adequately reported. 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) while not sensitive to cephalosporins <sup>[19, 25]</sup>. Delayed diagnosis and inappropriate antibiotic administration could decrease the probability of a favorable outcome among *Listeria* affection cases <sup>[23, 26]</sup>. In this study, the high proportion (6/12) of the infections occurred in the middle pregnancy, and the delayed diagnosis and unreasonable antibiotic use, were responsible for the high death rate of the 12 perinatal listeriosis cases.

Among the 12 maternal patients, only Case 5 had positive cultured *Listeria* in the samples obtained from her kitchen, since various sources of *Listeria* made it difficult to trace the pathogens. Food contamination was the major source of infection, and the inspection reports <sup>[27, 28]</sup> showed the average prevalence of *Listeria* in Chinese food products was about 4.42% <sup>[27]</sup>, and in the retail markets of Beijing 15.20% of the raw pork was

contaminated <sup>[28]</sup>. Listeriosis is a typical foodborne disease, therefore, improving the awareness of food safety among the high-risk group of Listeria infection, especially the pregnant women and immune compromised population, can facilitate prevention. Due to that doctors are the most credible source of health information, campaigns about food safety education are recommended for pregnant women.

## 5. Conclusions

We retrospectively analyzed all the culture-confirmed perinatal listeriosis cases over the course of six years at a high-level maternity hospital in Beijing, China. In this study, all the 7 fetuses of the six women (including one twin pregnancy) infected in the middle trimester pregnancy were dead, while among the 7 infants of the other six maternal patients, only one deceased day 2 after birth. Among the six survivors, although four had septicaemia with two of them got CNS infection additionally, their outcomes were quite well. This was consistent with the reports <sup>[12, 13]</sup> that the prognosis of neonate from maternal listeriosis patients infected during the third trimesters of pregnancy were quite excellent even the infants were infected with Listeria, while the outcomes of pregnancy women infected during the second trimester were very bad. The effect of listeria infection on early pregnancy is not clear, since the etiological examination of early abortion is generally not carried out in clinical terms. Finally, the awareness of healthy diet habits should be improved among pregnant women, especially those during the first and second trimester of pregnancy.

## 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; SpO<sub>2</sub>: oxygen saturation from pulse oximetry; SOB: shortness of breath; DIC: disseminated intravascular coagulation; NRDS: neonatal respiratory distress syndrome.

## 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)"<sup>[1]</sup> 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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## Tables

Table 2 Clinical characteristics of 12 maternal listeriosis cases

Case	Gastation (wk)	Fever Tmax	Clinical manifestations			Initial antibiotic	Switch antibiotic	Underlying diseases		Maternal complications	Maternal outcomes
			diarrhoea	Flu-like symptoms	Obstetrical manifestations			Autoimmune disease	GDM		
1	31.3	39.3	No	No	decreased fetal movement 3d; fetal distress	metronidazole + amoxicillin 4d	No	No	No	premature delivery; C-section; severe meconium stained amniotic fluid	recovered
2	24.4	38.5	No	No	decreased fetal movement 3d; lower abdominal pain; twin pregnancy; PROM	cefuroxime 3d	No	No	No	stillbirth	recovered
3	20.0	38.7	No	No	abdominal pain; fetal movement disappear 3d; chill	amoxicillin 3d	No	No	No	inevitable miscarriage; induced labor	recovered
4	34.3	38.8	No	Yes	decreased fetal movement 1d; uterine contraction; fetal distress	cefmetazole 1d	moxifloxacin 6d	No	No	premature delivery; severe meconium stained amniotic fluid	recovered
5	26.0	39	No	No	lower abdominal pain 17h; PROM; fetal distress; septicaemia	cefuroxime 3d	metronidazole 3d	No	No	stillbirth; induced labor	recovered
6	36.1	38	No	No	decreased fetal movement 2d; fetal distress; polyhydramnios	cefuroxime 3d	No	No	Yes	premature delivery; C-section; severe meconium stained amniotic fluid	recovered
7	38.1	39.2	No	No	fetal distress	metronidazole + ceftriaxone 4d	No	No	No	normal labor; postpartum hemorrhage; C-section; severe meconium stained amniotic fluid	recovered
8	21.7	39.1	No	Yes	fever 15d; intrauterine fetal death 1d; lower abdominal pain	cefuroxime 8d + cefdinir 5d	moxifloxacin 6d	SLE	No	inevitable miscarriage; induced labor	recovered
9	35.6	38.4	No	No	fetal distress; threatened premature; twin pregnancy; septicaemia	ceftriaxone 5d	No	No	Yes	premature delivery; postpartum hemorrhage	recovered
10	24.9	39.3	No	No	fever 7d; fetal distress; abdominal pain; septicaemia	ceftriaxone 7d	PNG 4d	No	No	stillbirth	recovered
11	35.4	afebrile	No	No	fetal distress; decreased fetal movement 1d	cefuroxime 3d	No	No	No	premature delivery	recovered
12	27.3	39	No	Yes	fever 2w;	clindamycin +	azithromycin	No	No	premature	recovered

threatened  
premature;  
vaginal  
bleeding;  
uterine  
contraction;  
septicaemia

ceftriaxone 2d + PNG 7d

delivery;  
postpartum  
hemorrhage;  
C-section;  
mild  
meconium  
stained  
amniotic fluid

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Abbreviations: Tmax, maximal temperature; GDM, gestational diabetes mellitus; PROM, premature rupture of the membranes; C-section, cesarean section; PNG, penicillin-G.

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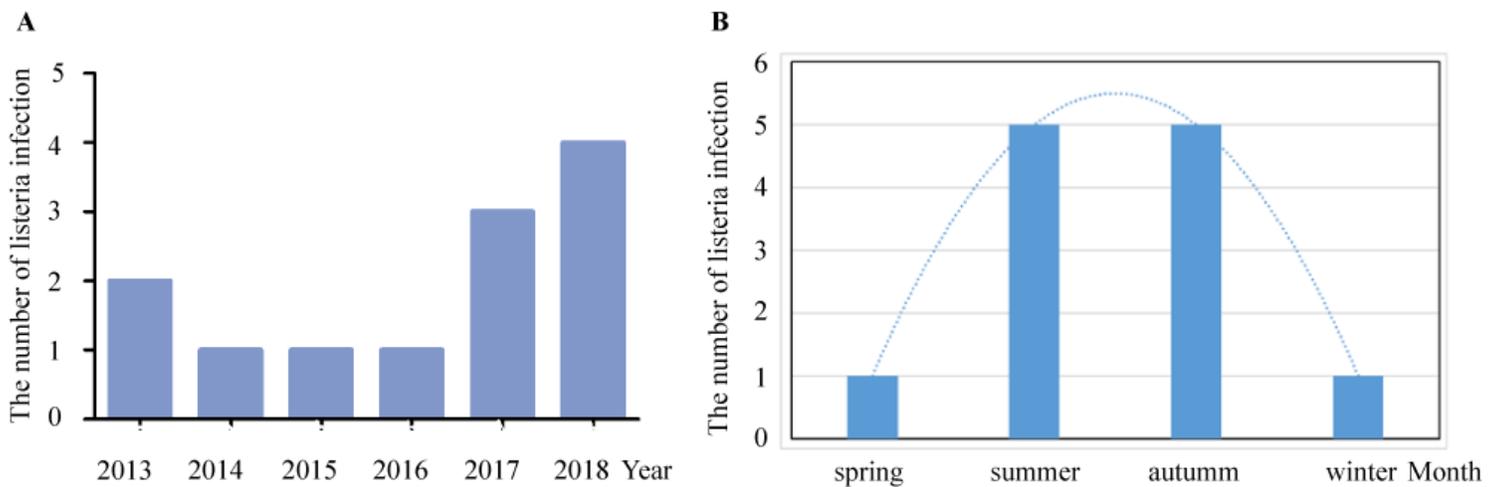
Table 3 Clinical characteristics and outcomes of all the 14 offsprings

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	survived; infant listeriosis

10	620	fetal distress	/	/	/	No	/	/	/	foramen ovale; patent ductus arteriosus	death
11	2810	fetal distress; apgar 10; SpO2 96% on ambient air; cyanosis	(-)	/	(-)	No	PNG+latamoxef 7d	cefepime 7d	No	stillbirth preterm birthr; 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 breath; DIC, disseminated intravascular coagulation; NRDS, neonatal respiratory distress syndrome; CSF, cerebrospinal fluid; PNG, penicillin.

## 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).