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Review

Risk factors for neonatal sepsis: an overview

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Abstract

Neonatal sepsis is still a significant cause of mortality and morbidity at the Neonatal Intensive Care Unit (NICU) and an important cause of long hospitalization time, even though it has diminished with the improvement of neonatal care. The aim of this study was to systematically review data on the risk factors for neonatal sepsis, so that the incidence of neonatal sepsis can be minimized.

A PubMed literature search for all relevant studies from 1999 to 2019 was conducted and after a first analysis based on titles and abstracts and a second analysis based on the full texts, a total of 35 articles were selected to review.

Based on the evidence extracted from these articles, the risk factors for neonatal sepsis can be divided into three categories: maternal factors, neonatal factors and factors associated with the NICU. Thus, the identified maternal risk factors were premature rupture of membranes and maternal infection. In terms of neonatal risk factors, prematurity, low birth weight, low Apgar score, meconium-stained amniotic fluid, birth asphyxia, not crying immediately after birth and need for resuscitation were the primary risk factors identified. Regarding the NICU, the central venous catheter was the most isolated risk factor, both its use and duration, followed by mechanical ventilation and parenteral nutrition.

However, some variable results were inconsistent, which reinforces the need for further multicenter studies to evaluate these risk factors in order to understand their association with neonatal sepsis, so that preventive measures can be implemented.

Keywords

Neonatal sepsis, neonatal infection, early-onset sepsis, late-onset sepsis, risk factors, Neonatal Intensive Care Unit.

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Introduction

Sepsis is a systemic response to infection, meaning that there is a release of vasoactive mediators that cause suppression of the autonomic nervous system regulation leading to diffuse vasodilatation and hypoperfusion [1] which may cause multi-organ failure and result possibly in death.

Neonatal sepsis is still a significant cause of mortality and morbidity in the Neonatal Intensive Care Unit (NICU) and an important cause of long hospitalization [2] even though it has decreased with the improvement of neonatal care [3].

According to the World Health Organization (WHO), in 2016, 46% of deaths in children under-five were neonates and 7% of these were caused by neonatal sepsis. In Portugal, in the same year, the percentage of neonatal deaths due to sepsis or other infection condition was 8.2% [4]. This means a significant decrease from 21.8% in 2000 [5]. The incidence of neonatal infection in the United Kingdom was 6.1 cases per 1,000 live births, in 2017, and this incidence has been reducing over time in both early-onset (EOS) and late-onset sepsis (LOS) with the introduction of infection prevention care bundles [6].

EOS occurs during the first 72 hours of life, has an acute onset and often develops rapidly with multi-organ failure [7, 8]. It is caused by pathogens, often colonizers of the maternal genitourinary tract, transmitted vertically and this transition can occur during the gestation or the delivery [3, 9]. When it comes to the pathogens, 70% of infections are caused by *Group B Streptococcus* (GBS) and *Escherichia coli* (*E. coli*); however, it is important to keep in mind other less common pathogens like *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Enterococcus spp.*, *Enterobacter spp.*, *Haemophilus influenzae* and *Listeria monocytogens* [6, 9]. *E. coli* is the main cause in preterm infants and the second most common cause in term infants and has been associated with severe infections and meningitis [3]. Medical interventions, such as amniocentesis and cervical cerclage, disrupt the amniotic cavity and enhance the probability of intra-amniotic infection, which may lead to neonatal sepsis. However, the most important maternal risk factors occur during delivery, meaning prolonged rupture of membrane, fever, chorioamnionitis, positive colonization with GBS or history of previous infant with GBS infection and GBS bacteriuria. Less studied risk factors, but important to keep in mind, are the social and ethnic factors such as poor or late prenatal care, low socioeconomic status of the mother, poor maternal nutrition, maternal substance abuse, male sex and African American mother [9].

LOS occurs after the 72 hours' period and can be acquired during the postnatal period by vertically or horizontally transmitted microorganisms [3, 9]. The main pathogens are Gram-positive, mainly *coagulase-negative Staphylococcus* (CoNS) (48%), [3, 6], but the highest mortality rates are due to *Pseudomonas aeruginosa*, *Candida albicans*, *Serratia marcescens* and *E. coli* [3, 10]. The GBS can also cause LOS; however, they are not as common as the ones previously mentioned. Despite that, they remain a common cause of meningitis with severe neurologic sequelae [3].

Staphylococcus epidermidis incidence is growing, being mostly associated with invasive procedures. This microorganism complicates the diagnostic even more because it belongs to the normal skin flora, which makes the distinction between contamination and sepsis more difficult [11].

Taking into consideration the difficult process of diagnosing and treating neonatal sepsis, the best course of action is prevention and, for that reason, different protocols have been developed to decrease nosocomial infection. In Portugal, a nosocomial infections preventive bundle was implemented in 2010, which reduced in the incidence density of nosocomial sepsis by 44% [2, 11].

The aim of this systematic review was to evaluate the recent literature on risk factors for neonatal sepsis, in order to understand which factors should physicians be attentive to so that the incidence of neonatal sepsis can be minimized.

Methods

Protocol

This review was conducted based on the Preferred Reporting of Systematic Reviews and Meta-Analysis (PRISMA) guidelines [12].

Systematic literature search

In January 2019, a PubMed literature search for all potentially relevant studies from 1999 to 2019 was executed. A combination of the following MESH

terms and keywords was used: "Shock, Septic"[Mesh], "Infant, Newborn"[Mesh], "Neonatal Sepsis/complications"[Mesh], "Neonatal Sepsis"[Mesh], "Risk Factors"[Mesh], "Neonatology"[Mesh], "Intensive Care Units, Neonatal"[Mesh], "late-onset"[All Fields], "early-onset"[All Fields]. References were then crosschecked in order to include articles missed by the initial search strategy, using the same inclusion and exclusion criteria.

Eligibility criteria

Prospective, retrospective observational studies and clinical trials whose aim was to identify risk factors for neonatal sepsis were eligible. All articles needed to concern human subjects between the age of 1-28 days. Case reports, comments, narrative or systematic reviews and meta-analyses were excluded, as well as studies that did not include the outcome. Duplicate articles or articles without full-length text availability were also excluded. In regards to language, both articles in English and Portuguese were accepted.

Study selection

All titles and abstracts were reviewed to identify all relevant articles. After a first analysis, the relevant articles' full-length texts were reviewed and their bibliography lists were manually searched, in order to find more references not obtained by the original Pubmed search.

Data items

The data were collected on year of publication, country, study design, numbers of patients enrolled in the study, duration of the study, and identified risk factors.

Summary measurements and synthesis of results

The principal summary measures included were risk ratios. All data were collected from the different studies, then combined according to the different risk factors and then summarized.

Results

Study selection

From the PubMed research, 642 articles were found, 248 of which were duplicates and therefore removed. 394 articles remained and were screened based on their titles and abstracts. After this first analysis, 73 articles were selected for full-text review and 321 were excluded: 20 were systematic reviews, 45 were case reports, 61 did not include the neonatal population of this review and 195 did not address the outcome of interest. Of the 73 included, 36 were excluded after full-length text review because they did not address the outcome of interest and 3 articles were not possible to include because we did not have access to the full text, remaining 34 articles (**Fig. 1**).

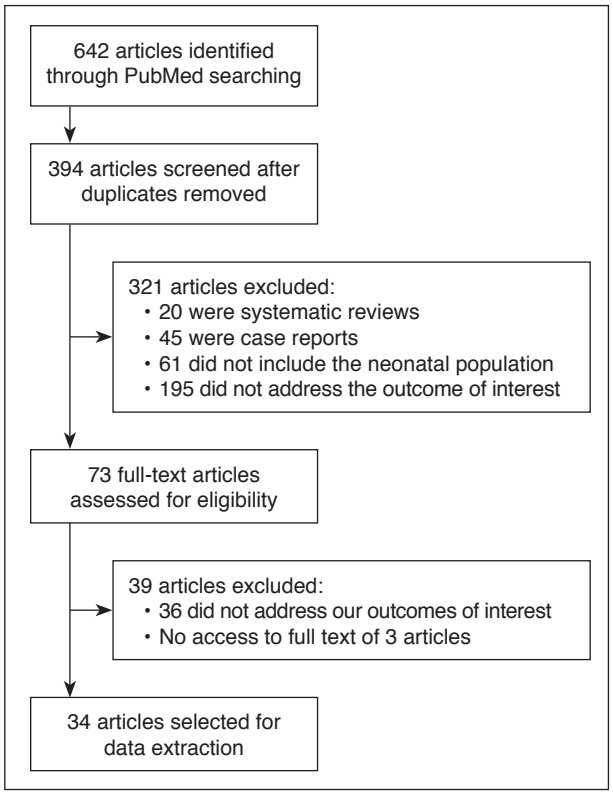

Figure 1. Flowchart of the systematic review.

Study characteristics

This review included many prospective and retrospective case-controls and cohort studies, as well as a randomized clinical trial. Most studies were single-center from developed and developing countries. The studies characteristics are summarized in **Annex 1**.

Results of individual studies

The identified risk factors for each study and the results from their statistic tests are summarized in **Tables 1-6**.

Table 1. Identified maternal risk factors for neonatal sepsis.

Category	Risk factor	Effect size	Confidence interval	p-value	Measurement	Reference
Maternal infection	PROM (EOS)	9.33	2.12-46.73	0.001	OR	[18]
	PROM	5.75	3.20-10.40		AOR	[16]
	PROM ≥ 24 hours (EOS)	3.38	1.80-6.32	< 0.0001	RR	[20]
	PROM (EOS)	0.207	0.078-0.547	0.001	OR	[19]
	PROM	7.43	2.04-27.71		AOR	[14]
	PROM ≥ 18 hours to hospital admission	3.08	1.15-8.49	0.009	OR	[15]
	PROM ≥ 15 hours during hospitalization	7.32	2.32-30.37	< 0.001	OR	[15]
	PROM ≥ 48 hours to delivery	5.77	1.93-16.11	< 0.001	OR	[15]
	PROM	5.677	0.055-0.565	< 0.001	OR	[13]
	PPROM ≥ 18 hours to hospital admission	2.95	1.05-8.72	0.019	OR	[15]
	PPROM ≥ 38 hours during hospitalization	4.03	1.41-11.94	0.002	OR	[15]
	PPROM ≥ 59 hours to delivery	5.69	1.96-17.67	0.002	OR	[15]
	PPROM ≥ 4 weeks	0.21	0.10-0.41		OR	[24]
	Maternal infection (EOS)	2.28	1.12-4.63	0.009	OR	[18]
	UTI	5.9	1.9-18.3	0.001	OR	[25]
	UTI/STI	3.007	1.477-6.425	0.002	OR	[22]
	UTI/STI	5.23	1.82-15.04		AOR	[14]
	UTI	2.9	1.489-5.527	0.002	AOR	[26]
	Chorioamnionitis on chorioamniotic plate (EOS)	34.46	3.60-329.28	< 0.0021	OR	[27]
	Chorioamnionitis on amniotic membrane (EOS)	8.72	2.10-36.14	< 0.0028	OR	[27]
	Peri-partum pyrexia	2.25	1.05-4.78		AOR	[16]
	Peri-partum pyrexia	6.08	1.29-28.31		AOR	[14]
	Fever at home (EOS)	10.00	2.3-43.5		RR	[21]
Birth route	CS	1.895	1.087-3.303	0.032	OR	[23]
	CS (EOS)	0.207	0.041-0.258	0.000	OR	[19]
	CS	4.3	1.025-17.924	0.046	AOR	[26]
	Elective CS	0.15	0.07-0.36	< 0.001	OR	[35]
	Elective CS (EOS)	0.17	0.07-0.41	< 0.001	OR	[35]
Delivery	Delivery at health centre	5.70	1.71-19.00		AOR	[14]
	Delivery at clinic	3.3	1.195-9.333	0.022	AOR	[26]
	Delivery at health centre	4.2	1.934-8.967	0.000	AOR	[26]
	Delivery at hospital	2.6	1.197-5.443	0.015	AOR	[26]
	Instrumental delivery	6.3	1.252-31.768	0.026	AOR	[26]
	Prolonged labour	2.97	1.82-4.86		AOR	[16]
Socio-economic factors	Lower socio-economic status	3.08 (EOS) 4.01 (LOS)	1.86-5.11 (EOS) 2.37-10.53 (LOS)		AOR	[16]
	Place of domicile	2.27	1.01-5.11	0.047	OR	[33]
	Good cord care	0.42	0.25-0.82	0.009	OR	[33]
	Poor feeding	6.24	3.37- 11.53	0.000	OR	[33]
	Lack of antenatal care	2.39	1.05-5.49	0.02	OR	[34]
	Prenatal care < 6 consultations (EOS)	10.77	1.4-80.8		RR	[21]
Demographic	Maternal age > 35 years old (EOS)	4.835	1.170-19.981	0.029	OR	[19]
	Maternal age 31-40 years old	0.390	0.161-0.919	0.017	OR	[22]
	Black, non-Hispanic	1.51	1.24-1.85		HR	[29]
	Hispanic	1.95	1.16-3.28		OR	[24]
	Hispanic	1.55	1.11-2.17		HR	[29]
	Primiparous	3.436	1.784-6.884	0.000	OR	[22]
	Increasing parity	1.18	1.01-1.37	0.032	OR	[28]
	Primiparous	1.89	1.050-4.498	< 0.001	OR	[13]
Mother diseases	HIV mother	0.46	0.23-0.93	0.029	OR	[28]
	Maternal bleeding disorder	8.76	2.746-28.004	< 0.001	OR	[13]
	Low Vitamin D (EOS)			< 0.001		[30]
	Low cord blood 25(OH)D < 30 ng/mL (EOS)	5.6	1.3-23.5		OR	[31]

AOR: adjusted odds ratio; CS: caesarean section; EOS: early-onset sepsis; HIV: human immunodeficiency virus; HR: hazard ratio; OR: odds ratio; PPROM: preterm premature rupture of membranes; PROM: premature rupture of membranes; RR: risk ratio; STI: sexually transmitted infection; UTI: urinary tract infection.

Table 2. Identified neonatal risk factors for neonatal sepsis.

Category	Risk factor	Effect size	Confidence interval	p-value	Measurement	Reference
Demographic	BW < 2,500 g (EOS)	24.8	5.16-27.04		OR	[18]
	BW < 2,500 g (EOS)	21.47	7.3-63.2		RR	[21]
	BW < 2,500 g	2.75	1.454-5.20	0.001	OR	[23]
	BW < 1,500 g	3.30 (EOS)	1.84-5.93 (EOS)		AOR	[16]
		3.12 (LOS)	0.83-12.05 (LOS)			
	BW < 1,500 g (LOS)	1.37	0.91-2.06		RR	[38]
	BW < 1,500 g (EOS)	3.96	1.22-12.87	0.022	OR	[35]
	GA (EOS)	0.09	0.017-0.007	0.017	OR	[36]
	GA < 37 weeks (EOS)	92.86	12.6-684.7		RR	[21]
	GA < 37 weeks	4.073	2.180-7.609	0.000	OR	[23]
	GA < 32 weeks	6.18 (EOS)	2.60-15.00 (EOS)		AOR	[16]
		10.2 (LOS)	2.37-10.53 (LOS)			
	GA < 37 weeks (EOS)	2.19	1.41-3.40	< 0.0001	RR	[20]
	GA < 37 weeks (EOS)	0.059	0.010-0.329	0.001	OR	[19]
	GA < 37 weeks	5.765	3.006-11.511	0.000	OR	[22]
	GA < 37 weeks (EOS)	14.9	2.3-94.4		OR	[31]
	GA < 37 weeks	2.35	1.39-3.96		HR	[29]
	GA < 28 weeks (LOS)	2.29	0.81-5.81		RR	[38]
	GA < 28 weeks	18.59	2.90-774.57	< 0.001	OR	[15]
	GA 28-34 weeks	77.08	8.33-713.29	< 0.001	OR	[15]
	GA 34-37 weeks	22.48	2.89-174.22	0.003	OR	[15]
	GA 37-42 weeks	2.90	1.742-4.842	< 0.001	OR	[13]
	GA > 42 weeks	4.70	1.553-14.273	< 0.001	OR	[13]
	Increasing infant age	1.07	1.01-1.13	0.021	OR	[28]
	Infant age < 7 days	6.73	3.47-13.07	< 0.001	OR	[35]
	Male sex	1.96	1.17-3.29	0.01	OR	[34]
	Male sex	1.806	1.021-3.224	0.040	OR	[22]
Perinatal period	5th min Apgar < 7 (EOS)	19.5	9.0-41.9		RR	[21]
	1st min Apgar score < 7	5.198	2.800-9.952	0.000	OR	[22]
	5th min Apgar < 7	68.9	3.63-1307.90		AOR	[14]
	5th min Apgar ≤ 3 (LOS)	2.45	1.04-5.76		RR	[38]
	1st min Apgar < 7	2.05	1.355-3.120	< 0.001	OR	[13]
	5th min Apgar < 7	2.39	1.495-3.849	< 0.001	OR	[13]
	1st min Apgar < 7 (EOS)	2.69	1.36-5.53	0.005	OR	[35]
	5th min Apgar < 7 (EOS)	2.45	1.12-5.36	0.025	OR	[35]
	Perinatal asphyxia	4.30	2.62-7.04		AOR	[16]
	Perinatal asphyxia (LOS)	5.15	1.92-13.83	0.001	RR	[20]
	Crying at birth	0.081	0.003-0.425	0.001	OR	[22]
	Crying at birth	0.01	0.00-0.16		AOR	[14]
	Resuscitation at birth	5.274	1.630-24.558	0.004	OR	[22]
	No need for resuscitation at birth	0.87	0.485-1.563	< 0.004	OR	[13]
	Nasal flaring	0.54	0.31-0.96	0.034	OR	[28]
	Pallor	0.36	0.14-0.94	0.037	OR	[28]
	MSAF	2.535	1.225-5.245	0.029	OR	[23]
	MSAF	3.625	1.730-8.103	0.000	OR	[22]
	MSAF (EOS)	4.43	1.94-10.12	< 0.001	OR	[35]
	Abnormal amniotic fluid (EOS)	1.67	1.25-2.23	0.007	RR	[20]
	Foul smelling	13.599	2.606-5.655	0.001	OR	[22]
Comorbidities	IVH	2.68	1.20-5.99	0.017	MOR	[44]
	Respiratory complication (EOS)	42.48	25.53-70.67	< 0.0001	RR	[20]
	Respiratory complication (LOS)	16.36	3.39-78.91	< 0.0001	RR	[20]

AOR: adjusted odds ratio; BW: birth weight; EOS: early-onset sepsis; GA: gestational age; HR: hazard ratio; IVH: intraventricular hemorrhage; LOS: late-onset sepsis; MOR: median odds ratio; MSAF: meconium-stained amniotic fluid; OR: odds ratio; RR: risk ratio.

Table 3. Identified NICU risk factors for neonatal sepsis.

Category	Risk factor	Effect size	Confidence interval	p-value	Measurement	Reference
NICU interventions	Use of CVC	1.70	1.21-2.41		HR	[17]
	Use of CVC (LOS)	3.44	2.39-4.93		RR	[38]
	Parenteral nutrition	4.04	2.61-6.25		HR	[17]
	Parenteral nutrition	6.07	1.14-32.32	0.034	MOR	[44]
	Mechanical ventilation	2.43	1.67-3.53		HR	[17]
	Mechanical ventilation (LOS)	2.71	1.56-4.69	< 0.0001	RR	[20]
	Mechanical ventilation	9.34	6.55-13.32		HR	[29]
	Assisted ventilation	4.36	3.05-6.23		RR	[38]
	O_2 inspiration fraction > 60% (EOS)	3.21	1.95-5.28	< 0.0001	RR	[20]
	O_2 inspiration fraction > 60% (LOS)	2.85	1.57-5.15	0.001	RR	[20]
	Continuous positive airway pressure	3.66	1.30-10.27	0.013	RR	[20]
	Invasive medical procedure required (EOS)	3,01	2.13-4.26	< 0.0001	RR	[20]
	Invasive medical procedure required (LOS)	12.5	6.37-24.56	< 0.0001	RR	[20]
	Surgery required (LOS)	28.97	6.99-120.01	< 0.0001	RR	[20]
	Surgery	2.03	1.12-3.70		RR	[38]
	Tocolytic drugs (EOS)	4.8	1.1-1.6	0.019	OR	[36]
	Long stay in hospital	3.73 (LOS)	1.75-7.99 (LOS)		AOR	[16]
	Duration of stay > 2 weeks	16.6	5.08-54.31	< 0.001	OR	[35]
	Duration of stay 1-2 weeks (EOS)	5.28	1.62-17.10	0.006	OR	[35]
	Duration of stay > 2 weeks (EOS)	32.97	4.09-266.13	< 0.001	OR	[35]
	Duration of stay > 3 weeks	0.03	0.009-0.118	< 0.001	OR	[13]
	Higher number of infants < 32 weeks in NICU	1.02	1.00-1.03		HR	[29]

AOR: adjusted odds ratio; CVC: central venous catheter; EOS: early-onset sepsis; HR: hazard ratio; LOS: late-onset sepsis; MOR: median odds ratio; NICU: Neonatal Intensive Care Unit; OR: odds ratio; PROM: premature rupture of membranes; RR: risk ratio.

Table 4. Identified risk factors for nosocomial neonatal sepsis.

Category	Risk factor	Effect size	Confidence interval	p-value	Measurement	Reference
Maternal	PROM	1.51	1.15-1.99	0.0033	HR	[17]
	Maternal infection	1.57	1.18-2.07	0.0017	HR	[17]
Neonatal	BW < 1,000 g	8.82	4.80-16.21		OR	[40]
	BW 1,000-1,499 g	2.35	1.02-5.38		OR	[40]
	BW < 1,500 g	2.8	2.2-3.6	< 0.001	OR	[41]
	Male sex	1.86	1.04-3.35		OR	[40]
	Gastrointestinal disease	2.7	2.0-3.6	< 0.001	OR	[41]
	Renal insufficiency	1.9	1.1-3.3	0.018	OR	[41]
NICU	CVC (including umbilical)	1.70	1.21-2.41	0.0024	HR	[17]
	Use of CVC	2.27	1.28-4.02		OR	[40]
	Duration of CVC use	0.1182		< 0.001		[42]
	Parenteral nutrition	4.04	2.61-6.26	0.0001	HR	[17]
	Parenteral nutrition	6.4	3.2-12.8	< 0.001	OR	[41]
	Mechanical ventilation	2.43	1.67-3.53	0.0001	HR	[17]
	Mechanical ventilation	0.79824		< 0.001		[42]
	Mechanical ventilation	1.4	1.0-1.8	0.023	OR	[41]
	Duration of mechanical ventilation	0.1362		< 0.001		[42]
	Abdominal surgery	1.5	1.0-2.3	0.054	OR	[41]
	Cardiac surgery	2.9	2.0-4.1	< 0.001	OR	[41]
	Other type of surgery	2.8	1.7-4.5	< 0.001	OR	[41]
	Longer stay at NICU	0.0054		0.004		[42]

BW: birth weight; CVC: central venous catheter; HR: hazard ratio; NICU: Neonatal Intensive Care Unit; OR: odds ratio; PROM: premature rupture of membranes.

Table 5. Identified risk factors for neonatal sepsis in very low birth weight neonates.

Category	Risk factor	Effect size	Confidence interval	p-value	Measurement	Reference
Neonatal	GA	0.80	0.681-0.938	0.006	OR	[37]
	Gastrointestinal tract pathology	5.2	1.5-18.4	0.011	OR	[43]
NICU	Catheter duration 10-21 days	32.4	3.2-323.2	0.003	OR	[43]
	Catheter duration > 21 days	80.6	6.9-944.6	< 0.001	OR	[43]
	Use of NC-CPAP	5.9	1.5-22.6	0.010	OR	[43]
	Duration of parenteral nutrition	1.22	1.122-1.332	< 0.0001	OR	[37]

GA: gestational age; NC-CPAP: nasal cannula continuous positive airway pressure; NICU: Neonatal Intensive Care Unit; OR: odds ratio.

Table 6. Identified risk factors for catheter associated bloodstream infection.

Category	Risk factor	Effect size	Confidence interval	p-value	Measurement	Reference
Neonatal	BW < 1,000 g	5.13	2.1-12.5	< 0.0001	OR	[39]
	BW 100 g increase	0.97	0.96-0.99	0.006	ARR	[47]
	Postnatal age > 7 days	2.74	1.1-6.7	< 0.0001	OR	[39]
NICU	Catheter care	2.96	1.13-7.79	0.03	RR	[45]
	Hub colonization	44.1	14.5-134.4	< 0.0001	OR	[39]
	Exit site colonization	14.4	4.8-42.6	< 0.0001	OR	[39]
	Hub and exit site colonization	0.06	0.01-0.5	< 0.0001	OR	[39]
	Total parenteral nutrition	1.04	1.0-1.08	< 0.0001	OR	[39]
	Concurrent PICCs	2.04	1.12-3.71	0.019	ARR	[47]
	PICC dwell time 8-13 days	2.02	1.21-3.38	0.007	RR	[47]
	PICC dwell time 14-22 days	3.27	2.04-5.24	< 0.001	RR	[47]
	PICC dwell time ≥ 23 days	2.71	1.71-4.27	< 0.001	RR	[47]

ARR: adjusted risk ratio; BW: birth weight; NICU: Neonatal Intensive Care Unit; OR: odds ratio; PICC: peripherally inserted central catheter; RR: risk ratio.

Maternal risk factors

Different maternal factors were examined in the different studies included in this review. First of all, the most frequently referred risk factor was premature rupture of membranes (PROM). It was examined in 11 studies: 8 of them found it was an independent risk factor with statistical significance, with a level of evidence 3B in five of them [13-20] (**Tab. 1**, **Tab. 4**, and **Annex 1)**, while three other studies did not find a significant association [21-23]. The risk of infection is associated to a prolonged time of rupture, more specifically one study explored different times and concluded that PROM with more than 18 hours to hospital admission, more than 15 hours during hospitalization and more than 48 hours to delivery were all associated to an increased risk of neonatal sepsis [15]. These time marks did not correspond when regarding EOS, whose time mark was over 24 hours [20].

Besides PROM, preterm premature rupture of membranes (PPROM) before 37 weeks was also identified as a risk factor by one study, as shown in **Tab. 1**, and just like term PROM the risk of infection was associated to a prolonged time of rupture, being that in this case more than 18 hours to hospital admission, more than 38 hours during hospitalization and more than 59 hours to delivery were associated to neonatal sepsis [15]. However, in the setting of PPROM before 34 weeks, another study concluded that prolonged latency was actually associated with decreased risk and the neonates delivered soon after PPROM were at highest risk [24].

Secondly, different maternal infections during gestation were research in 10 studies, as shown in **Tab. 1** and **Tab. 4**. First of all, urinary tract infection (UTI) was identified as risk factor for neonatal sepsis by four studies, all with a level of evidence 3B [14, 22, 25, 26] and two of these also found sexually transmitted infections (STI) to be a significant risk factor [14, 22]. In terms of time of infection, some studies identified the third trimester as the most problematic [25], but others found no relation with the period of gestation [14, 18, 22, 26]. Regarding EOS, maternal infection was also a risk factor, and the most frequent infections were UTIs (62.1%), vulvovaginitis (24.2%) and chorioamnionitis (4.2%) [18]. Histologically confirmed chorioamnionitis was also concluded

to be an important risk factor and this study also showed a significant association between neonatal infection and the presence of polymorphonuclear leukocytes (PMNL) on the chorioamniotic plate and on the amniotic membrane but not on the umbilical cord, level of evidence 2B [27]. Besides UTI, bacterial vaginosis was also studied, but it did not reach statistical significance [21] and this same study did not find significant bacteriuria.

Peripartum pyrexia's results were inconclusive, being that it was researched by four studies and it was identified as a risk factor by two of them [14, 16], as shown in **Tab. 1**, while the other two studies did not find an association [18, 22].

In addition, factors such as parity, ethnicity (Hispanic and Black, non-Hispanic mothers) and vitamin D deficiency were less explored; however, they are possibly risk factors as an association was found in most of the articles that investigated them, as shown in **Tab. 1**, more specifically three when regarding parity [13, 22, 28], two when regarding ethnicity [24, 29] and two when regarding vitamin D deficiency [30-32]. In regards to these risk factors, only parity was not found as a significant risk factor in one study [14].

Socioeconomic factors such as maternal education, low social class and prenatal care were also less studied, but these results do not appear to be risk factors, as most studies did not find an association. More specifically, the two studies researching maternal education [13, 22], the three [13, 14, 22] of five [13, 14, 16, 22, 33] studies researching low socioeconomic class and the four [13, 14, 18, 22] of six [13, 14, 18, 21, 22, 34] studying prenatal care, did not find any association.

Concerning variables such as birth route, place of residence and maternal age, the results were inconclusive because the number of studies that found an association and the ones that did not was the same. Namely, three [19, 23, 26] of the six studies that explored birth route [14, 18, 19, 22, 23, 26]; one [33] of the two studies that investigated the place of residence [14, 33] and two [19, 22] of the four studies that researched maternal age [13, 18, 19, 22] found an association between these risk factors and neonatal sepsis, as shown in **Tab. 1**.

Variables such as fever at home [21], previous gestation with neonatal infection [18], elective caesarean [35], bleeding disorder [13], prolonged labour [16], instrumental labour [26], poor cord care and poor feeding [33] were, all of them, found to be risk factors for neonatal sepsis (**Tab. 1**).

It was found that home deliveries were associated with an increased risk of culture-confirmed sepsis and delivery at health centres were at a higher risk when compared to hospital deliveries [14]. However, these results were contradicted by another study, whose results demonstrated that the neonates born at home by traditional birth attendants developed less sepsis when compared to those who were born at the health centre [26].

In one study, in HIV (human immunodeficiency virus) mothers a reduction of neonatal sepsis risk was observed, with an evidence level 3B [28], **Tab. 1**.

Neonatal risk factors

Several neonatal risk factors were identified, but the most prevalent were low birth weight and gestational age, namely prematurity. However, some studies did not reach statistical significance. In terms of prematurity, 12 out of 16 studies showed statistical significance, with an evidence level 3B in seven and 2C in four [15, 16, 19-23, 29, 31, 36-38], **Tab. 2** and **Tab. 5**. The other four studies did not reach a significant association. A more recent study found an increased risk for gestational ages between 37 and 42 weeks and over 42 weeks, with level of evidence 3B [13].

Infant age was also studied in three articles, and in two of them it was shown that the increased infant age was associated with an increased risk of sepsis, with an evidence level 3B [28]. The third one observed that a postnatal age over seven days was associated with catheter-associated bloodstream infection (CABSI) [39], **Tab. 6**.

Nine out of 15 studies showed that low birth weight was a risk factor for neonatal sepsis, with an evidence level 2B in five and 3B in three of them [16, 18, 21, 35, 37-41], **Tables 1, 4 and 6**. The other six articles did not conclude birth weight to be a risk factor [13, 14, 17, 20, 26, 42].

Risk factors such as low 1st and 5th minute Apgar score [13, 14, 21, 22, 35, 38], perinatal asphyxia [16, 20], not crying immediately after birth [14, 22], need for resuscitation [13, 22] and meconium-stained amniotic fluid (MSAF) [22, 23, 35] were studied, showing a significant association, with the exception of perinatal asphyxia and need for resuscitation [23, 35], **Tab. 2**. The evidence level was 3B for Apgar score in four out of six studies, 3B for not crying after birth in both two studies, and 3B for MSAF in the three publications studied.

Other risk factors such as abnormal amniotic fluid [20] and neonatal comorbidities, namely gastrointestinal disease [41, 43] and respiratory complications [20], were identified as a risk factor for neonatal sepsis by a small number of studies, **Tables 2, 4 and 5**. Intraventricular haemorrhage (IVH) was identified, in another article, as an independent risk factor. However, this study could not clarify if it was a consequence of neonatal sepsis or, indeed, a preceding factor [44].

Three [18, 26, 35] out of five studies that investigated male sex [18, 22, 26, 34, 35], two [14, 35] out of three studying foul smelling [14, 22, 35] and both two studies that included congenital malformations [17, 23] did not find a statistically significant association.

NICU associated risk factors

In terms of risk factors associated with neonatal care, the central venous catheter (CVC) was the most studied, namely the association between its use and neonatal sepsis and the association between the duration of its use and neonatal sepsis, as shown in **Tables 3**, **4** and **5**. In regards to the first hypothesis, it was found to be a risk factor in three studies, with an evidence level 2B [17, 38, 40], while another article did not manage to establish a significant association [44]. In regards to its duration, the association was statistically significant in both studies, and the risk became statistically significant after the first 10 days [42, 43]. Besides its use and duration, other factors were identified as risk factors for CABSI, such as catheter care [45], hub colonization and exit site colonization [39], as shown in **Tab. 6**.

Secondly, mechanical ventilation was also a variable present in many of the studies included in this review and only three out of 10 articles that included this variable in their research did not find an association [39, 40, 43]. The other seven found a significant association [17, 20, 29, 38, 41, 42], with a level of evidence 2B in all of them, as shown in **Tab. 3** and **Tab. 4**.

Parenteral nutrition was also tested in five different studies and all revealed statistically significant results, with an evidence level 2B in 3 and 3B in one [17, 39, 41, 44], as shown in **Tables 3**, **4**, **5** and **6**. Interestingly, electrolyte disturbances, for example hypophosphatemia, hypokalemia and hypercalcemia, which can be a result of nutritional support, were also associated with an increase in the incidence of sepsis [46].

In a less significant way, surgery [20, 38, 41], length of stay [13, 35] and use of tocolytic drugs [36] were also identified as risk factors, as shown in **Tab. 3** and **Tab. 4**, being that all studies that included these factors found an association, with the exception of one [17] that did not find the length of stay at the facility a risk factor for neonatal sepsis. Peripherally inserted central catheters (PICC) studies were inconclusive: one found it was a risk factor [47], and another one did not [17], as shown in **Tab. 6**. The use of steroids [36, 44] and umbilical and urinary catheters were not identified as risk factors for neonatal sepsis, with level of evidence 3B.

Interestingly, one of the studies found that the occupancy was a higher risk when the NICU had a greater percentage of premature neonates (< 32 weeks), with a level of evidence 2B [29], **Tab. 3**.

Discussion

In regards to maternal related risk factors, PROM and maternal infection were the most prominent risk factors found in this review, being also the most accepted risk factors in the scientific community. Several articles look over the association between PROM or PPROM and neonatal sepsis, and most studies found a significant association, not only with its occurrence but also with the time of rupture, being the risk of infection higher for neonatal sepsis when the rupture time exceeds 18 hours [15] and over 24 h for EOS [20]. Additionally, PPROM can also be responsible for premature labour, and prematurity was also found to be a risk factor for neonatal sepsis [24].

Concerning maternal infection, different types such as UTIs, STIs, vulvovaginitis and chorioamnionitis were identified as risk factors. However, it is still not clear the importance of the time of the infection, since one of the articles identified the third trimester to be the most important to have an infection [25], while other articles found that the trimester of pregnancy was not a relevant risk factor for neonatal sepsis [14, 18, 22, 26].

On the other hand, when looking at the association between neonatal sepsis and other risk factors, such as peripartum pyrexia, history of previous infant with neonatal sepsis, socioeconomic factors, prenatal care attendance, birth route, location of birth, parity and maternal demographic characteristics (age, race), the results were not as clear as the risk factors previously

mentioned. These inconsistent results can be explained by the inclusion of articles from both developing and developed countries, meaning that the population background included in each study differed from the others, showing considerable studies heterogeneity, making comparisons difficult. This different background can also justify the contrasting results regarding socioeconomic factors. Most studies that were able to reach a statistically significant association were studies from developing countries where issues such as lack of hygiene, overcrowded homes, homes without clean portable water for bathing the neonate and preparation of feeds, and non-access to vaccines or antenatal care clinics are more common.

Finally, maternal comorbidities were also explored, more specifically, HIV infection, bleeding disorder and vitamin D deficit. All the variables were associated with an increased risk of neonatal sepsis, with the exception of the HIV infection, which was concluded to be protective, which could be due to the prophylactic treatment that these neonates receive when having an HIV positive mother [28]. Regarding the vitamin D deficit, low levels of maternal vitamin D during pregnancy result in low levels of vitamin D deficit in the neonate. It seems that vitamin D has a relevant role in the immune system and its deficit may lead to a more susceptible neonate and therefore increase the risk of neonatal sepsis. This finding opens up the idea that maternal vitamin D supplementation during gestation may act as a preventive measure for neonatal sepsis, but further investigations are needed [30-32].

Besides the maternal factors, several neonatal risk factors were identified in this review. First of all, both prematurity and low birth weight were heavily researched and demonstrated similar positive results in most studies, as expected, since preterm infants usually have a lower birth weight. These results could be explained by the fact that premature infants usually have an immature immune system, which makes them more susceptible to acquired vertically or horizontally infections. Medical procedures or colonization of medical devices essential to assist these neonates such as parenteral nutrition, mechanical ventilation and CVC are well-known risk factors discussed latter on [2, 11].

Factors such as 1st and 5th min Apgar score < 7, not crying at birth, need for resuscitation and MSAF were not as researched as birth weight and gestational age. However, they were found to be statistically significant risk factors, as well [14, 22]. In regards to perinatal asphyxia and need for resuscitation, one study could not find a statistically significant association. Risk factors associated with fetal distress such as MSAF and birth asphyxia are usually interconnected; namely, MSAF could have been a result of *in utero* asphyxia caused, for example, by PROM and amniotic fluid drainage, and these asphyxiated neonates are more likely to need to be resuscitated [35].

Another less researched risk factor was male sex, studied, in this review, only in five articles, and only in two of them a significant association was found [22, 34]. Interestingly, glucose-6-phosphate dehydrogenase deficiency was found to be a risk factor for male neonatal sepsis in one publication [48].

Regarding neonatal comorbidities, several were included in the different articles, namely, gastrointestinal diseases, congenital malformations, respiratory complications and IVH. With the exception of congenital malformations [17, 23], all of these reached statistical significance. On that account, infants with comorbidities are at a higher risk for neonatal sepsis, which could be due either to the weakened general state of the newborn infant or to the comorbidities that may need medical support, such as parenteral nutrition or mechanical ventilation, which are also risk factors.

At last, a large number of risk factors were associated with NICU procedures or devices. Firstly, CVC was largely associated with neonatal sepsis, not only due to its use but also due to its duration, being the risk higher after the first 10 days of CVC and increasing with its duration [42, 43]. The higher risk associated with a longer time duration reinforces the need for physicians to assess its use daily. Besides its use and duration, other factors for CABSI were identified as risk factors, as well, such as catheter care, hub colonization and exit site colonization.

In addition to CVC, PICC were also investigated, but its results were inconclusive. In terms of other devices, both urinary catheter and umbilical catheter (arterial and venous) were tested by one study, but were not found to be significant risk factors, which means that the incidence of catheter-related infection is also dependent on its location [40].

Besides CVC, mechanical ventilation and parenteral nutrition were also identified as risk factors, and in similarity to CVC, not only was its use a risk factor, but also its duration. In terms of mechanical ventilation, one of the reasons it can

cause neonatal sepsis is due to the nasal trauma, which is usually colonized by Gram-positive microbes, or because these infants have more frequently suctioning, which allows the introduction of bacteria from the patients' environment. Another possible explanation is that infants receiving mechanical ventilation can develop gastrointestinal distension, which can be responsible for Gram-negative bacilli translocation across the gastrointestinal epithelium [43]. Parenteral nutrition besides the possibility of causing mechanical trauma can also cause electrolyte disturbances, for example hypophosphatemia, hypokalemia and hypercalcemia, which were associated with an increase in the incidence of sepsis [46].

In terms of treatments, both the use of medication and surgery were identified as risk factors for neonatal sepsis. More specifically, the use of tocolytic drugs was found to be an independent risk factor for EOS, which could be explained by the fact that these drugs are usually used to delay a delivery which can be dangerous if, for example, the mother has subclinical chorioamnionitis [36].

In regard to the length of stay, it was concluded that longer stays were associated to a higher risk for neonatal nosocomial sepsis, which is explained by the fact that neonates with longer stays are preterms with immature immune system or term infants with major pathologies, both being exposed to all risk factors in NICU. Additionally, infants that usually have a need for longer hospitalization may have other comorbidities, which are also risk factors for sepsis [35].

The occupancy was another evaluated variable, and it was found to be a higher risk of neonatal sepsis when the NICU had a greater percentage of premature neonates (< 32 weeks). However, the authors considered this occupancy as a proxy for the real risk factor, which could be the increased number of visitors, alteration of the clinical care practices due to time constraints or change of preventive measures, such as hand washing and gloving [29].

Limitations

For this systematic review, only the database Pubmed was used, which means that some articles could have been missed. Moreover, some articles were excluded due to no access to the full text.

In regards to the studies included in this review, most had similar limitations in their study design. Firstly, most studies were observational, which limits their ability to draw causal interferences. Secondly, several studies are retrospective, which means some important information can be lacking from the medical reports and clinical charts, and different physicians provided the diagnoses. Thirdly, most were single-centre studies with small sample sizes, which may lack generalizability and may not have enough statistical power to identify some risk factors.

Conclusion

From this systematic review, it was possible to conclude that maternal risk factors, such as PROM and maternal infection, were the primordial risk factors for neonatal sepsis. Other risk factors, such as peripartum pyrexia, history of previous infant with neonatal sepsis, socioeconomic factors, prenatal care attendance, birth route, location of birth, parity and maternal demographic characteristics (age, race), were inconsistent and therefore would need more investigation. In terms of neonatal risk factors, prematurity and low birth weight were the most important ones, having several studies corroborating this statement. However, other risk factors were identified, such as low Apgar score, MSAF, birth asphyxia, not crying immediately after birth and need for resuscitation. Even though these were not as popular as the previous ones mentioned, most articles concluded they are risk factors, as well. Finally, in terms of NICU interventions, the CVC, mechanical ventilation and parenteral nutrition were the most isolated risk factors (both their use and duration), which strengthens the need for physicians to daily assess the need for these invasive procedures, while taking into consideration its benefits and risks. Finally, it is important to remember that neonates that require surgery or have other comorbidities are at a higher risk for neonatal sepsis and should receive close attention.

However, some variable results were inconsistent, which can be due to the lack of power of some study designs or might be due to confounding factors. Therefore, further multicentre studies to evaluate these risk factors are needed in order to understand their association with neonatal sepsis, to implement preventive measures.

Declaration of interest

The Authors have no conflicts of interest or financial ties to disclose.

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Annex 1. Characteristics of the studies included in this review and identified risk factor (continues on the next page).

Study design	Level of evidence	Year	Country	Population	Risk factors	Reference
Prospective study	2B	1999	Brazil	224 neonates	Chorioamnionitis on choriamniotic plate and on amniotic membrane	[27]
Prospective cohort study	2B	2001	Brazil	1,544 neonates	PROM; maternal disease (mostly infection); MV; CVC use; TPN	[17]
Prospective cohort study	2B	2001	Belgium	862 neonates	Extreme low weight (< 1,000 g) at the time of catheter insertion	[39]
Prospective open cohort study	2B	2006	Brazil	1,051 neonates	Longer duration of CVC use; use of MV; longer duration of MV; longer duration of NICU stay	[42]
Prospective case-control study	3B	2006	Brazil	200 neonates (50 cases, 150 controls)	LBW; maternal infection; history of previous son with sepsis; PROM	[18]
Case-control study	3B	2006	USA	217 neonates < 1,500 g (48 cases, 169 controls)	CVC duration, NC-CPAP use, GI tract pathology	[43]
Prospective cohort study	2B	2006	Uganda	293 neonates	Male sex; lack of antenatal care	[34]
Retrospective case-control study	3B	2006	Germany	786 VLBW neonates (50 cases, 736 controls)	Tocolytic drugs, low GA	[36]
Prospective longitudinal cohort study	2B	2007	Brazil	302 mothers and their neonates	Lack of prenatal care; fever at home; prematurity; LBW; 5th min Apgar score < 7	[21]
Retrospective cohort study	2B	2008	Japan	871 neonates	Male sex; BW < 1,500; use of CVC	[40]
Retrospective cohort study	2B	2010	Romania	34 neonates	GA < 32 weeks; BW < 1,500 g; long hospital stay	[49]
Case-control study	3B	2010	Indonesia	97 neonates (31 cases, 66 controls)	LBW; premature delivery; MSAF; CS	[23]
Retrospective (2006-2007), prospective (2008) study	2C	2011	Nigeria	1,050 neonates	PROM, maternal peri-partum pyrexia, prolonged labour and birth asphyxia were RFs for EOS. Long stay in hospital was a RF for LOS. LBW; lower social classes; EGA < 32 weeks were RFs for both EOS and LOS	[16]
Case-control study	3B	2012	Iran	114 neonates	Maternal UTI during 3rd trimester	[25]
Prospective cohort study	2B	2012	Mexico	11,790 neonates	Prematurity; abnormal amniotic liquid; PROM; abnormal placenta were RFs for EOS. Perinatal asphyxia, MV and continuous positive pressure were RFs for LOS. Invasive medical procedures, O_2 IF ≥ 60 %, respiratory complication and surgical procedures were RFs for both EOS and LOS	[20]
Prospective cross-sectional study	3B	2012	Nigeria	218 neonates	Socio-economic factors (place of domicile, poor feeding, poor cord care)	[33]
Case-control study	3B	2013	China	735 neonates (147 cases, 588 controls)	Maternal age; PROM; CS; GA	[19]
Retrospective cohort study	2B	2013	USA	3,967 neonates	PICC	[47]
Prospective case-control study	3B	2014	Ghana	196 neonates (96 cases, 100 controls)	Maternal age (31-40 years), history of foul smelling liquor, MSAF, parity; history of maternal UTI/STI; male sex, Apgar score at 1st min > 7; GA < 37 weeks; resuscitation at birth and not crying immediately at birth	[22]

Annex 1. Characteristics of the studies included in this review and identified risk factor (continues from the previous page).

Study design	Level of evidence	Year	Country	Population	Risk factors	Reference
Prospective study	3B	2015	Turkey	100 term neonates	Lower maternal and neonatal 25(OH)D levels	[30]
Case-control study	3B	2015	Turkey	83 neonates (40 cases, 43 controls)	Low cord blood 25(OH)D < 30 ng/mL; prematurity	[31]
Prospective cohort study	2B	2015	Belgium	5,134 neonates > 72 hours of life	RFs for the total cohort: TPN; BW ≤ 1,500 g; MV; GI disease; surgery (abdominal, cardiac and other type); renal insufficiency. RFs BW ≤ 1,500 g cohort: MV, GI disease, cardiac surgery and other type of surgery. RFs BW > 1,500 g cohort: TPN, GI disease and cardiac surgery	[41]
Randomized controlled trial	1B	2016	USA	1,596 patients with PPROM	Prolonged latency in the setting of PROM was associated with decreased risk for neonatal sepsis, and that infants that are delivered soon after PPROM are at highest risk	[24]
Case-control study	3B	2016	Ethiopia	234 neonates (78 cases, 156 controls)	History of maternal UTI/STI; place of delivery; PROM; intrapartum fever; low Apgar score at 5th minute; not crying immediately at birth	[14]
Retrospective cohort study	2B	2016	USA	18,810 neonates	Shorter gestations; non-Hispanic Black and Hispanic mothers	[29]
Cross-sectional observational study	3B	2016	Zambia	313 neonates	Increased parity and increasing neonatal age were risk factors. HIV infection, nasal flaring and pallor were associated to reduce odds of neonatal sepsis	[28]
Retrospective case-control study	3B	2016	Taiwan	328 neonates (164 cases, 164 controls)	TPN; IVH	[44]
Retrospective observational study	3B	2016	Portugal	461 VLBW neonates	GA and duration of TPN	[37]
Prospective observational study	2B	2017	Bosnia and Herzegovina	200 neonates	Extreme prematurity (GA < 28 weeks); 5-minute Apgar score ≤ 3	[38]
Prospective cross-sectional study	3B	2017	Ethiopia	306 neonates	Place of delivery (hospital, clinical, health centre), mode of delivery (CS, instrumental labour), maternal UTI	[26]
Case-control study	3B	2018	Ghana	383 neonates born via CS (67 cases, 316 controls)	BW; neonatal age; meconium passed; reason for CS; duration of stay	[35]
Prospective population-based cohort study	2B	2018	Switzerland	429 neonates	RFs for death: EOS, MV, septic shock. Fatality ratio decreased with increasing GA for each additional week and increasing BW	[50]
Cross-sectional study	3B	2018	Indonesia	405 mothers with PROM	Prolonged PROM before hospital admission, during hospitalization and until birth	[15]
Retrospective case-control study	3B	2019	Ghana	900 neonates (103 cases, 797 controls)	Apgar scores at the 1st and 5th minutes; resuscitation at birth; PROM; maternal parity	[13]

BW: birth weight; CS: caesarean section; CVC: central venous catheter; EOS: early-onset sepsis; GA: gestational age; GI: gastrointestinal; LBW: low birth weight; LOS: late-onset sepsis; MSAF: meconium-stained amniotic fluid; MV: mechanical ventilation; NICU: Neonatal Intensive Care Unit; PICC: peripherally inserted central catheter; PPROM: preterm premature rupture of membranes; PROM: premature rupture of membranes; RF: risk factor; STI: sexually transmitted infection; TPN: total parenteral nutrition; UTI: urinary tract infection; VLBW: very low birth weight.