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ORIGINAL ARTICLE

Early sepsis in premature infants in Neonatal Intensive Care Units

Sepse precoce em prematuros de Unidades de Terapia Intensiva Neonatal

Sepsis temprana en bebés prematuros en Unidades de Cuidados Intensivos Neonatales

Raquel Cristina Gomes Lima[1,2] ORCID 0000-0001-5344-3508
Danielle Souto de Medeiros[3] ORCID 0000-0002-2480-8990
Verônica Cheles Vieira[2,3] ORCID 0000-0002-2480-8990
Carla Silvana de Oliveira e Silva[4] ORCID 0000-0002-2752-1557

[1]Universidade Estadual de Montes Claros, Montes Claros, Minas Gerais, Brazil.
[2]Universidade Estadual do Sudoeste da Bahia, Vitória da Conquista, Bahia, Brazil.
[3]Instituto Multidisciplinar em Saúde, Universidade Federal da Bahia, Vitória da Conquista, Bahia, Brazil.
[4]Graduate Program in Health Sciences, Universidade Estadual de Montes, Montes Claros, Minas Gerais, Brazil.

Address: Rua Pastor Valdomiro Oliveira 455, apartamento 102. CEP: 45028-742
Bairro: Candeias. Vitória da Conquista-BA
E-mail: rcglima@gmail.com

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ABSTRACT

Justification and Objectives: despite great advances in neonatal care, deaths in this age period remain high throughout the world, highlighting prematurity and neonatal sepsis as the main causes. This study aimed to assess the incidence of early neonatal sepsis and associated maternal and neonatal risk factors in premature infants admitted to Neonatal Intensive Care Units in a city in the countryside of Bahia. **Methods**: a non-concurrent cohort study including 268 preterm infants admitted on the day of birth between January 2016 and December 2017 and followed during the neonatal period. The incidence of early neonatal sepsis and its risk factors were calculated. Poisson regression with robust variance was used for multivariate analysis, obtaining estimates of Relative Risk (RR) and respective 95% Confidence Intervals (CI). Statistical significance was considered when p-value ≤ 0.05. **Results:** incidence of early sepsis was 38% (102), of which 12.3% (33) had sepsis treated by the clinic and 25.7% (69) also presented at least one laboratory alteration. The diagnosis of presumed early sepsis was identified in 63.4% (170); no sepsis was confirmed with culture; and sepsis was ruled out in 25.5% (68) of premature infants. The following were positively associated with the outcome: being born by vaginal delivery (RR: 1.53; 95%CI: 1.19-1.97), gestational age less than 32 weeks (RR: 1.86; 95%CI: 1.35-2.57), less than 28 weeks (RR: 2.16; 95%CI: 1.59-2.94) and 5-minute Apgar score less than 7 (RR: 1.45; 95%CI: 1.14-1.83). **Conclusion:** there was a high incidence of early sepsis compared with international and national research. The results suggest the need for strategies to prevent prematurity and improve care during childbirth.

Keywords: *Premature Newborn. Neonatal Sepsis. Neonatal Intensive Care Units. Longitudinal Studies.*

RESUMO

Justificativa e Objetivos*:* apesar dos grandes avanços na assistência neonatal, os óbitos nesse período etário continuam elevados em todo o mundo, destacando-se a prematuridade e a sepse neonatal como as principais causas. Este estudo objetivou avaliar a incidência de sepse neonatal precoce e os fatores de risco materno e neonatal associados de prematuros internados nas Unidades de Terapia Intensiva Neonatais em uma cidade no interior da Bahia. **Métodos:** estudo de coorte não concorrente, incluindo 268 prematuros internados no dia do nascimento, entre janeiro de 2016 e dezembro de 2017, acompanhados no período neonatal. Foram calculados a incidência de sepse neonatal precoce e seus fatores de risco. Utilizou-se, para análise multivariada, a regressão de Poisson com variância robusta, obtendo-se estimativas do Risco Relativo (RR) e dos respectivos Intervalos de Confiança (IC) de 95%. Considerou-se significância estatística quando valor de $p \leq 0,05$. **Resultados:** incidência da sepse precoce foi 38% (102), sendo que 12,3% (33) tiveram sepse tratada pela clínica e 25,7% (69) apresentaram, também, pelo menos uma alteração laboratorial. O diagnóstico de sepse precoce presumida foi identificado em 63,4% (170); nenhuma sepse foi confirmada com cultura; e a sepse foi afastada em 25,5% (68) dos prematuros. Associaram-se positivamente ao desfecho nascer de parto vaginal (RR: 1,53; IC95%: 1,19-1,97), idade gestacional menor que 32 semanas (RR: 1,86; IC95%: 1,35-2,57), menor que 28 semanas (RR: 2,16; IC95%: 1,59-2,94) e Apgar 5º minuto menor que 7 (RR: 1,45; IC95%:1,14-1,83). **Conclusão:** houve elevada incidência de sepse precoce, comparada com as pesquisas internacionais e nacionais. Os resultados sugerem necessidade de estratégias para a prevenção da prematuridade e melhoria da assistência durante o parto.

Descritores: *Recém-Nascido Prematuro. Sepse Neonatal. Unidades de Terapia Intensiva Neonatal. Estudos Longitudinais.*

RESUMEN

Justificación y Objetivos: a pesar de los grandes avances en la atención neonatal, las muertes en este período de edad siguen siendo elevadas en todo el mundo, destacando la prematuridad y la sepsis neonatal como principales causas. Este estudio tuvo como objetivo evaluar la incidencia de sepsis neonatal temprana y factores de riesgo maternos y neonatales asociados en bebés prematuros ingresados en Unidades de Cuidados Intensivos Neonatales en una ciudad del interior de Bahía. **Métodos**: estudio de cohorte no concurrente, que incluyó 268 prematuros hospitalizados el día del nacimiento, entre enero de 2016 y diciembre de 2017, seguidos en el período neonatal. Se calculó la incidencia de sepsis neonatal temprana y sus factores de riesgo. Para el análisis multivariado se utilizó la regresión de Poisson con varianza robusta, obteniendo estimaciones del Riesgo Relativo (RR) y los respectivos Intervalos de Confianza (IC) del 95%. Se consideró significación estadística cuando el valor de $p \leq 0,05$. **Resultados**: La incidencia de sepsis temprana fue del 38 % (102), el 12,3 % (33) recibió tratamiento de sepsis en la clínica y el 25,7 % (69) también tuvo al menos una anomalía de laboratorio. El diagnóstico de presunta sepsis temprana se identificó en el 63,4% (170); no se confirmó sepsis con cultivo; y se descartó sepsis en el 25,5% (68) de los bebés prematuros. Se asociaron positivamente con el resultado de nacer por vía vaginal (RR: 1,53; IC95%: 1,19-1,97), edad gestacional menor de 32 semanas (RR: 1,86; IC95%: 1,35-2,57), menos de 28 semanas (RR: 2,16; IC95%: 1,59-2,94) y Apgar al quinto minuto inferior a 7 (RR: 1,45; IC95%: 1,14-1,83). **Conclusión**: hubo una alta incidencia de sepsis temprana, en comparación con la investigación nacional e internacional. Los resultados sugieren la

necesidad de estrategias para prevenir la prematuridad y mejorar la atención durante el parto.

Palabras Clave: *Recién Nacido Prematuro. Sepsis Neonatal. Unidades de Cuidados Intensivos Neonatales. Estudios Longitudinales.*

INTRODUCTION

In Brazil, despite the downward trend in infant mortality in recent years, a slow reduction in the early neonatal component has been observed, with 1/5 of deaths occurring on the first day of life and the majority of causes considered preventable when adequate attention is provided to women's and newborns' health.[1] Investigation of this component highlights neonatal sepsis as one of the main causes of these deaths, especially in premature and very low birth weight newborns. [2,3]

Early-onset neonatal sepsis is characterized as a clinical syndrome with systemic signs of infection that occurs in the first 72 hours of life, originating from bacterial pathogens transmitted vertically from mother to newborn before or during delivery.[4,5] The microorganisms most involved in its pathogenesis are group B *Streptococcus* (GBS), *Escherichia coli* and *Listeria monocytogenes*, which together account for approximately 65% to 70%, respectively, of all systemic neonatal bacterial diseases.[6]

The incidence of culture-proven early-onset sepsis in the United States from 2005 to 2008 ranged from 0.75 to 0.77 cases/1,000 live births, and mortality was 10.9%. Black preterm infants had higher rates (5.14 cases/1,000 live births), and 24.4% died.[7] Research at the Vermont Oxford Network, from 2007 to 2016, identified 3.7% of early sepsis in extremely premature infants.[8] In the *Rede Brasileira de Pesquisas Neonatais* (RBPN, Brazilian Neonatal Research Network), from 2006 to 2017, the prevalence of this sepsis was 15.5 cases/1,000 very low birth weight newborns, and 52.9% evolved to death.[2]

"Suspected" early neonatal sepsis is one of the most common and challenging diagnoses in Neonatal Intensive Care Units (NICUs), given that the signs and symptoms may be minimal or nonspecific and confused with clinical conditions typical of birth and adaptation to the extrauterine environment, especially in premature infants. [2,9] Therefore, there is a great challenge for healthcare professionals in identifying newborns with a high probability of early sepsis and initiating antimicrobial therapy as well as discontinuing this therapy when infection is considered unlikely.[10]

Several risk factors are involved in the genesis of early sepsis, being grouped into maternal or neonatal factors, highlighting premature labor, rupture of amniotic

membranes 18 hours or more before delivery, chorioamnionitis, maternal colonization by EGB, maternal fever during or immediately after delivery,[11] premature newborns with low 5-minute Apgar scores and need for resuscitation at birth.[12,13]

Most studies on this topic are concentrated in large centers, mainly in university hospitals, where research and prophylaxis for GBS in pregnant women are routinely carried out, and neonatal units have strict management for carrying out cultures and using antimicrobial agents, which does not occur in most maternal and child hospitals in the countryside of Brazil. Little is known about the true incidence of early neonatal sepsis in low- and middle-income countries.[14] Therefore, this research aims to assess the incidence of early neonatal sepsis, the associated maternal and neonatal risk factors and the evolution of premature infants admitted to three NICUs in a city in the countryside of Bahia.

METHODS

This is a non-concurrent, hospital-based cohort study, including premature infants admitted to the three NICUs on the first day of life, from January 1, 2016 to December 31, 2017. The research was carried out in the city of Vitória da Conquista, the third largest city in the state of Bahia, headquarters of the Southwest Regional Health Center.

The study population was monitored until 27 days of life. Since this was a larger study, the exclusion criterion was being premature with a congenital anomaly (complex congenital heart disease, gastrointestinal tract atresia, abdominal wall defects, hydrocephalus, encephalocele and diaphragmatic hernia).

The data were obtained by analyzing medical records stored in the medical and statistical archive service of the three hospitals. NICUs have ten beds each, two of which are located in public hospitals and the other in a private hospital.

The sample was obtained by convenience (n=268). However, the smallest sample size necessary to represent the population of premature infants in the region was estimated at 120, considering the following parameters: infinite population size (given that it is not possible to estimate the total number of premature infants who would require neonatal intensive care); expected frequency of early neonatal sepsis of 8.5%, according to Barbosa *et al*. (2014), in Uberlândia;[15] 5% accuracy; and 95% Confidence Interval.

Data were obtained through a specific questionnaire based on the Birth Survey for Brazil[3] instrument by volunteer health researchers, after training and under the

supervision of neonatologists. The main fieldwork took place from June 2018 to April 2019, using a digital questionnaire through the Kobo Toolbox 1.4.8® software.

The dependent variable was early neonatal sepsis. The diagnostic description in medical records and the use of an empirical therapeutic regimen of ampicillin or crystalline penicillin G associated with gentamicin (protocol in the units) in the first 72 hours of life were considered.

Sepsis was categorized as presumed early-onset neonatal sepsis (PES) when clinical signs and symptoms compatible with the disease occurred, and an antimicrobial regimen was initiated. Confirmed early-onset neonatal sepsis (CNS) was considered if a positive blood culture was obtained. PES was divided into rule out neonatal sepsis (RNS), whose clinical and laboratory evolution allowed the suspension of antibiotics within four days, and treated neonatal sepsis (TNS), which were those who received the antimicrobial regimen between five days and more.[16]

Within the TNS group, a subdivision was made into clinically treated neonatal sepsis (CTNS) and clinically treated neonatal sepsis with at least one laboratory alteration (CTNSL). According to Procianoy *et al*. (2020), the number of leukocytes above 25,000 or below 5,000 and the immature neutrophil to total ratio (I/T) above 0.2 or C-reactive protein above 10.[17] The death certificates of premature infants with PES who died in the first four days of life were assessed. When the declared cause was early neonatal sepsis or septic shock, the TNS category was assigned to those who had been treated for less than four days. For these premature infants, a sensitivity analysis was performed by comparing the results of the analyses, including these premature infants in the group described above and excluding them from the analyses for subsequent decision-making.

For these premature infants, a sensitivity analysis was performed to compare the results obtained from the decision to include deaths in the category described above and exclude them from the analysis.

In cases of suspected early sepsis, it was routine in the three units to collect a blood culture sample before starting antimicrobial agents. Microorganism isolation was performed using the manual or automated blood culture method in the three units by an outsourced laboratory.

The independent variables analyzed were divided into two chunks. Chunk I contained maternal demographic characteristics, maternal morbidities, and prenatal and delivery care. The variables used were maternal age (<20 years, ≥20 years), marital status (with partner and without partner), preterm labor (no or yes), hypertensive syndrome (no

or yes), number of prenatal consultations (up to five consultations or six and more consultations), and type of delivery (cesarean or vaginal).

Chunk II included the characteristics of premature infants, neonatal care received and clinical evolution, such as the sex of premature infants (male or female), estimated gestational age in weeks, categorized as extremely premature (less than 28 weeks), very premature (28 to less than 32 weeks) and moderate/late premature (32 to less than 37 weeks). Birth weight was measured in grams and divided into ≥ 1,500 g or < 1,500 g, 5th-minute Apgar (< 7 or ≥ 7), hypothermia on admission to the NICU (no or yes). Clinical outcomes were assessed through the diagnosis of late neonatal sepsis and neonatal death, both categorized as no or yes.

In order to obtain information regarding the missing medical records, the nursing admission books of the NICUs were analyzed. The assessment of losses was made by comparing the sample obtained with the total population using Pearson's chi-square test or linear trend.

Initially, a descriptive analysis of the variables studied was performed, presenting absolute and relative frequencies. All variables were also described according to the categories of early neonatal sepsis, such as absent, ruled out and treated (CTNS and CTNSL), compared using Pearson's chi-square test or Fisher's exact test. Sensitivity analysis was performed using Pearson's chi-square test.

For the bivariate analysis, the early neonatal sepsis variable was recategorized as absent and treated (CTNS and CTNSL). The RNS category was removed from the analyses due to its behavior being different from the other sepsis categories (absent or TNS) and the insufficient number of observations for an analysis as an isolated category. The assessment of the progression to late neonatal sepsis and death was performed according to the groups of absent and treated early neonatal sepsis. Bivariate analysis between independent variables and treated early neonatal sepsis was performed using Poisson Regression with robust variance, obtaining estimates of the unadjusted Relative Risk ($_u$RR) and their respective 95% Confidence Intervals (95%CI).

For multivariate analysis, the independent variables from chunks I and II were used, which met the following criteria: p-value ≤ 20% (by the Wald test); loss of less than 10%; and the assumption of independence between variables. The models were compared by the Akaike criterion, and adequacy was assessed by the chi-square test. For all tests and for the permanence of the variables in the final model, a p-value ≤ 0.05 was used.

The Stata, version 15.1 (Stata Corporation, College Station, USA), was used for data analysis.

This research was carried out taking into account the guarantee of ethical and legal principles that govern research on human beings, recommended in Resolutions 466/2012, 510/2016 and 580/2018 of the Ministry of Health, approved by the Research Ethics Committee, with *Certificado de Apresentação para Apreciação Ética* (CAAE, Certificate of Presentation for Ethical Consideration) 42401920.0.0000.5049, on February 5, 2018.

RESULTS

During the two years of study, 592 premature infants were admitted to the NICUs, 37 of whom were excluded due to congenital malformations, and 155 medical records were not located, leaving a sample of 400 premature infants. Medical records that were not located were assessed as possible losses. No differential loss was observed, and the use of calibration factors was not necessary to conduct the other analyses. The following variables were analyzed: hospital of origin (p=0.261); birth weight (p=0.917); gestational age (p=0.948); death (p=0.939); and according to 2016 and 2017 (p=0.827).

For the present study, 268 premature infants were included. Concerning maternal characteristics, most mothers were over 20 years old, lived without a partner and evolved to cesarean delivery. In relation to the characteristics of premature infants and neonatal care, the majority were male, classified as moderate/late premature, weighed over 1,500 g, had a 5-minute Apgar score greater than or equal to 7 and were hypothermic upon admission to the NICU (Table 1).

Table 1. Description of the characteristics of the premature population (n=268). Vitória da Conquista, BA, Brazil, 2016/2017

Variables	n	%
Mother's age		
< 20 years	44	16.4
≥ 20 years	224	83.6
Mother's marital status		
With partner	113	46.5
Without partner	130	53.5
Premature labor		
No	130	50.2
Yes	129	49.8
Hypertensive syndrome		
No	179	66.8

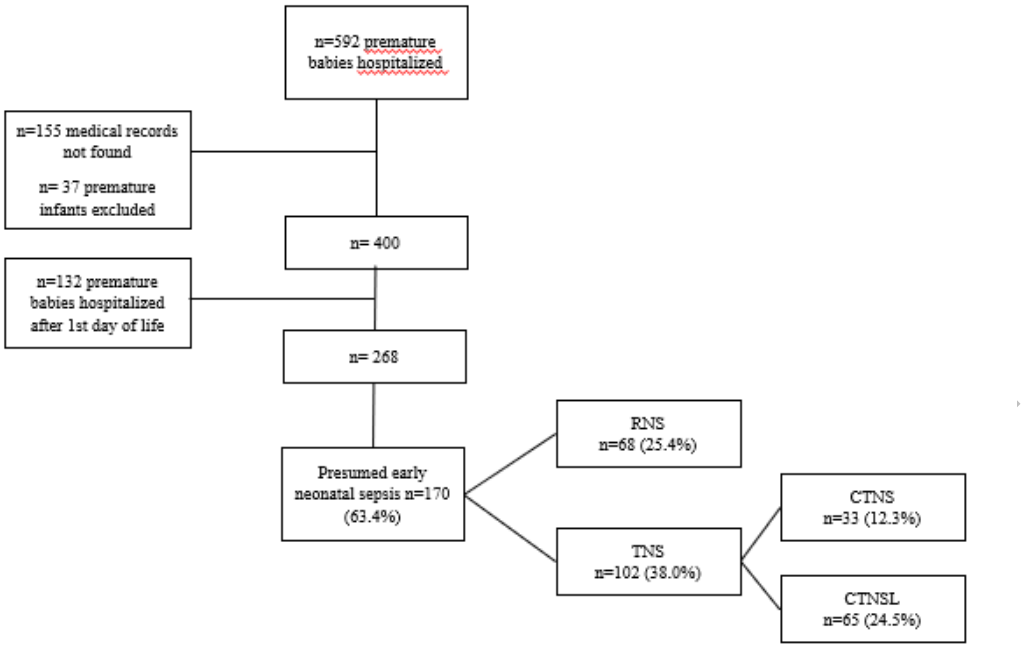
Yes	89	33.2
Number of prenatal consultations		
Up to 5	118	50.0
6 and more	118	50.0
Type of delivery		
Caesarean section	193	72.3
Vaginal	74	27.7
Sex		
Male	143	53.4
Female	125	46.6
Gestational age at birth		
Moderately premature/late premature	166	61.9
Very premature	67	25.0
Extremely premature	35	13.1
Birth weight		
≥ 1,500g	163	60.8
< 1,500g	105	39.2
5-minute Apgar		
≥7	232	88.2
< 7	31	11.8
Hypothermia on admission to the Neonatal Intensive Care Unit		
No	67	32.7
Yes	138	67.3
Late neonatal sepsis		
No	205	76.5
Yes	63	23.5
Neonatal death		
No	232	86.6
Yes	36	13.4

Note: authors according to *Coorte Nascer Prematuro*, 2016/2017.

Fourteen premature deaths were recorded before 4 days of life, of which nine had early sepsis or septic shock as the cause of death (death certificate). These patients were removed from the RNS group and included in the CTNS or CTNSL groups. To perform a sensitivity assessment, the analyses were repeated excluding these nine newborns, and no differences were observed between the results. It was therefore decided to keep them in the analyses.

A total of 170 (63.4%) (95%CI: 57.4-69.0) premature infants had PES, of which 68 (25.4%) (95%CI: 20.4-30.9) had RNS and 102 (38.0%) (95%CI: 32.4-44.0) had TNS. Of the total number of premature infants in the study (268), 33 (12.3%) (95%CI: 8.8-16.8) had CTNS, and 65 (24.5%) (95% CI: 20.8-31.3) had CTNSL (Figure 1).

Figure 1. Premature infants admitted to Neonatal Intensive Care Units and their distribution according to evolution, such as ruled out neonatal sepsis, neonatal sepsis treated, neonatal sepsis treated due to clinical alterations, neonatal sepsis treated due to clinical alterations and at least one laboratory alteration



Note: authors according to *Coorte Nascer Prematuro*, 2016/2017.

When comparing the groups and the variables of chunks I and II, it was found that there is an association between maternal age (p=0.008), hypertensive syndrome (p=0.014), premature labor (p=0.013), type of delivery (p<0.001), gestational age at birth (p<0.001), birth weight (p<0.001) and 5-minute Apgar (p=0.001) (Table 2).

Table 2. Distribution of variables from chunks I and II according to the following groups of early neonatal sepsis, as absent, ruled out, treated with clinical alterations and treated with clinical and laboratory alterations, p value (n=268). Vitória da Conquista, BA, Brazil, 2016/2017

	Absent		Rule out early neonatal sepsis		Early neonatal sepsis treated				
					With clinical changes		With clinical and laboratory changes		
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**p-value***
Age									0.008
< 20 years	7	15.9	18	40.9	5	11.4	14	31.8	
≥ 20 years	91	40.6	50	22.3	28	12.5	55	24.6	
Marital status									0.080
With partner	51	45.1	27	23.9	11	9.7	24	21.3	
No partner	38	29.2	37	28.5	18	13.8	37	28.5	
Hypertensive syndrome									0.014
No	55	30.7	54	30.2	21	11.7	49	27.4	
Yes	43	48.3	14	15.7	12	13.5	20	22.5	
Prenatal consultations									0.077
Up to 5	36	30.5	33	28.0	15	12.7	34	28.8	
6 and more	55	46.6	28	23.7	12	10.2	23	19.5	
Premature labor									0.013
No	59	45.4	32	24.6	10	7.7	29	22.3	
Yes	36	27.9	34	26.4	21	16.3	38	29.4	
Type of delivery									< 0.001
Caesarean section	90	46.6	47	24.4	17	8.8	39	20.2	
Vaginal	8	10.8	21	28.4	16	21.6	29	39.2	
Sex									0.087
Male	51	35.6	43	30.1	12	8.4	37	25.9	
Female	47	37.6	25	20.0	21	16.8	32	25.6	
Gestational age									< 0.001
Moderate/late preterm	84	50.6	41	24.7	11	6.6	30	18.1	
Very premature	12	17.9	17	31.3	15	19.4	23	31.4	
Extremely premature	2	5.7	10	28.6	7	20.0	16	45.7	

Birth weight									< 0.001
≥ 1,500 g	77	47.2	44	27.0	11	6.7	31	19.0	
< 1,500 g	21	20.0	24	22.9	22	20.9	30	36.2	
5-minute Apgar									0.001
≥7	94	40.5	59	25.4	18	7.8	61	26.3	
< 7	4	12.9	7	22.6	12	38.7	8	25.8	
Hypothermia on admission									0.606
No	26	38.8	19	28.4	8	11.9	14	20.9	
Yes	55	39.9	29	21.0	16	11.6	38	27.5	

Note: *Pearson's chi-square test or Fisher's exact test.

The bivariate analysis of the variables in chunk I demonstrated a higher risk for TNS in mothers under 20 years of age, who lived without a partner, who developed premature labor and who had a vaginal delivery. And a protective factor for the outcome included mothers with some hypertensive syndrome during pregnancy and who had six or more prenatal consultations. Regarding the variables in chunk II, a positive association, gestational age less than 32 weeks, birth weight less than 1,500 g and 5-minute Apgar score less than 7 were evidenced.

The variables maternal age, hypertensive syndrome during pregnancy, type of delivery, gestational age, birth weight and 5-minute Apgar met the adopted criteria and were included as a chunk in the multivariate analysis. After adjustment, being born by vaginal delivery, with a gestational age of less than 32 weeks and a 5-minute Apgar score of less than 7 remained significantly associated with the outcome (Table 3).

Table 3. Result of bivariate and multivariate analysis between the independent variables of chunk I and II and treated neonatal sepsis, unadjusted and adjusted relative risk with their respective 95% confidence intervals (n = 200). Vitória da Conquista – BA, 2016/2017.

Variables	Unadjusted RR	95%CI	Adjusted RR	95%CI
Mother's age				
≥ 20 years	1.00		-	-
< 20 years	1.53	1.15-2.02	-	-
Mother's marital status				
With partner	1.00	-		
No partner	1.45	1.06-1.97		
Premature labor				
No	1.00	-		
Yes	1.56	1.16-2.08		
Hypertensive syndrome				
No	1.00	-	-	-
Yes	0.76	0.56-1.03	-	-
Number of prenatal consultations				
Up to 5	1.00	-		
6 and more	0.67	0.49-0.92		
Type of delivery				
Caesarean section	1.00	-	1.00	-
Vaginal	2.21	1.74-2.80	1.53	1.19-1.97
Sex				
Male	1.00	-		
Female	1.08	0.82-1.42		
Gestational age				
Moderate/late preterm	1.00	-	1.00	-
Very premature	2.31	1.72-3.11	1.86	1.35-2.57
Extremely premature	2.80	2.12-3.69	2.16	1.59-2.94
Birth weight				

≥ 1,500 g	1.00	-	-	-
< 1,500 g	2.09	1.59-2.76	-	-
5-minute Apgar				
≥7	1.00		1.00	-
< 7	1.82	1.43-2.32	1.45	1.14-1.83
Hypothermia on admission				
No	1.00	-		
Yes	1.08	0.75-1.55		

Note: RR: relative risk; 95%CI: 95% Confidence Interval.

Late-onset neonatal sepsis and neonatal death occurred in 41 (40.2%) and 25 (24.5%) premature infants, respectively, who had TNS. The two conditions analyzed were significantly associated with the outcome (Table 4).

Table 4. Evolution of premature infants in the groups with no and treated early neonatal sepsis according to progression to late neonatal sepsis and neonatal death, p-value, unadjusted relative risk with their respective 95% confidence intervals (n=200). Vitória da Conquista, BA, Brazil, 2016/2017

Variables	Late neonatal sepsis				Neonatal death			
	No	Yes			No	Yes		
	n (%)	n (%)	p-value*	$_{U}$RR (95%CI)	n (%)	n (%)	p-value*	$_{U}$RR (95%CI)
Absent early neonatal sepsis	92(93.9)	6(6.1)	< 0.001	6.56 (2.91-14.79)	96(98.0)	2(2.0)	< 0.001	12.00 (2.91-49.53)
Early neonatal sepsis treated	61(59.8)	41(40.2)			77(75.5)	25(24.5)		

Note: *Pearson's chi-square test or Fisher's exact test; $_{U}$RR: unadjusted relative risk; 95%CI: 95% Confidence Interval.

DISCUSSION

This study demonstrates the difficulties faced in the management of early neonatal sepsis in premature infants, in which it was found that most of them had clinical signs and symptoms that motivated the introduction of antimicrobial agents. As a result of rigorous clinical and laboratory monitoring, it was possible to suspend antibiotics in 25.4% of cases. Different results were verified by the RBPN, in which 74.3% of premature infants did not require antibiotics in the first 48 hours of life, and it was possible to interrupt them in 44% of cases within 48-72 hours. This demonstrates the impact of the strategies used in the institution for the rational use of antimicrobial agents.[2]

Despite the routine collection of blood cultures in units before starting antibiotics, no positive culture results were detected, making diagnostic accuracy more difficult. Obtaining insufficient blood volume (due to prematurity) and the absence of automated systems (due to a lack of vials in public services) in all cultures may have influenced the results. No similar results were identified in this cohort. International and national studies demonstrate low culture positivity in early neonatal sepsis, being 5.93% in India (2017),[18] 2.9% in Uberlândia (2011)[15] and 1.3% in Campinas (2006-2017).[2]

It was found that 12.3% of premature infants treated did not have any laboratory abnormalities identified and were treated based on clinical manifestations. This is the difficulty in achieving diagnostic accuracy, since the signs and symptoms may be minimal or nonspecific and confused with other non-infectious inflammatory syndromes, and diagnostic tests have a low positive predictive value. Therefore, the decision to treat a newborn also depends on other factors, such as the presence of maternal risk factors, the frequency of observations and the degree of prematurity of newborns.[2,9,10]

The incidence of early sepsis in this cohort was similar to that observed in public hospitals in Ethiopia in 2019 (38%),[13] but high when compared with other studies. In England, the incidence in extremely premature infants (2007-1016) was 3.7%.[8] In Brazil, in 2011, 8.5% of newborns presented the aforementioned outcome.[15]

It is worth highlighting the methodological differences found in several studies on this topic. Some studies only include CNS through culture, others include all neonates, which made the comparative aspect difficult. Also regarding the calculation of the incidence of sepsis, most sources demonstrate the rates for every 1,000 live births.

In this cohort, being born vaginally remained an independent factor for early sepsis. This finding was also evidenced in other studies.[12,19] This type of delivery may be associated with prolonged rupture of the amniotic membranes (> 18 hours), chorioamnionitis or exposure to GBS[11,13]. In this cohort, being born at a gestational age of less than 32 weeks was associated with an increased risk of early sepsis, which can be supported by several international and national studies.[2,10,13,20,21] It is known that premature infants present immunological dysfunction due to the absence of maternal transplacental transfer of IgG, immature cellular responses, and deficiencies of soluble proteins and peptides.[21]

Being born with a 5-minute Apgar score of less than 7 led to a 45% higher risk of early-onset sepsis. Similar results were found in public hospitals in southern Ethiopia.[12] This association can be explained by the fact that perinatal asphyxia causes an immunological insult, contributing to a worsening of the response to combat infections in premature infants who already have an impaired innate immune status.[11, 22]

It was found that premature infants with early neonatal sepsis had a 6.5 and 12.0 times greater risk of developing late-onset sepsis and neonatal death, respectively. These findings support the research conducted by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network, which followed premature infants treated for early-onset sepsis. The presence of this diagnosis was associated with late-onset sepsis, necrotizing enterocolitis and death.[23]

Following the Ministry of Health recommendations, there is no routine screening for GBS in prenatal care provided by the Unified Health System in this region.[24] This contributes to the lack of knowledge about the prevalence of colonization of pregnant women by this agent combined with the negativity of all blood cultures, which led to difficulties in identifying the microorganisms responsible for sepsis. In order to clarify this gap, a pioneering study carried out in this city screened GBS in pregnant women and identified a prevalence of 18.1%, highlighting the importance of implementing this routine in prenatal care practices in the public health system.[25]

Among the limitations of this study, retrospective design with possible information bias, in addition to not obtaining some important maternal variables for the outcome studied, such as time of rupture of amniotic membranes, status of colonization

by EGB, use of antimicrobial agents by the mother and diagnosis of chorioamnionitis, stood out.

Early-onset neonatal sepsis is one of the main diagnoses in NICUs. Its management is also one of the greatest challenges in neonatology, given that the clinical signs and symptoms are nonspecific, especially in premature infants, and can be confused with non-infectious conditions, combined with the low sensitivity of laboratory tests. In this cohort, a high incidence of TNS was identified, with most premature infants requiring antibiotics after birth and no microorganisms being isolated in blood cultures. The independent risk factors for early-onset neonatal sepsis include being born by vaginal delivery, with a gestational age of less than 32 weeks and a 5-minute Apgar score below 7. Furthermore, early-onset sepsis behaved as a risk factor for late-onset neonatal sepsis and death. These findings demonstrate the need to improve the quality of prenatal care, strategies to prevent prematurity, and management during birth to avoid perinatal asphyxia.

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Authors' contributions:

Raquel Cristina Gomes Lima contributed to project administration, literature search, abstract writing, introduction, methodology, discussion, interpretation and description of results, preparation of tables, conclusions, review and statistics**. Danielle Souto de Medeiros** contributed to project administration, literature search, abstract writing, introduction, methodology, discussion, interpretation and description of results, preparation of tables, conclusions, review and statistics. **Verônica Cheles Vieira** contributed to abstract writing, methodology, interpretation of results, conclusions, review and statistics. **Carla Silvana de Oliveira e Silva** contributed to the literature

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All authors approved the final version to be published and are responsible for all aspects of the work, including ensuring its accuracy and integrity.