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CLINICAL STUDY

Risk Factors for Sepsis in the Neonatal Intensive Care Unit of a Tertiary Hospital in Mexico

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ABSTRACT

Neonatal Sepsis (NS) is a systemic infection caused by bacteria, fungi, or viruses during the first month of life. Although various studies have identified the factors associated with NS, it is a public health problem due to its high morbidity and mortality. The study aimed to identify the risk factors associated with neonatal sepsis in the Neonatal Intensive Care Unit (NICU) of a tertiary hospital in Mexico. A case-control study was carried out using records of neonates (with sepsis 39 and without sepsis 39) from January to December 2017. The risk factors studied were the sociodemographic and clinical characteristics of the mother and clinics of the neonate. The data were analyzed using the Chi² test, Fisher's exact test, Student's t-test, and the Odds Ratio (OR). The risk factors associated with NS were gestational age (OR 0.77, CI 95% = 0.64-0.91, $p = 0.004$), newborn weight (OR 0.45, CI95% = 0.23-0.86, $p = 0.017$) and days of hospital stay (OR 1.06, CI95% = 1.02-1.10, $p = 0.0014$). The mother's sociodemographic and clinical factors were not associated with NS. Risk factors associated with NS were gestational age, newborn weight, and days of hospital stay.

INTRODUCTION

Neonatal Sepsis (NS) is a clinical syndrome characterized by symptoms of systemic infection caused by the colonization of the newborn by pathogenic germs during the first month of life [1]. Although it has a low incidence, it can cause severe consequences in the newborn's prognosis [2]. In developed countries, the incidence ranges from 2.2 to 9.8 events per 1000 live births [3]; however, it ranges from 49 to 170 in developing countries [2].

Different factors associated with NS are reported in the literature, both related to the mother and the neonate. For example, Lekić, et al. [4] reported those related to premature birth, low birth weight, maternal preeclampsia, premature rupture of membranes, and perinatal asphyxia. Moreover, Mogollón, et al. [5] reported the prolonged period of hospital stay, gestational age, and urinary tract infection in women during the third trimester of gestation. Similarly, Anaya-Prado, et al. [2] informed an association with the procedures used in the intensive care unit for management of resuscitation, intubation, and ventilator support.

Since the clinical manifestations of NS are nonspecific and most of the epidemiological information originates in developed countries, it is necessary to identify the causes of neonatal sepsis in developing countries to generate strategies and programs that allow the prevention, diagnosis, and adequate treatment of NS

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to reduce the high morbidity and mortality associated with this syndrome. For that reason, we aimed to identify the Risk Factors (RF) associated with NS in the Neonatal Intensive Care Unit (NICU) of a tertiary hospital in Mexico.

MATERIALS AND METHODS

A retrospective, not paired case-control study was conducted in a tertiary hospital in Mexico. It is a "No risk" level I research according to the Ley General de Salud Regulation regarding health research. The Hospital Research Committee approved the methodology and ethical aspects, registration number 36/19.

In the study design, for a minimum power of 80% in bilateral hypothesis contrast tests at a significance level of $p < 0.05$, a prevalence of bacteremia of 20% was considered among the controls, with a higher prevalence among the cases, estimating a population of 36 subjects per group. However, this study included 39 cases and 39 controls detected from January to December 2017 obtained from the hospital's informatics department. The group of cases was not stratified into Early-Onset Sepsis (EOS) and Late-Onset Sepsis (LOS); the population was the records of all preterm newborns ≥ 24 weeks of gestation.

The mother and the newborn clinical's records were analyzed to identify the associated factors. The cases were determined by evaluating serum Procalcitonin (PCT) levels greater than 0.5 ng/mL [6]. PCT has satisfactory characteristics as a good marker for the diagnosis of NS than IL-6, and C-reactive protein, with high sensitivity (83-100%) and specificity (70-100%) to bacterial infection [1,6,7].

The sociodemographic characteristics of the mother studied were sex, education, occupation, marital status, locality, and maternal age. On the other hand, the mother's clinical factors included the route of birth, Premature Rupture of Membranes (PROM), number of pregnancies, multiple pregnancies, and comorbidities. In addition, for the newborn, sex, gestational age, weight, and days of hospital stay were analyzed as RF.

Absolute and relative frequencies were calculated for the descriptive statistical analysis. In the inferential analysis, the Chi² and Fisher tests measured the association between sepsis and qualitative variables. The student's t-test determined the relationship between sepsis and the quantitative variables. The significance level of $p < 0.05$ was considered in all tests. For risk factors, the odds ratio was calculated. The software used was SPSS version 22 and STATA 15.

DEFINITIONS

Neonatal Sepsis (NS) is a generalized bacterial infection of the neonate's blood during the first month of life.

Procalcitonin (PCT) is a sensitive and specific biomarker to bacterial infection.

Risk Factors (RF) are characteristics, conditions, or behaviors that increase the possibility of disease or injury.

RESULTS

Mother's sociodemographic factors

The mother's sociodemographic factors did not show an association with the development of NS in the NICU (Table 1).

Maternal clinical factors

The maternal clinical factors did not show an association with the development of NS (Table 2). In the population studied were found the maternal comorbidities, illustrated in table 3.

Neonate's clinical factors

Neonate's sex was not associated with sepsis. However, we found statistically significant differences in the gestational age, the weight of the newborn, and the days of hospital stay, between the group of cases compared to controls, as illustrated in table 4.

Table 1: Mother's sociodemographic factors.

Variable	Control (n = 39)	Case (n = 39)	p
Scholarity			
-With studies	11 (50%)	11 (50%)	1 ^A
-Without studies	28 (50%)	28 (50%)	
Occupation			
-With job	31 (49%)	32 (51%)	0.78 ^B
-Without job	4 (44%)	5 (56%)	
Marital status			
-Single	13 (59%)	9 (41%)	0.2 ^A
-Married	20 (43%)	27 (57%)	
Locality			
-Rural	9 (53%)	8 (49%)	0.78 ^A
-Urban	30 (47%)	31 (51%)	
Maternal age	25.5 ± 7.5	23.5 ± 6.9	0.25 ^C

Absolute and relative frequencies. Mean ± standard deviation. ^AChi squared, ^BFisher's test, ^CStudent's t-test.

Table 2: Maternal clinical factor.

Variable	Control (n = 39)	Case (n = 39)	p
Birth delivery			
-Vaginal	13 (33%)	12 (31%)	0.80 ^A
-Cesarian section	26 (67%)	27 (69%)	
PROM			
- ≤18 hours	25 (64%)	21 (54%)	0.36 ^A
- >18 hours	14 (36%)	18 (46%)	
Number of pregnancies	2.02 ± 1.06	2.33 ± 1.26	0.29 ^C
Multiple pregnancies			
-Yes	7 (58%)	5 (42%)	0.53 ^B

PROM: Premature Rupture of Membranes.

Absolute and relative frequencies.

Mean ± standard deviation. ^AChi squared, ^BFisher's test, ^CStudent's t-test.

In addition, we analyzed the possible association of the newborn clinical manifestations (Table 5) with NS since the differences found could reflect worse general status, conditioned in some cases by the septic state. However, we did not find significant differences.

Table 3: Maternal comorbidities.

Variable	Control (n = 39)	Case (n = 39)
Gestational diabetes	3 (75%)	1 (25%)
UTI	3 (60%)	2 (40%)
Preeclampsia	2 (50%)	2 (50%)
Chorioamnionitis	--	1 (100%)
Hypertension	--	2 (100%)
PROM complications	3 (75%)	1 (25%)

UTI: Urinary Tract Infection; PROM: Premature Rupture of Membranas.
Absolute and relative frequencies.

Table 4: Neonate's clinical factors.

Variable	Control (n = 39)	Case (n = 39)	p
Neonate's sex			
-Male	20 (45%)	19 (56%)	0.36 ^A
-Female	24 (55%)	15 (44%)	
Gestational age (week)	36.09 ± 2.97	33.8 ± 3.01	0.001 ^B
Weight (kg)	2.43 ± 0.79	1.99 ± 0.73	0.015 ^B
Days of hospital stay	12.3 ± 10.04	27.92 ± 21.16	0.001 ^B

Absolute and relative frequencies. Mean ± standard deviation. ^AChi squared, ^BFisher's test, ^CStudent's t-test.

Table 5: Newborn clinical manifestations.

Variable	Control (n = 39)	Case (n = 39)	p
Premature newborn	24 (49%)	25 (51%)	0.81 ^A
RDS I	17 (40%)	25 (60%)	0.069 ^A
Hyperbilirubinemia	10 (59%)	7 (41%)	0.41 ^B
Gastroschisis	1 (100%)	--	--
Apnea	1 (25%)	3 (75%)	0.61 ^B
SWOGI	3 (38%)	5 (62%)	0.71 ^B
Early neonatal sepsis	3 (33%)	6 (67%)	0.24 ^B
Hypoglycemia	--	1 (100%)	--
Obstetric trauma	1 (33%)	2 (67%)	0.5 ^B
Perinatal asphyxia	3 (60%)	2 (40%)	0.5 ^B
Meconium aspiration	2 (100%)	--	--
Suitable weight	8 (89%)	1 (11%)	0.013 ^B
Hemorrhage	1 (100%)	--	--
Neuroinfection	1 (50%)	1 (50%)	0.75 ^B
Encephalopathy	--	1 (100%)	--
Lung adaptation	1 (100%)	--	--
Jaundice	4 (57%)	3 (43%)	0.5 ^B

RDS I: Respiratory distress syndrome I; SWOGI: Sepsis without Germ Isolated.
Absolute and relative frequencies. ^AChi squared, ^BFisher's test.

Risk factors associated with NS

Based on the results obtained, those variables where the $p < 0.05$ were taken to calculate the Odds Ratio (OR) and evaluate the risk of NS for each variable. These results are presented in table 6.

Table 6: Risk factors associated with NS.

Variable	OR	CI 95%	p
Gestational age	0.77	0.64 - 0.91	0.004
Weight	0.45	0.23 - 0.86	0.017
Days of hospital stay	1.06	1.02 - 1.10	0.001

OR: Odds ratio; CI95%: 95% Confidence interval.

DISCUSSION

The purpose of this study was to evaluate the possible association of the mother's sociodemographic and clinical characteristics and the neonate's clinical characteristics with NS to determine risk factors. The results indicate no association between the sociodemographic characteristics (scholarity, occupation, marital status, locality, and maternal age) and the mother's clinical characteristics (birth delivery, PROM, number of pregnancies, and multiple pregnancies) with NS.

A previous study reported that a low educational level, being a primiparous woman, and delivering via cesarean section are factors associated with neonatal sepsis [3]. Similarly, the results obtained in this study differ from the reported by Lekić, et al. [4] who associated PROM as a risk factor. However, we did not find that association; this may be explained due to the methodological differences, since in the one carried out by Lekić, patients with sepsis were classified as early-onset sepsis (EOS; <72 h) and late sepsis (LOS; >72 h). In addition, they considered blood culture results and C-reactive protein levels for sepsis diagnosis, while we used PCT levels to the diagnosis. Moreover, they considered a time > 24 h for PROM, and in this study, we considered a time > 18 h.

Only neonate's sex was not associated with NS; gestational age, weight, and days of hospital stay are risk factors associated with sepsis in the NICU. These results are congruent with those reported by Lekić, et al. [4] who found that low birth weight and premature birth are risk factors for sepsis. Similarly, Mogollón, et al. [5] showed that a long hospital stay, gestational age, and urinary tract infections as risk factors for EOS [4]. These results are relevant considering that PCT was used as a marker of sepsis in the present study [6].

A limitation of the study was the use of PCT in sepsis diagnosis since it can be elevated in non-infectious conditions that cause tissue destruction, i.e., surgical events,

acute myocardial infarction, burns, and trauma [8,9]. However, high sensitivity and specificity have been reported in contrast to other methods [1,7]. Moreover, blood cultures have the disadvantage that the sample volume is sometimes insufficient; it can become contaminated and generate false negatives [10].

Furthermore, some studies have reported a high fatality rate for sepsis; however, in the present study, we could not evaluate this situation because the records of the deceased neonates were not available, so it was an exclusion criterion from the study [11,12]. Finally, the results are single-center, with limited potential to extrapolate to different settings. So, it is necessary to consider making a multicenter study.

Future research aims to consider other maternal (days of gestation, infections, age <15 years) and neonate (use of invasive methods, respiratory complications, low Apgar score) risk factors, as well as the pharmacological treatment of patients, previously reported [2,4,12,13], in addition to the bacteriological profile associated with sepsis [14]. Also, we considered stratifying the cases into EOS and LOS, using PCT as a marker of sepsis since EOS occurs mainly by infections acquired from the mother before or during delivery, and the postnatal environment plays a direct role in developing LOS [4].

CONCLUSION

According to the study, gestational age, newborn weight, and days of hospital stay are risk factors for neonatal sepsis in the Neonatal Intensive Care Unit, so they can be considered to increase newborns' prognosis and life expectancy.

AUTHOR CONTRIBUTION

ILVV and LIPM jointly collected the data, written and reviewed the manuscript. OLVL and ECP analyzed and interpreted the results, format, style, writing, and review of the manuscript. PEMP and JLE interpreted and discussed the results, writing, and review. MOPV and OLVL jointly participated in the conception, interpretation, and discussion of the manuscript's results, writing, and review. All the authors have read the final manuscript and approved the submission.

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