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RESEARCH ARTICLE

PREDICTOR VARIABLES OF NEONATAL MORTALITY IN VERY-LOW-BIRTH-WEIGHT INFANTS

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Abstract

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The aim of this study is to investigate the mortality profile in very-low-birth-weight infants, as well as model the association of some variables with neonatal mortality, in order to detect possible preventable causes of death. This retrospective cross-sectional study included a total of 109 Very-Low-Weight-Infants admitted to a Neonatal Intensive Care Unit in a municipality in Minas Gerais, Brazil, between January 2012 and December 2016. The neonates were divided into two groups: death and non-death. Frequency distributions were constructed for the variables maternal age, sex, birth weight, gestational age, type of delivery, asphyxia (Apgar at five minutes), administration of antenatal corticosteroids, hypothermia, twinning, and amniotic membrane rupture. The survival curve was plotted using the Kaplan-Meier non-parametric estimator, and theassociation between death and the observed explanatory variables was modeled via Logistic Regression. In the survivor group, most infants exhibited normothermia and weight ≥1,000g. As for the death group, weight below 1,000g and hypothermic infants were predominant. In both groups, maternal age between 18 and 35 years prevailed, as well as the male sex, gestational age of 224 days, cesarean delivery, and fifth minute Apgar scores ≥7. The survival rate, estimated using the Kaplan-Meier method, showed a decrease from 1.0 to 0.55 at the beginning of the observation period. The adjusted logistic regression model included fetal weight and the fifth minute Apgar score. No significant relationship was found between death and the variables type of delivery, hypothermia, and antenatal corticosteroid use.Logistic regression indicated a high probability of death associated with birth weight and the Apgar score at five minutes. The low association with the other variables may be related to the good quality of prenatal, intrapartum, and postpartum care provided in the region and the analyzed hospital.

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Introduction:-

A recent report by the World Health Organization (WHO) - Levels & Trends in Child Mortality Report (2019) - evidenced a significant drop in the worldwide infant mortality rate in recent decades. Nevertheless, the age distribution of mortality in children and adolescents continues to reveal that the risk of infant death predominates during the neonatal period (the first 28 days of life). In this sense, current trends anticipate the death of 52 million children under age 5 between 2019 and 2030, half of which will be infants. Also, according to that study, the worldwide neonatal mortality rate reached 37 deaths per 1,000 births in 1990, a rate that was reduced to 18 deaths per thousand births in 2018.Although mortality indicators have increasingly proven to be more reasonable each year, the report considers it imperative that further progress be made in preventing child mortality (You et al.,2019).

In the Brazilian scenario, data published by the United Nations Childen's Fund (UNICEF) indicate that neonatal mortality is also declining. In 1990, the neonatal mortality rate in Brazil was 25.3 for every 1,000 live births, a number that reduced to 8.1 in the year 2018 (UNICEF). Despite this decrease, an even greater reduction in this index can be achieved since neonatal mortality is mainly related to modifiable factors, such as low birth weight, prematurity, neonatal asphyxia, and deficiencies in prenatal care (Veloso et al., 2019). Therefore, the study of risk factors for neonatal death comprises an important tool for understanding, monitoring, and preventing unfavorable outcomes and is useful in action planning(Veloso et al., 2019).

Among these risk conditions, low birth weight and, particularly, very low birth weight constitute predictors of neonatal death and should, therefore, be considered in this context (Veloso et al., 2019; Castro et al., 2007; Gaiva et al, 2014). It is described in the literature that the risk of death among very-low-birth-weight infants, *i.e.*, weighing less than 1,500g (VLBWI), can be up to 30 times higher than those born with 2,500g or more (Veloso et al., 2019). Thus, the VLBWI represent an important subgroup in the assessment of mortality in the first 28 days of life. In this sense, the present study aims to contribute to the analysis of variables that may influence VLBWI mortality.

In this context, a review of the literature on neonatal mortality was conducted, focusing on very-low-birth-weight infants. Exploratory and confirmatory statistical analyses were performed to describe the profile of the VLBWI under study and assess which factors influence the chance of death.

This article is the result of a study that was approved by the Research Ethics Committee of the Federal University of São João del-Rei, MG - Brazil.

Materials And Methods:-

Population

The present retrospective cross-sectional study included VLBWI admitted to the NICU of the *Santa Casa de Misericórdia* in São João del-Rei from January 2012 to December 2016. Infants with complex malformations and congenital heart diseases were excluded from the survey. The final sample consisted of 109 VLBWI.
During admission to the neonatal unit, the following variables were recorded: maternal age (in years), sex (Male -M / Female -F), birth weight (in grams), gestational age (in days), type of delivery (vaginal/surgical), the Apgar score at five minutes (from 0 to 10 or unknown), antenatal corticosteroid use (used, not used, or unknown), hypothermia (yes if axillary temperature < 36.5°C, no, or unknown), twinning (yes or no), and the occurrence of amniotic membrane rupture (yes, no, or unknown).

Statistical Analysis

Exploratory statistical analyses were conducted to describe relevant aspects present in the obtained data. Such analyses refer to frequency distributions for each of the variables considered herein and measures of position and dispersion for quantitative variables.

In order to establish the frequency distribution, the infants were divided into two groups: Group 1 (non-death) and Group 2 (death); the quantitative variables were categorized as follows: maternal age less than 18 years, between 18 and 35 years, and over 35 years; gestational age of 224 days and 224 days or more; weight below 1,000g or greater than or equal to 1,000g; and fifth minute Apgar score less than seven or greater than or equal to seven.

The survival of the infants who progressed to death (Group 2) was calculated using the Kaplan-Meier non-parametric estimator, the most used method in clinical studies (Kaplan et al., 1958; Fontelles, 2012). The survival function is defined as the probability of an individual to not progress to death in a considered time interval (Colosimo et al., 2006; Giolo, 2017).

In view of the need to investigate the influence of the observed variables on the infants' mortality, death was considered a response variable and the others explanatory variables in order to model the association between them through Logistic Regression, a widely used form of statistical analysis in Medicine that does not require assumptions of normality, as does Linear Regression (Fontelles, 2012).

The initial Logistic Regression model was constructed considering the main effects of the ten predictor variables and the second-order interactions of interest, namely: type of delivery, gestational age, and weight with hypothermia and fifth minute Apgar score with type of delivery and weight. Thus, the probability *p(x)* of death is related to the explanatory variables $x_1, ..., x_{15}$, according to the following logistic model:

$$\ln\left[\frac{p(x)}{1-p(x)}\right] = \beta_0 + \sum_{j=1}^{15} \beta_j x_j,$$

where β_0 represents the logarithm of the baseline chance of any individual to progress to death and β_j, j=1, ..., 15, comprise unknown parameters to be estimated that represent the effect of the jth covariate (Colosimo et al., 2006; Giolo, 2017; Kleinbaum, 1994).

In this analysis, among the 109 VLBWI, 81 infants for whom there was information on all the studied variables were considered. The selection of the variables that made up the model was initially carried out using the stepwise process and the information criterion proposed by Akaike (AIC) (Akaike, 1974). Subsequently, the likelihood ratio test (LRT) was performed, which was confirmatory in the selection of the model, establishing the inclusion or not of the variables. The significance of the effect of the variables present in the model selected in the previous step was investigated using the Wald test (Wald, 1943). For decision making, a 5% level of significance was adopted in both assessments.

The adequacy of the selected model was evaluated in stages. The Pearson residuals were considered, adopting limits of ±2.5, as well as deviance residuals (Colosimo, 2006; Giolo, 2017; Davison et al., 1989). Due to the continuous nature of the Weight variable, the statistical test proposed by Hosmer and Lemeshow was also used, under the null hypothesis that the model fitted well with the data (Hosmer et al, 1989; Hosmer et al., 2000).Another utilized diagnostic method was the quantile-quantile graph with a simulated envelope, constructed using the deviance residuals (Davison et al, 1989). The inclusion of the simulated envelope in the graph supports the decision that the points differ significantly from a straight line (Atinkson, 1985). All analyses were carried out using the R statistical software (2019) (R Core Team, 2020).

Considering the predictor variables of neonatal mortality in this study, *i.e.*, variables whose effect was statistically significant, the ratios between *p(x)* and *1 – p(x)* were estimated for the two groups of infants. These ratios define chances and are denominated odds ratios. This is the only associative measure directly estimated using the logistic regression model, regardless of the study design and without assumptions (Kleinbaum, 1994).

Results:-

Tables 1 and 2 result from the exploratory statistical analysis of the obtained data. The distribution of absolute and percentage frequencies for the variables analyzed in the study for each group (G1 – non-death; G2 – death) are shown in Table 1. Meanwhile, Table 2 displays the measures of position (minimum, maximum, mean, and median) and dispersion (standard deviation and coefficient of variation), in addition to the sample size, related to the quantitative variables.

Table 1:- Distribution of frequencies of the variables considered in the present study, regarding groups G1 (non-death) and G2 (death).

Variables		**G1 (non-death)**	**G2 (death)**
		n = 82	**n = 27**
Maternal Age	< 18 years	7 (8.5%)	3 (11.1%)
	Between 18 and 35 years, or 35	50 (60.9%)	18 (66.7%)

	Above 35 years	14 (17.1%)	0 (0%)
	Unknown Maternal Age	11 (13.4%)	6 (22. 2%)
Sex	Male	42 (51.2%)	17 (63%)
	Female	40 (48.8%)	10 (37%)
Birth weight	Less than 1,000g	21 (25.6 %)	18 (66.7 %)
	More than or equal to 1,000g	61 (73.4 %)	9 (33.3 %)
Gestational Age	Less than 224 days	63 (76.8 %)	25 (92.6 %)
	224 days or more	19 (23.2 %)	2 (7.4 %)
Type of delivery	Vaginal	21 (25.6 %)	9 (33.3 %)
	Surgical/Cesarean	61 (74.4%)	18 (66. 7%)
Fifth minute APGAR score	APGAR < 7	6 (7.32 %)	12 (44.4 %)
	APGAR > or = to 7	74 (90.24 %)	14 (51.9 %)
	Unknown	2 (2.44 %)	1 (3.7 %)
Antenatal corticosteroide use	Yes	13 (15.9 %)	2 (7.4 %)
	No	68 (82.9 %)	25 (92.6%)
	Unknown	1 (1.2%)	0 (0%)
Hypothermia (AXT<36.5°C)	Yes	34 (41.46%)	14 (51.9 %)
	No	41 (50.0 %)	11 (40.7 %)
	Unknown	7 (8.54 %)	2 (7.4 %)
Twinning	Yes	16 (19.5 %)	5 (18.5 %)
	No	66 (80.5 %)	22 (81.5 %)
Amniotic membrane rupture	Yes	15 (21.7 %)	6 (22.2 %)
	No	65 (78.3 %)	18 (66.7 %)
	Unknown	2 (2.4%)	3 (1.1 %)

Table 2:- Descriptive measures for the quantitative variables.

Variables	N*	Minimum	Maximum	Mean	Median	Standard Deviation	Coefficient of Variation(%)
Maternal Age (years)	92	13	41	27.13	27	7.051	25.98
Weight (grams)	109	356	1495	1113.4	1190	295.626	26.55
Gestational Age (days)	109	128	259	204.19	203	23.152	11.34
Apgar score	106	0	10	8.085	9	1.977	24.45

*N: sample size.

The estimated curve of the survival function of the individuals who progressed to death, obtained using the Kaplan-Meier estimator, is shown in the graph in Figure 1.

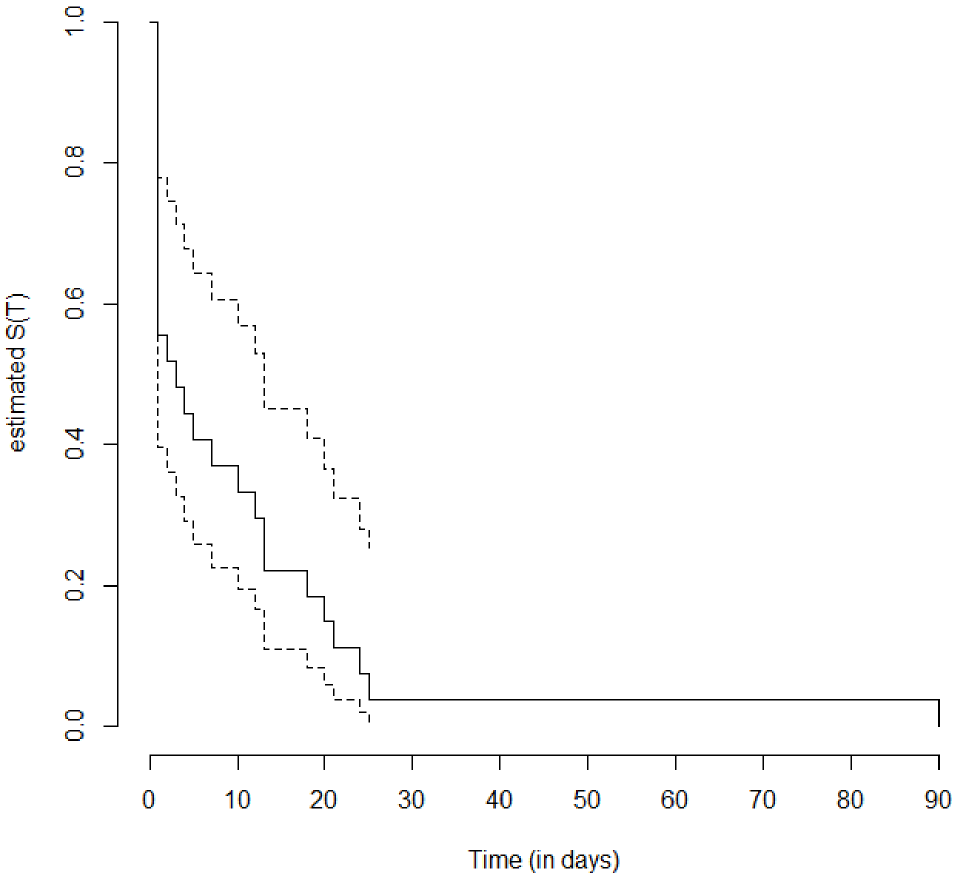

Figure 1:- Curve of the survival function for infants that progressed to death. The continuous line represents the survival estimate and the dashed lines correspond to the 95% confidence limits.

Regarding the modeling through logistic regression, the model selected by the stepwise process and the AIC criterion was composed of the variables: Weight and Apgar score at five minutes. The values obtained for the AIC criterion are shown in Table 3, as well as the results of the likelihood ratio test (LRT) for models containing only one of these variables when compared with the model containing both. Considering the model that includes the variables Weight and the fifth minute Apgar score, the estimates of the selected parameters β_0 (Intercept), β_1 (Weight), and β_2 (Apgar score), their respective probabilities of significance by the Wald test, odds ratio, and their 95% confidence limits are shown in Table 4.

Table 3:- Deviance and Likelihood Ratio Test for the models that include Weight and/or Fifth Minute Apgar Score as death predictor variables.

Model	AIC	Deviance	LRT Statistic	df	p-value
Null	-	85.812	-	-	-
Weight	71.081	67.081	18.732	1	1.51E-05
Apgar score	66.597	56.475	10.605	1	0.001128
Weight+Apgar score	62.475	-	-	-	-

AIC: Akaike information criterion; LRT: likelihood ratio test.

Table 4:- Estimates of the final adjusted Logistic Regression model.

Parameter	Estimate	SE	p-value	OR	LL 95%	UL 95%
□ 0	6.738523	2.094	0.00129	-	-	-
□ 1: Weight	-0.003040	0.001	0.01791	0.99696	0.99446	0.99948

$\square$ 2: Apgar	-0.622723	0.226	0.00589	0.53648	0.34441	0.83566
$\square_0$: logarithm of the baseline chance of a given individual; $\square_1$: effect of weight; $\square_2$: effect of the fifth minute Apgar score. SE: standard error; OR: odds ratio; LL and UL: respective lower and upper limits of the odds ratios.						

The evaluation of the selected model's adequacy involved the graphs of the Pearson and Deviance residuals, the test proposed by Hosmer and Lemeshow, and the quantile-quantile graph with simulated envelope, shown in Figure 2. The Pearson and Deviance residuals were randomly distributed in the interval (-2,5; 2,5). The statistic obtained by the test proposed by Hosmer and Lemeshow was 6.135978, and the probability of significance (p-value), with 8 degrees of freedom (df), was 0.6320034.The distribution of frequencies enabled us to identify that, in the survival group (G1 – non-death), there was a more significant occurrence of normothermic infants (thermal range between 36.5°C and 37.5°C) and weight greater than or equal to 1,000g (Table 1). In the death group (G2), around 67% of the infants weighed less than 1,000g, and 51.9% presented hypothermia. Regarding the other variables, maternal age between 18 and 35 years, male sex, gestational age less than 224 days, surgical delivery (cesarean section), and fifth minute Apgar scores greater than or equal to 7 prevailed in both groups. Also, in G1 and G2, most of the infants did not have a history of antenatal corticosteroid use (85.3%), nor did they have a history of amniotic membrane rupture (76.1%) or twinning (80.7%).

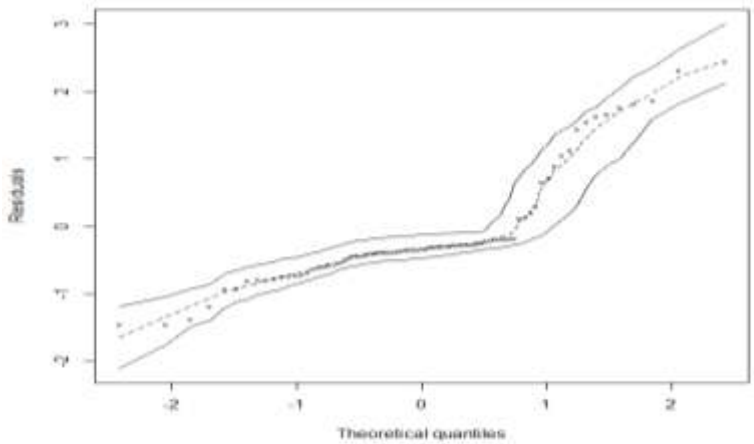

Figure 2:- Q-Q graph of the deviance residuals.

The descriptive measures obtained for the quantitative variables indicate that, on average, the infants had a gestational age below 224 days, with 50% aged up to 203 days (Table 2). The mean fifth minute Apgar score was 8 and 50% of the infants obtained a score greater than or equal to 9. Considering weight, the mean weight of the infants was 1,113g, with 50% weighing less than 1,190g. As for variability, the lowest dispersion in relation to the mean occurred for gestational age (11.34%).

In Figure 1, at the beginning of the observation period, the estimated survival rate dropped from 1.0 to 0.55. This was because only individuals who died in the interval (0, 90) were considered, *i.e.*, there were no survivors in the analyzed group. It can also be noted that the confidence intervals are somewhat wide-ranging, which can be explained by the relatively small sample size (27 infants).

The selection of variables that influence the death of infants, according to the Logistic Regression model, indicated Weight and the Apgar score in the composition of the model. These variables were selected using the stepwise method and the AIC criterion, which presented the lowest value (62.475) for the model containing the two variables (Table 3). The LRT revealed p-values lower than the 5% significance level for models containing only one of the two variables, suggesting that the discriminated model includes both variables.

Considering the significance of each of the parameters in the discriminated model, the Wald test showed p-values below 5% (Table 4).Therefore, it can be stated that death in VLBWI has a high probability of being associated with fetal weight and the fifth minute Apgar score and a low probability of association with the other variables.

The adequacy of the model, which included fetal weight and the fifth minute Apgar score as the variables with a high probability of predicting neonatal mortality in the present study, can be verified by the results obtained for the Pearson and deviance residuals, which indicate an absence of outliers that require further investigation. In addition, Figure 2 shows that the deviance residuals were within the simulated envelope, inferring that the adjusted model is satisfactory. Furthermore, the p-value of 0.632, obtained in the adequacy test using the statistic proposed by Hosmer and Lemeshow (2000), corroborates favorably with the adjusted model (Hosmer et al., 1989; Hosmer et al., 2000).

The Apgar score represents an important parameter in the assessment of extra-uterine vitality conditions in infants and is determined through the analysis of the following characteristics: heart rate, respiratory effort, muscle tone, reflex irritability, and skin color (Oliveira et al., 2012) This score varies from 0 to 10 and, when less than 7, it represents a warning signal indicating the possible need for additional care for the infant (Reis et al., 2014) The Apgar score at five minutes is pointed out in the literature as a useful parameter for predicting neonatal mortality (Veloso et al., 2019; Castro et al., 2007).

Discussion:-

The results obtained in the present study corroborate with the described literature. The negative value of the estimate of the Apgar-associated parameter (Table 4) indicates that increases in the value of this variable reduce the chances of death. Moreover, the odds ratio among infants with a difference of 1 unit in the Apgar scale results in an OR of 0.536 (Table 4). In other words, when evaluating an infant with an Apgar score of 6 and another with an Apgar of 7, both evaluated at five minutes, for example, the infant presenting Apgar 6 has 1.86 (1/0.536) times more chances of death than the infant with Apgar 7.

The occurrence of low weight at birth, in turn, triggers several events (respiratory, hemodynamic, metabolic, or infectious) that may lead to death on account of the infant's deficient compensation mechanisms (Oliveira et al., 2012; Reis et al., 2014; Rodrigues, 2017). This fact was also evidenced by the negative estimate obtained for the Weight-associated parameter, indicating that the increase in fetal weight incurs lesser chances of death for the infant. Furthermore, the odds ratio among infants with a difference of 1.0g in weight was 0.997 (Table 4). This means that, for infants with a difference of 500g in weight, the odds ratio is 0.997^{500}, or 0.223. Therefore, infants weighing 1,000g have 4.48 (1/0.223) times more chances of death than individuals weighing 1,500g, thus evidencing the relevance of low weight in relation to mortality in this group of neonates.

It is important to point out that there is evidence in the literature implicating the variables antenatal corticosteroid use, type of delivery, and hypothermia as factors that have a direct relationship with unfavorable neonatal outcomes (Castro et al., 2012; Nunes et al., 2019; Cardoso et al., 2010; Balbi et al. 2016; Villar et al., 2007; MacDorman et al., 2006; Jahnukainen et al., 1993; Lyu et al, 2015). Some studies show that the absence of antenatal corticosteroid use is a closely related factor to death (Castro et al., 2012). One study, for example, conducted in 2019 in Brazil, evaluated the effects of antenatal corticosteroids in 496 VLBWI and identified a 78% reduction in the incidence of death (Nunes et al., 2019). Regarding cesarean section, this factor has been shown in some studies to be associated with increased neonatal mortality (Castro et al., 2007; Cardoso et al., 2012; Balbi et al., 2016; Villar et al., 2007). As for the variable hypothermia, it should be noted that the regulation of body temperature in infants is not as efficient as in adults, thus rendering them more vulnerable to variations in ambient temperature. Preterm infants, given their constitutional immaturity, are also more susceptible to such variations (Jahnukainen et al., 1993).The relationship between admission temperature and adverse neonatal outcomes, such as intraventricular hemorrhage and fetal death, is represented by a U-shaped curve, *i.e.*, both hypothermia and hyperthermia may be related to unfavorable neonatal outcomes (Jahnukainen et al., 1993; Lyu et al., 2015).

In the study sample, there were no statistically significant influences of antenatal corticosteroid use, the type of delivery, or hypothermia on death. However, cesarean section was indicated in around 73% of the cases, and corticosteroids were not used in approximately 85% (Table 1). It is believed that this fact reflects the adequate care in the region and the hospital where the study took place and may be a consequence of the good quality of care, both in prenatal care and intra- and postpartum.

Regarding the other analyzed variables (maternal age, sex of the infant, twinning, and amniotic membrane rupture), no significant influences on death were observed. Since these are non-modifiable factors, they were not widely discussed in this study.

Conclusions:-

The adjusted logistic regression model identified that Weight and the Apgar score at five minutes were the variables that presented a high probability of being associated with neonatal mortality. Considering the variables type of delivery, corticosteroid use, and hypothermia, the absence of such an association is very positive since it reflects the quality of prenatal, intrapartum, and postpartum care at the hospital, contrasting with the reported evidence in the literature, which correlate the relationship of these variables with unfavorable neonatal outcomes. These findings substantiate the fact that the chances of death can be reduced by acting on modifiable factors, especially regarding more vulnerable infants, such as VLBWI. Thus, the analysis of these determinants is of paramount relevance for the planning of actions that aim to improve the quality of care in prenatal, intrapartum, and postpartum practice, helping health professionals and managers identify possible modifiable factors in the reduction of neonatal mortality (Veloso et al., 2019; Castro et al., 2007).

Conflict Of Interests
The authors declare no conflict of interests concerning the present study.

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