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Higher maternal age is associated with higher occurrence of cleft lip/palate in neonates under intensive care

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Aim: To assess the prevalence of cleft lip and/or cleft palate (CL/P) and associated variables in neonates admitted to neonatal intensive care units (ICU). **Methods:** Medical charts for neonates born and admitted to the ICU between 2012 and 2018 were reviewed. Obstetric and neonatal variables were collected by a trained researcher. In the case group, all neonates with CL/P were included. The control group was formed by matching sex, prematurity and month of birth using random number generation. Neonates with congenital malformations were excluded from the control group. Adjusted logistic regression was used ($p<0.05$). **Results:** The prevalence of CL/P was 0.43% (n=15). Five cases were excluded, as pairing was not possible. Twenty neonates were included in the control group. In the final multivariate model, CL/P was only associated with increased maternal age. For each year of increase in maternal age, neonates had a 35.2% higher chance of presenting CL/P (95% confidence interval: 1.021–1.792). **Conclusions:** Higher maternal age was associated with higher occurrence of CL/P in neonates admitted to the ICU. No other neonatal or maternal independent variables were associated with CL/P. Due to missing data, interpretation of study results must be approached with caution.

Keywords: Cleft palate. Congenital abnormalities. Infant, newborn. Intensive care, neonatal.

Introduction

Congenital malformation is defined as a change in the structure, metabolism or function present at birth which causes a physical–motor or mental limitation and, in severe cases, death[1,2]. Many studies have reported that the overall prevalence of congenital malformation is 2.3% to 3.8%[3,4]. Moreover, between 5% and 38% of neonatal deaths are related to malformations[5].

Cleft lip (CL) is a congenital malformation that occurs due to non-fusion of the medial nasal prominence with the maxillary prominence and palate[6]. In contrast, cleft palate (CP) is a problem with the fusion of the primary and secondary palates that occurs during different weeks of pregnancy[6]. Only 30% of patients with CP also present with other malformations or syndromes[7]. Furthermore, literature demonstrated that the occurrence of CL is higher in comparison to CP[8], and that a higher occurrence has been observed in male than in female individuals[9]. The same study demonstrated that the prevalence of CL with or without CP was 14.8 per 10,000 births, while the prevalence of CL with CP was 6.9 per 10,000 births[9].

Neonates with cleft lip/palate (CL/P) may require multidisciplinary treatment starting at birth[8]. Many such patients are also transferred to intensive care units (ICU), as specialized feeding and respiratory support may be necessary[10]. A higher mortality rate is expected for neonates admitted to ICUs when compared to neonates not admitted to ICUs[11]. It has been suggested that the occurrence of CL/P is multifactorial, triggered by environmental, genetic and multifactorial causes[12], with more than 400 associated genes with mendelian and non-mendelian inheritance[13]. When considering all factors, several variables may be associated with CL/P, including maternal smoking and use of alcohol during pregnancy[14].

Furthermore, other malformations in different systems may be associated with CL/P, such as nervous, circulatory, respiratory, genitourinary system and poly-malformative chromosomal abnormalities (trisomy 13 and 18)[15]. However, it is important to highlight that most of the available data in this area originate with studies that involved CL/P neonates without intensive care needs. It remains necessary to determine what variables are associated with CL/P neonates admitted to ICUs. Therefore, the present study aimed to assess the prevalence of CL/P and its associated variables in neonates admitted to ICUs when compared to neonates without any malformations.

Material and Methods

Study Design and Ethical Aspects

This is a case-control study, nested to a retrospective cohort of live neonates admitted to a neonatal ICU. This study was approved by the local Ethics Committee (under protocol #2.876.678). Hospital administration approved the study.

Sample, Inclusion and Exclusion Criteria

Medical charts were reviewed for all neonates born and admitted to the neonatal ICU of Hospital Universitário de Canoas, Canoas, Rio Grande do Sul, Brazil, between

2012 and 2018. Canoas is located in the metropolitan region of Porto Alegre, the state capital. The Hospital Universitário de Canoas is a tertiary referral center to many surrounding cities for high-risk pregnancies and neonatal intensive care. The hospital primarily serves users of Brazil's public health system.

Both the case and control groups were composed of neonates admitted to the hospital's ICU. In the case group, only neonates with CL/P were included. As all neonates with CL/P born between 2012 and 2018 were included in the present study, no sample size calculation was performed. Ten neonates were included in the case group. Detailed information is provided in the Results section.

The control group was composed of neonates randomly chosen through use of a number generator. In order to be included in the control group, all neonates had to present no congenital malformations. All neonates selected were aged 0 to 28 days. Neonates who were not born in the Hospital Universitário de Canoas were excluded.

Sampling Strategy in the Control Group

For each neonate initially detected with CL/P, two control neonates without any malformations were included. Therefore, 20 control neonates were included. The control group was randomly chosen and paired by month of birth (±1 month), sex and presence (<37 weeks) or not (≥37 weeks) of prematurity.

A numbered list of all neonates admitted to the ICU between 2012 and 2018 was obtained. Overall, 3,463 newborns were admitted during this period. With the support of a website (www.randomizer.org), random numbers were selected between 1 and 3,463. A researcher otherwise uninvolved in data collection (FWMGM) performed this process. Random numbers were selected until a sufficient number of control neonates were included.

Data Collection and Variables

During the first phase of the present study, all medical charts were reviewed in order to detect all neonates with CL/P. These charts were reviewed by four medical students previously trained to detect information related to any malformation. Students identified malformations using a Latin American Collaborative Study of Congenital Malformations (ECLAMC) form[16]. Based on this information, a previously trained researcher (LSM) collected all data from both the case and control groups. Training consisted of lectures on how to manage the charts and how to locate the data in the system. Lectures were given by a more experienced researcher, who was involved only in data collection for the prevalence of malformations.

A Microsoft Excel spreadsheet was specifically developed in order to collect this data. The following variables were extracted from patient charts: sex (male or female), month and year of birth, gestational age (in weeks + days), delivery method (vaginal or caesarean), toxoplasmosis serologies (IgG and IgM+ status), maternal age (in years), number of previous pregnancies, number of previous vaginal deliveries, number of previous caesarean deliveries, Apgar (5'), length (in cm), cephalic

perimeter (in cm), thoracic perimeter (in cm), weight at birth (in Kg), length of stay in ICU (in days), weight at discharge (in Kg), death before discharge (yes or no) and syndromic diagnosis before discharge (yes or no).

Serologies for HIV, syphilis, hepatitis B and hepatitis C were collected. In addition, exposures to smoking, alcohol and illicit drugs were extracted from the charts. However, as few charts presented information for these variables, it was ultimately impossible to consider them in the statistical analysis.

Statistical Analysis

The main outcome of the present study was the presence of CL/P. Categorical variables were expressed as observed and percent; continuous variables were expressed as mean and standard deviation. Toxoplasma serologies were categorized into immune (IgG+ and IgM-), susceptible (IgG- and IgM-) or active infection (IgG- and IgM+, or IgG+ and IgM+). Both cephalic perimeter and weight at birth were converted into percentiles. Cephalic perimeter percentiles for all neonates, as well as weight at birth percentiles for premature neonates, were obtained using the INTERGROWTH-21st Newborn Size Application Tool, adjusted to the gestational age. Weight at birth percentiles for term newborns were obtained through the World Health Organization (WHO) AnthroPlus software[17].

The study groups were compared using Chi-square and Mann-Whitney tests for categorical and continuous variables, respectively. Moreover, bi- and multivariate analyses were performed using binary logistic regression. The initial multivariate model was formed with all independent variables that presented $p<0.25$ in the bivariate analysis. However, weight at birth was included in the final multivariate model regardless of the p-value detected in the univariate analysis, as the literature shows a strong association between weight at birth and occurrence of CL/P[18]. A backward strategy was used for the final multivariate model. The maintenance of independent variables was determined using a combination of statistical significance and changing effect model. A p-value of <0.05 was established for statistical significance. All analyses were performed using the software SPSS, version 21.0 (IBM Corp., Armonk, NY, USA).

Results

Between 2012 and 2018, the prevalence of CL/P was 0.43% (n=15), meaning that for every 10,000 neonates admitted to the ICU, 43.32 of them presented with CL/P. Among these, CL alone was detected in one neonate (6.67%) while CL + CP was detected in 3 of them (20%). More than one associated malformation was observed in 11 neonates (73.33%), of which six, four and one, respectively, presented with CL + CP, CP and CL. However, due to missing data (e.g., information on sex and gestational age), three of these neonates were excluded, as pairing was not possible. In two cases, ambiguous data were extracted from charts regarding sex. Figure 1 presents a flowchart of patient inclusion in the present study.

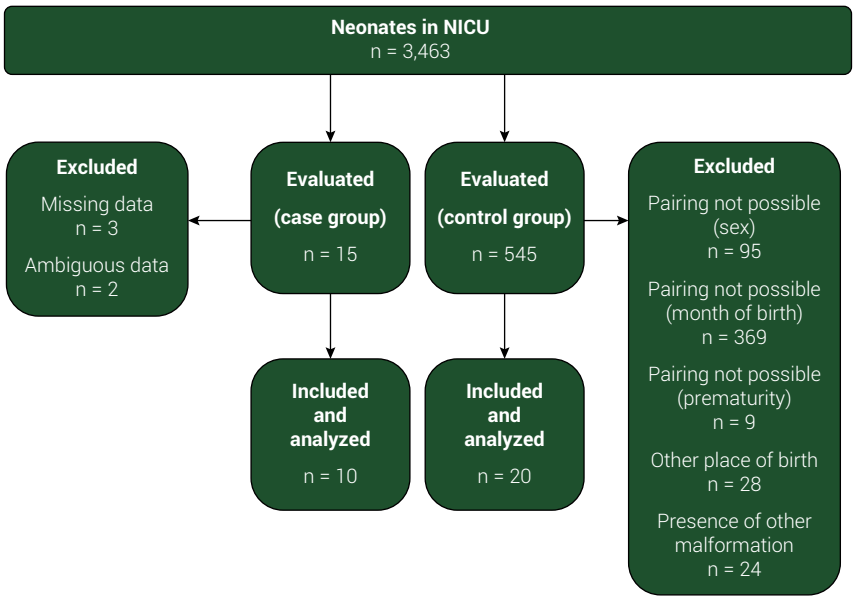

Figure. Flowchart of the participants in the study.

Neonates in the control group were admitted to the ICU due to respiratory distress (n=9; 45%), exposure to perinatal vertical infections (n=6; 30%), weight problems (n=5; 25%), hypoglycemia (n=5; 25%), prematurity (n=7; 35%) or other reasons (n=9; 45%). All patients in the case group were admitted due to malformation (n=10; 100%); however, it was unclear whether CL/P was the main cause of admission. Thus, other causes of admission were detected in the case group as well, including weight problems (n=1; 10%), hypoglycemia (n=1; 10%) and prematurity (n=2; 20%). For both groups, more than one cause of admission was detected. All included neonates were admitted on the day of delivery.

Among the included patients, three (30%) had isolated CL + CP, one (10%) had CL associated with other malformations, two (20%) had CP and other malformations and four (40%) had CL + CP and other malformations. No patient had isolated CL or CP. Other malformations were also observed in the case group, including gastrointestinal malformations (n=1), cardiovascular malformations (n=2), urogenital malformations (n=3), upper limb malformations (n=5) and other craniofacial malformations (n=6). Overall, up to the date of discharge, no patient died in either group. Furthermore, no patient was given a syndromic conclusive diagnosis before neonatal discharge or underwent surgical procedures to correct CL/P while in the ICU.

Ultimately, seven male neonates and three female neonates were included in the case group. When considering patient weight according to gestational age, seven neonates were adequate for gestational age (AGA) in the case group, while 11 were AGA in the control group. Conversely, five and two neonates small for gestational age (SGA) were detected in the control and case groups, respectively. Four and one neonates large for gestational age were included in the control and case groups, respectively. The majority of the included neonates presented a cephalic perimeter within the normal range (80% in the case group and 85% in the control group).

The frequency of distribution for independent variables between cases and controls is expressed in Table 1. When considering the whole sample, five women gave birth with advanced maternal age (≥35 years of age), two of whom were from the case group. The minimum maternal ages were 14 years for the control group and 17 years for the case group. Meanwhile, the maximum maternal ages were 39 years for the control group and 42 years for the case group. No statistically significant difference between cases and controls was observed for any obstetric variables. However, length of stay in ICU was significantly higher among cases (25.89 days±19.82) when compared to controls (10.00±7.13) (p=0.011).

Table 1. Frequency distribution of independent variables among cases and controls, Canoas, 2012–2018.

Variables	Cases (n=10)	Controls (n=20)	P-value
Sex			
Male – n (%)	7 (70.0)	14 (70.0)	-
Female – n (%)	3 (30.0)	6 (30.0)	
Delivery method			
Normal birth – n (%)	3 (30.0)	9 (45.0)	0.694#
Caesarean – n (%)	7 (70.0)	11 (55.0)	
Toxoplasmosis serologic status			
Immune – n (%)	2 (25.0)	12 (70.6)	0.081#
Susceptible – n (%)	6 (75.0)	5 (29.4)	
Absent (n)	2	3	
Maternal age (years)			
Mean±SD	29.40±8.67	25.65±5.82	0.248β
Absent (n)	0	0	
Number of pregnancies			
Mean±SD	2.6±2.12	2.55±1.46	0.713β
Absent (n)	0	0	
Number of vaginal deliveries			
Mean±SD	1.40±1.90	1.05±1.39	0.681β
Absent (n)	0	0	
Number of caesarean deliveries			
Mean±SD	1.20±1.48	1.25±1.41	0.983β
Absent (n)	0	0	
APGAR (5')			
Mean±SD	8.70±0.67	8.55±1.36	0.681β
Absent (n)	0	0	
Length (cm)			
Mean±SD	47.07±3.48	46.95±3.47	0.962β
Absent (n)	1	1	

Continue

Continuation			
Cephalic perimeter (percentile)			
Mean±SD	68.60±39.72	54.37±26.13	0.135β
Absent (n)	3	1	
Thoracic perimeter (cm)			
Mean±SD	31.38±3.11	31.97±3.64	0.605β
Absent (n)	2	2	
Weight at birth (percentile)			
Mean±SD	44.68±35.19	50.37±33.49	0.764β
Absent (n)	1	0	
Length of stay in ICU (days)			
Mean±SD	25.89±19.82	10.00±7.13	0.011β
Absent (n)	1	0	
Weight at discharge (Kg)			
Mean±SD	3.04±0.56	3.01±0.86	0.847β
Absent (n)	1	1	

Legend: #Fisher's exact test; *Chi-square test; β Mann-Whitney test.

The univariate analysis for the comparison between CL/P and both obstetric and neonatal variables is shown in Table 2. Women susceptible to toxoplasmosis presented a 7.2 times higher chance of having a child with oral facial cleft (OFC) (95% confidence interval [95%CI]: 1.066–48.639) in comparison to immune women. Regarding the neonatal length of stay in ICU, a significantly higher age was demonstrated in the case group (odds ratio [OR]: 1.109; 95%CI: 1.013–1.214). No other variable was significantly associated with CL/P. Both variables were included in the initial multivariate model, along with maternal age and weight percentile at birth.

Table 2. Univariate analysis for the association between independent variables and cleft lip and/or palate.

Variables	OR (95% CI)	P-value
Delivery method		
Normal birth	1	0.432
Caesarean	1.909 (0.380–9.590)	
Toxoplasmosis serologic status		
Immune	1	0.043
Susceptible	7.200 (1.066–48.639)	
Maternal age (years)	1.084 (0.966–1.218)	0.171
Number of pregnancies	1.019 (0.644–1.612)	0.938
Number of vaginal deliveries	1.155 (0.713–1.871)	0.559
Number of caesarean deliveries	0.974 (0.560–1.694)	0.926

Continue

Continuation		
APGAR (5')	1.138 (0.532–2.435)	0.739
Length (cm)	1.011 (0.797–1.282)	0.930
Cephalic perimeter (percentile)	1.018 (0.985–1.052)	0.288
Thoracic perimeter (cm)	0.949 (0.741–1.215)	0.677
Weight at birth (percentile)	0.995 (0.971–1.019)	0.668
Length of stay in ICU (days)	1.109 (1.013–1.214)	0.026
Weight at discharge (Kg)	1.000 (0.999–1.001)	0.929

The final multivariate model for the association between outcome and independent variables is presented in Table 3. Analysis demonstrated that neither toxoplasmosis serologies nor percentile of weight at birth were significantly associated with CL/P ($p>0.05$). However, for each year of increase in maternal age, neonates had a 35.2% higher chance of presenting CL/P (95% CI: 1.021–1.792).

Table 3. Multivariate analysis for the association between independent variables and cleft lip and/or palate.

Variables	OR (95% CI)	P-Value
Toxoplasmosis serologic status		
Immune	1	0.093
Susceptible	11.264 (0.670–189.493)	
Maternal age (years)	1.352 (1.021–1.792)	0.036
Weight at birth (percentile)	1.058 (0.999–1.120)	0.051

Discussion

The present study evaluated the prevalence of CL/P and compared maternal and neonatal variables between neonates with malformations and those without. Analytical results demonstrated that higher maternal age is significantly associated with higher chances of CL/P. Conversely, other collected variables, such as serologies for toxoplasmosis and weight at birth, were not significantly associated with CL/P.

Approximately 7 to 15 in every 10,000 live births present with CL/P, representing one of the most common craniofacial malformations in the world[19]. A population-based study conducted in Foz do Iguaçu, Brazil demonstrated that the prevalence of CL/P was 9.5 in 10,000 live births[20]. A higher rate was observed in the present study (43.32 in 10,000 ICU admissions), likely because the sample was composed of neonates requiring intensive care. In addition, the Hospital Universitário de Canoas is a referral center for many high-risk pregnancies, including those involving congenital malformations. Moreover, this hospital has a highly demanding neonatal intensive care facility, which partially explains the high rate observed in this study.

It was determined that 73.34% of the case group had CL/P and another malformation. Two prior studies have identified that 39%[15] to 41%[20] of neonates with CL/P will present with at least one additional malformation[20]. However, different prevalence rates for multiple associated malformations in neonates with CL/P have been described in the literature, ranging from 25%[19] to 29.9%[21]. A systematic review concluded that cardiac malformation was eight times more frequent in apparently non-syndromic patients with CL/P when compared to the general population[22], demonstrating a strong association between CL/P and other malformations.

Although studies involving neonates admitted to ICUs are scarce in the literature, they are critical to current research, since a high mortality rate is detected in this group of individuals. One such study showed that the overall mortality rate was 20% (95%CI: 16.7–23.8%), of which 4.08% was related to congenital malformation, making congenital malformation the fifth leading cause of mortality[23]. As isolated CL was detected in only one patient and isolated CP was not detected, it can be hypothesized that this isolated malformation does not justify admission to a neonatal ICU. Higher mortality rates are also expected in neonates with CL/P when compared to neonates without this malformation (5.08 vs. 0.33 deaths in every 1,000 births per year, $p<0.001$)[24]. Despite these previous findings, no neonate in the present study with CL/P died before ICU discharge.

Regarding maternal age, only two mothers in the control group presented an advanced maternal age (age ≥35 years). The present study demonstrated that, for each year of increase in maternal age, there is a 35.2% increase in the OR of having a child with CL/P. In a population-based, cross-sectional study which used data from all live births between 2012 and 2017, CL/P was found to be the most common malformation at 9.5 per 10,000 live births (lip, n=3; palate, n=15; lip and palate, n=1)[20]. Among these patients, mean maternal age was 26.4±6.8, results which closely mirror those of the present study.

In addition to maternal age, the literature reports that the age of both parents is important when considering the occurrence of CL/P. For example, one study demonstrated that when one of the parents is young (up to 30 years), there is no significant association with isolated CP, regardless of the age of the other parent[25]. However, if an advanced age was observed in at least one of the parents (mother aged >40 years and/or father aged >50 years), there is a higher risk of CL. Furthermore, a significantly higher risk for CL (1.24 per 1,000) was detected in infants of mothers aged >40 years, even those with fathers aged <37 years. In this sense, it may be speculated that maternal age is crucial to the occurrence of CL/P, but that paternal age may not be disregarded. However, in this study, paternal age could not be extracted from the available charts, representing one of the limitations of the present study.

Furthermore, the literature reports that weight at birth is associated with CL/P[18]. For instance, one study showed that low birth weight children (<2,500g) presented a 2.5 higher chance of presenting CL/P when compared to those with normal weight at birth (≥2,500g)[18]. In consideration of this information, the percentile of weight at birth was included in the final multivariate model of the present study. However, no statistically significant association was detected between weight at birth and CL/P in neonates admitted to the ICU. Thus, it may be hypothesized that other vari-

ables are responsible for the similar lower weight at birth identified in the control group, including congenital infections, maternal use of alcohol or tobacco during pregnancy, placental insufficiency, previous maternal diseases and maternal nutrition. These health conditions are potential causes for admission to the ICU in neonates without congenital anomalies.

Prior literature has also demonstrated that exposure to maternal smoking, abuse of alcohol and use of other illicit drugs is associated with CL/P[13]. However, this information could not be retrospectively extracted from the available charts in the present study. Medical records were often found to be incomplete, possibly due to inadequate standardization of criteria. Thus, several data categories remain unexplored, and this is another limitation of the present study. Moreover, five neonates with CL/P had to be excluded from the analysis, as minimal data for pairing, such as missing sex or gestational age and ambiguous data, were available. In addition, many maternal infections may be associated with congenital malformations, including rubella, cytomegalovirus, syphilis and toxoplasmosis[26,27]. In the present study, only serologies for toxoplasmosis were analyzed due to missing data. Conversely, no statistically significant association with CL/P was observed.

The present study used international growth standard data, using percentiles of birth weight and cephalic perimeter according to sex (in all cases) and gestational age (in pre-term newborns). This approach was used in order to provide more accurate and adjusted data[28]. Neonatal anthropometry, when compared to growth patterns, can be a tool for predicting early and long-term postnatal complications, dysmorphology assessment and body surface estimation[29].

Public data from the Sistema Nacional de Nascidos Vivos (SINASC), a national system of population surveillance for live births, allowed for the recognition of CL/P at birth in Brazil between 2012 and 2018. The state of Rio Grande do Sul, where the present study was conducted, presented the highest incidence of orofacial clefts (0.072%) in Brazil. The national mean was 0.053%. However, the city of Canoas demonstrated a smaller incidence of CL/P (0.051%) during the same period as the present study (2012–2018)[30]. When considering all neonates admitted to the ICU, the prevalence of orofacial cleft in the present study was 0.43% (n=15), which is higher than all other comparisons. It is important to highlight that these data are restricted to neonates admitted to the ICU, and may not apply to all patients born in the referred hospital.

Some limitations of the present study must be disclosed. First, the sample was restricted to neonates admitted to the local ICU. Therefore, a lower external validity may be expected for neonates with CL/P but without intensive care needs. Second, several different health care professionals filled in the collected medical reports, and the hospital does not use a standardized reporting method. Thus, missing data were often detected, restricting data collection and analysis. Third, no sample size calculation was performed, as all neonates with CL/P and admitted to the ICU were included in the present study.

However, several strengths must also be pointed out. Only one trained researcher extracted all data for both the case and control groups. Two control neonates were

included for each neonate with CL/P, which increases the power of the present study. Moreover, three important variables were used to pair individuals from the case and control groups: sex, prematurity and month of birth. Additionally, both groups were composed of individuals from the same ICU, which increases the comparability between individuals, allowing for a higher internal validity. This is a case-control study nested to a retrospective cohort among a population admitted to an ICU. These characteristics are strengths of the present study.

Based on the present study, higher maternal age may be associated with higher incidence of CL/P. This information should be discussed with couples when planning for pregnancy. Further studies should rely on adjusted data using reliable medical records. These records should also be completed in a standardized manner to prevent missing data.

Ultimately, this study concluded that higher maternal age was associated with higher occurrence of CL/P in neonates admitted to the ICU. No other neonatal or maternal independent variables were associated with CL/P. Neonates with CL/P presented a significantly higher length of ICU stay; however, no etiological diagnosis was provided for this group during the stay in ICU. In addition, the lack of complete information in the studied medical records may impair the current results.

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Nathalia Preissler Vaz Silveira: Data collection manuscript editing

Melissa Camassola: Protocol development, data analysis, manuscript writing.

Bibiana Mello de Oliveira: Data analysis, manuscript writing.

All authors actively participated in the discussion of the manuscript's findings, revised, and approved the final version of the manuscript.

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