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RESEARCH

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FACTORS ASSOCIATED TO THE GESTATIONAL AGE OF PREMATUROS INHIBITED IN A NEONATAL INTENSIVE THERAPY UNIT

Fatores associados à idade gestacional de prematuros internados em unidade de terapia intensiva neonatal

Factores asociados a la edad gestacional de prematuros internados en unidad de terapia intensiva neonatal

Fabiane Coppetti Adams[1], Joseila Sonego Gomes[2], Márcio Júnior Strassburger[3], Pâmela Fantinel Ferreira[4], Christiane de Fátima Colet[5], Simone Zeni Strassburger[6]

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ABSTRACT

Objective: To describe factors associated with the gestational age of premature infants admitted to the Intensive Care Unit. **Methods:** A cross-sectional study with preterm infants referred to the discharge of the Unit. **Results:** 66 preterm infants, 59% boys, mean 32 gestational weeks, 26% preterm infants, 51% with adequate gestational age at birth participated. 38% of pregnant women presented pre-eclampsia, 18% had gestational diabetes. There was association of preterm groups with birth weight (p = 0.000), length of hospital stay (p = 0.000), time of invasive mechanical ventilation (p = 0.000), total oxygen time (p = 0.000), transfusion requirement (0.019) and use of surfactant (0.003). Among late and moderate preterm infants, there was a significant increase in the frequency of small infants for gestational age at discharge (p = 0.046 and p = 0.021). **Conclusion:** Pre-eclampsia was the most prevalent complication among pregnant women. Gestational diabetes was more frequent at delivery before 34 weeks. Restriction of extrauterine growth was observed at the time of discontinuation of the unit.

Descriptors: Prematurity; Gestational age; Neonatal intensive care unit.

1 *Universidade Regional do Noroeste do Estado do Rio Grande do Sul (UNIJUI), Brazil.* Physiotherapy Graduate, Postgraduate in Critical Care Physiotherapy by the *UNIJUI*, Physiotherapist at *Unimed Noroeste* Hospital.

2 *Universidade Regional do Noroeste do Estado do Rio Grande do Sul (UNIJUI), Brazil.* Nursing Graduate by the UNIJUI, MSc by the *Universidade de São Paulo (USP)*, Professor of the Life Sciences Department at *UNIJUI*.

3 *Universidade Regional do Noroeste do Estado do Rio Grande do Sul (UNIJUI), Brazil.* Physiotherapy Graduate by the *Universidade de Cruz Alta (UNICRUZ)*, PhD by the Pontifícia *Universidade Católica do Rio Grande do Sul (PUCRS)*, Professor of the Life Sciences Department at UNIJUI.

4 *Universidade Federal de Santa Maria (UFSM), Brazil.* Nutrition Graduate, PhD by the *UFSM*.

5 *Universidade Regional do Noroeste do Estado do Rio Grande do Sul (UNIJUI), Brazil.* Pharmacy Graduate by the *UNIJUI*, PhD in Pharmaceutical Sciences by the *Universidade Federal do Rio Grande do Sul (UFRGS)*, Professor of the Life Sciences Department at *UNIJUI*.

6 *Universidade Regional do Noroeste do Estado do Rio Grande do Sul (UNIJUI), Brazil.* Physiotherapy Graduate by the *UNICRUZ*, PhD by the *PUCRS*, Professor of the Life Sciences Department at *UNIJUI*.

RESUMO

Objetivo: Descrever fatores associados à idade gestacional de prematuros internados em Unidade de Terapia Intensiva. **Métodos:** Estudo transversal com recém-nascidos prematuros encaminhados à alta da Unidade. **Resultados:** Participaram 66 prematuros, 59% meninos, média de 32 semanas gestacionais, 26% prematuros moderados, 51% com peso adequado para idade gestacional ao nascimento. 38% das gestantes apresentaram pré-eclâmpsia, 18% diabetes gestacional. Houve associação dos grupos de prematuros com: peso ao nascimento (p=0,000), tempo de internação (p=0,000), tempo de ventilação mecânica invasiva (p=0,000), tempo total de oxigênio (p=0,000), necessidade de transfusão (0,019) e uso de surfactante (0,003). Entre os prematuros tardios e moderados, houve aumento significativo na frequência de recém-nascidos pequenos para idade gestacional no momento da alta (p=0,046 e p=0,021). **Conclusão:** Pré-eclâmpsia foi a complicação mais prevalente entre as gestantes. Diabetes gestacional foi mais frequente no parto antes das 34 semanas. Observou-se restrição do crescimento extrauterino no momento da alta da unidade.

Descritores: Prematuridade; Idade gestacional; Unidade de terapia intensiva neonatal.

RESUMEN

Objetivo: Describir factores asociados a la edad gestacional de prematuros internados en Unidad de Terapia Intensiva. **Métodos:** Estudio transversal con recién nacidos prematuros encaminados al alza de la Unidad. **Resultados:** Participaron 66 prematuros, 59% niños, media de 32 semanas gestacionales, 26% prematuros moderados, 51% con peso adecuado para edad gestacional al nacimiento. El 38% de las gestantes presentaron preeclampsia, 18% de la diabetes gestacional. Se observó una asociación de los grupos de prematuros con: peso al nacer (p = 0,000), tiempo de internación (p = 0,000), tiempo de ventilación mecánica invasiva (p = 0,000), tiempo total de oxígeno (p = 0,000), necesidad de transfusión (0,019) y el uso de surfactante (0,003). Entre los prematuros tardíos y moderados, hubo un aumento significativo en la frecuencia de recién nacidos pequeños para edad gestacional en el momento de la alta (p = 0,046 y p = 0,021). **Conclusión:** La pre-eclampsia fue la complicación más prevalente entre las gestantes. La diabetes gestacional fue más frecuente en el parto antes de las 34 semanas. Se observó restricción del crecimiento extrauterino en el momento del alza de la unidad.

Descriptores: Prematuridad; Edad gestacional; Unidad de terapia intensiva neonatal.

INTRODUÇÃO

Prematurity is the main cause of neonatal mortality and is considered a complex syndrome, with multiple etiological factors associated with a wide spectrum of clinical conditions that define survival and the pattern of growth and development of this population.[1]

The rate of prematurity in Brazil is 11.5%, which is higher in the South and Southeast. The Brazilian States showing the highest percentages are as follows: *Distrito Federal*, *Minas Gerais*, *São Paulo*, *Rio Grande do Sul* and *Rio de Janeiro*. Unlike the world scenario, the most developed Brazilian regions have a higher prevalence of premature births, occupying the tenth position in the world and presenting values twice as high as the rates of European countries.[2]

Prematurity increases the risk of developing complications in the neonatal period, related to greater comorbidities and worse quality of life.[2] Changes in neurodevelopment and chronic events in adult life such as hypertension, diabetes, dyslipidemia, and obesity are among the main morbidities.[3]

Studies addressing the clinical characteristics of premature newborns assisted at a Neonatal Intensive Care Unit (NICU) contribute to identifying the factors associated with hospitalization and the complications rates over this period.[4] Such studies are still incipient vis-à-vis the specific characteristics of premature newborns according to the gestational age (GA). Hence, this study meant to describe factors associated with the gestational age of premature newborns hospitalized in a NICU.

METHODS

It is a cross-sectional study that was performed with premature newborns, both genders, forwarded to discharge from the NICU of a level IV hospital located in the Northwest region of the *Rio Grande do Sul* State, Brazil, over the period from July 2016 to October 2017.

This research is part of a university research project named: Monitoring of Neuropsychomotor Growth and Development in Premature Newborns, with approval by the Research Ethics Committee under the Legal Opinion No. 1.379.984/2015. The premature neonates whose parents agreed to participate in the follow-up project after hospital discharge in the aforementioned period participated in this analysis. There were excluded premature newborns with length of hospital stay less than 24 hours or that died.

Data collection took place through a form designed for this research and validated by a pilot study. The variables assessed concerning premature newborns were as follows: GA, Apgar score for the 1st and 5th minutes, gender, birth weight and discharge from the NICU, classification of birth weight, length of hospital stay in the NICU, need for invasive mechanical ventilation (IMV) or non-invasive ventilation (NIV), oxygen therapy, transfusion requirement, use of surfactant and occurrence of neonatal sepsis. The variables related to maternal, prenatal and delivery conditions were as follows: type of delivery (vaginal or cesarean), number of prenatal consultations, number of pregnancies, maternal age, maternal conditions during pregnancy. Data were collected from medical records by previously trained collectors.

The research participants were classified according to the GA according to the established by the Brazilian Society of Pediatrics, as: Extremely Preterm: less than 28 weeks and 0 days; Very Preterm: 28 weeks and 0 days to 31 weeks and six days; Moderate Preterm: 32 weeks and 0 days to 33 weeks and 6 days or Late Preterm: between 34 weeks and 0 days and 36 weeks and six days.[1] For analysis purposes, the data of extremely preterm and very preterm was added.

Continuous variables were expressed as averages and standard deviations, or medians and interquartile ranges, according to their symmetry. Categorical variables expressed in absolute and relative frequency. The normality of the data was tested using the Kolmogorov-Smirnov Test. To verify the association between qualitative variables, the Pearson's Chi-Square Test was used. For the quantitative variables, the Analysis of Variance (ANOVA) was used for parametric

and independent samples, and the Student *t*-Test for two independent groups only. The software used for data analysis was the Statistical Package for the Social Sciences (SPSS), version 21.0., and considered statistically significant when $p < 0.05$.

RESULTS

A total of 66 premature newborns were considered in this study. Most of them were male, the average GA was 32.4 ± 2.8 weeks and 26 (40%) were classified as moderate preterm newborns, according to data presented in **Table 1**. The average birth weight was 1,679 ± 480.3 g and 51 newborns were classified as appropriate for gestational age (AGA). The other characteristics of hospitalized premature newborns are shown in **Table 1**.

The average maternal age was 26.4 ± 6.5 years old, and the average number of pregnancies was 1.7 ± 1.1, such variables were stratified according to GA according to the Brazilian Society of Pediatrics and were not found an association between them and the GA. Considering the types of delivery, 67% were cesarean sections, being more frequent in all GA, without association (p=0.567). In regard to the gestational comorbidities developed by the women studied, preeclampsia was more frequent in all GA (p=0.465), and gestational diabetes (p=0.051). Other results vis-à-vis maternal, prenatal and delivery conditions are shown in **Table 2**.

Table 3 addresses characteristics of birth, interventions, and complications during hospitalization at the NICU according to GA. There is a significant difference between the groups for the variables: birth weight (p=0.000), length of hospital stay in the NICU (p=0.000), time of IMV (p=0.000), total time of oxygen therapy (p=0.000), transfusion requirement (0.019) and use of surfactant (0.003).

The time of NIV was not different between groups (p=1.66). When assessing the occurrence of sepsis according to GA, no difference in frequency of this complication was identified between the groups (p=0.177). The weight at discharge from the NICU did not show difference between groups (p=0.093).

Considering the total premature newborns participants, 51 (77%) were classified as having AGA at birth, yet, only 30 (45%) remained with this classification at the time of discharge. It can also be observed that the frequency of small for gestational age (SGA) premature newborns increased from 13 (19%) at birth to 36 (54%) at discharge (p=0.001). Among late and moderate preterm newborns, there is a significant increase in the frequency of SGA newborns and a decrease in AGA at the time of discharge compared to the classification at birth (p=0.046 for the late and p=0.021 for the moderate). This comparison for very preterm and extremely preterm newborns found that four (18%) were discharged with adequate weight for GA, according to what is shown in **Table 4**.

DISCUSSION

This work assessed premature newborns hospitalized in the NICU of a level IV hospital from the countryside region of the *Rio Grande do Sul* State. It was observed that the majority of premature newborns were classified as moderate and late. A previous study, published in 2016, also showed a higher frequency of this classification of prematurity in Brazil, in which the late ones reached 74% of births, representing three quarters of all premature newborns in the country.[5]

As in other studies,[4,6] here, males were more frequent among hospitalized patients. In a comparative approach, a study undertaken in the Netherlands showed that male newborns were associated with an increased risk of fetal distress, while females have a protective effect for this outcome,[7] which could contribute to the higher frequency of premature newborns among the male gender.

The predominant route of birth in the present study was cesarean section, a result similar to two other studies that identified maternal and neonatal factors associated with prematurity.[8,9]

According to a study of three birth cohorts in Southern Brazil, concomitant with the increase in prematurity, observed over 22 years, there was a significant increase in pregnancy interruptions, and the rate of labor induction increased by 8.6% in the same period. Studies claim that the increasing number of pregnancy interruptions might be responsible for the increase in premature births, especially moderate and late preterms.[10]

Nevertheless, caution is needed when analyzing births by cesarean section in premature newborns, the maintenance of pregnancy must be carefully evaluated considering the risks of childbirth associated with the risks of premature birth.[11] The data from this study do not allow inferring whether there was a relationship between prematurity and interruption of pregnancy, which was considered a limitation of this work.

Regarding the maternal comorbidities investigated in the present study, there was a predominance of pregnant women diagnosed with preeclampsia and gestational diabetes. A study that evaluated the profile of newborns hospitalized in a NICU, concluded that termination of pregnancy was motivated by preeclampsia and its complications in 45% of cases, followed by gestational diabetes in 29% of pregnant women.[12] It is noteworthy that in this study frequency of gestational diabetes was higher in pregnant women who delivered before 34 weeks, suggesting an increased risk of premature birth related to this gestational morbidity.

When analyzing the length of hospital stay according to gestational age, it is clear that premature newborns less than 32 weeks remain longer in the NICU. There is consensus in the literature the inverse relationship between gestational age and complications and worsening of the babies' health during hospitalization, which justifies a longer stay and the need for hospital interventions.

It is noteworthy that the survival rate of babies under 32 weeks of gestation has been increasing in recent decades due to technological and scientific advances in prenatal care and in the intensive care unit.[13] Nonetheless, proportional to the survival rate, there is an increased incidence of chronic morbidities such as growth deficit and delayed neurodevelopment, as well as an increased risk of chronic

events in adult life, including: hypertension, diabetes mellitus, dyslipidemia, obesity and even greater chances of learning deficit and odd behavior.[1]

GA is directly related to the need for ventilatory support of premature newborns, both oxygen therapy and the use of mechanical ventilation.[14] This study did not found difference between the groups classified according to gestational age for the time of NIV. The wide use of non-invasive ventilation is justified by the maintenance of oxygenation and reduction of lung injury induced by IMV, this strategy of ventilatory support has been increased in intensive care units worldwide.[15]

Here, the time of IMV and the total time of oxygen therapy were significantly longer in premature newborns less than 32 weeks. The long stay in IMV has already been associated with the delay in the development of the swallowing function, which can negatively influence growth.[16] The need for oxygen therapy for long periods by premature newborns with lower GA is associated, for example, with the occurrence retinopathy of prematurity,[17] which implies the need for support and follow-up after hospital discharge for this population.

There is a high prevalence of sepsis in our population, and the frequency of this complication was similar between groups, results also evidenced in other studies.[4,14] Newborns hospitalized in the NICU undergo various invasive treatments and procedures that increase susceptibility to infections.[18] Neonatal sepsis (early and late) associated with the immune fragility of the premature neonate, makes it one of the main causes of mortality for this population.[19]

Considering this framework, it is important to establish measures to prevent neonatal sepsis based on the main risk factors for this complication. These measures should start in the prenatal period related to urinary tract infections, premature rupture of amniotic membranes, prematurity and intrauterine growth restriction and extend to the hospital environment.[18]

Concerning the classification of weight, there was observed a restriction of extrauterine growth that was verified by the significant increase in SGA newborns at the time of discharge from the NICU, regardless of GA at birth, which is in agreement with another study.[20] Adequate extrauterine growth depends on the interaction of a series of factors, of lesser and greater complexity, depending on the clinical condition of the premature newborns, which justifies the follow-up of this population based on specific growth curves, aiming to determine better ways to nourish and avoid future morbidities.[21] Herein, it was considered that the reduced number of extremely preterm and very preterm newborns was a limiter providing for more specific analyzes and conclusions about the data.

FINAL CONSIDERATIONS

Bearing the aforesaid in mind, it was possible to conclude that most of the premature newborns participating in this study were classified as moderate and late according to the GA. Preeclampsia was the most prevalent complication among pregnant women, regardless of GA. Gestational diabetes was more frequent at delivery before 34 weeks. Concerning the length of hospital stay in the NICU and the time of IMV, both were bigger in extremely preterm and very preterm newborns. When analyzing the time of NIV, there was found no difference between groups. Restriction of extrauterine growth with a significant increase in SGA newborns was observed at the time of discharge from the NICU, regardless of GA at birth.

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TABLES

Table 1 - Characterization of premature newborns hospitalized in the NICU of a level IV hospital located in the Northwest region of the *Rio Grande do Sul* State, Brazil. n=66

Variable	n (%)
Gender	
Male, n (%)	39 (59,1)
Weight at birth (g), average±SD	1679 ± 480,3
Length at birth (cm), average±SD	41 ± 4,3
Head circumference at birth (cm), average±SD	29,2 ± 2,8
Apgar 1st min, average±SD	6,8 ± 1,8
Apgar 5th min, average±SD	8,1 ± 1,5
Classification Weight/GA, n (%)	
AGA	51 (77,3)
BGA	2 (3)
SGA	13 (19,7)
Classification of weight at birth, n (%)	
Less than 1,000 g	5 (7,5)
From 1,000 to 1,499 g	16 (24,2)
From 1,500 to 2,499 g	42 (63,6)
More than 2,500 g	3 (4,5)
GA (weeks), average±SD	32,3 ± 2,8
Classification of Prematurity, n (%)	
Less than 28 weeks	5 (7,7)
From 28 up to <32 weeks	11 (16,9)
From 32 to <34 weeks	26 (40)
From 34 to < 36 weeks	23 (35,4)
Length of hospital stay, median (IQR)	21,5 (15-36,5)
Weight at discharge, average±SD	2171,8 ± 365,2

SD = Standard Deviation; GA = Gestational Age; AGA = Appropriate for Gestational Age; BGA= Big for Gestational Age; SGA= Small for Gestational Age; IQR = Interquartile Range.

Table 2 - Maternal, prenatal and delivery conditions of premature newborns hospitalized in the NICU of a level IV hospital located in the Northwest region of the *Rio Grande do Sul* State, Brazil. n=66

	VP/E	MP		LP		
	average±SD	average±SD	pa	average±SD	pa	pb
Maternal age	26,7±6,8	28,3±6,2	0,414	24,2 ± 6,1	0,75	0,119
No. of prenatal consult.	6,5±4,3	7,8 ± 2,9	0,413	6,6 ± 2,8	0,19	0,313
No. of pregnancies	1,8±1,5	1,5 ± 0,9	0,024	1,8 ± 1,0	0,19	0,433
Gestational Complications	n (%)	n (%)		n (%)		Pc
Preeclampsia	6 (60)	12 (52,2)		7 (58,3)		0,465
Gestational DM	3 (30)	8 (34,8)		1 (8,4)		0,051
Urinary infection	0	2 (8,7)		3 (25,0)		0,873
HELLP syndrome	1 (10)	1 (4,3)		1 (8,4)		-
Delivery						
Cesarean	10 (62,5)	18 (69,2)		17 (70,8)		0,567
Vaginal	6 (37,5)	8 (30,8)		7 (29,2)		

VP/E = Very Preterm/extremely; MP = Moderate Preterm; LP = Late Preterm; SD = Standard Deviation; DM = Diabetes Mellitus; a – Student t-Test; b – ANOVA; c- Pearson's Chi-Square Test.

Table 3 - Birth characteristics, interventions and complications during hospitalization of premature newborns according to their GA, who were hospitalized in the NICU of a level IV hospital located in the Northwest region of the *Rio Grande do Sul* State, Brazil. n=66

	VP/E	MP		LP		
	average±SD	average±SD	pa	average±SD	pa	pb
Weight at birth	1177,62 ± 373	1667± 323	0,00	1986 ± 438	0,000	0,000*
Weight at discharge	2325± 409	2072 ± 333	0,502	2203 ± 351	0,409	0,093*
Length of hospital stay	54 ± 27,81	27 ± 12,5	0,000	17,3 ± 6,3	0,000	0,000*
Time of NIV	5 ± 4,88	5,5 ± 8,4	0,06	2,1 ± 1,9	0,120	0,166*
Time of IMV	30,31 ± 26,39	3,6 ± 5,5	0,001	1,6 ± 3,8	0,000	0,000*
Total time of O2	34,3 ± 22,6	10,7 ± 8,5	0,000	7,3 ± 6,5	0,000	0,000*
Complications	n (%)	n (%)		n (%)		Pc
Sepsis	14 (81,8)	19 (73,1)		22 (84,6)		0,177**
Transfusion	16(100)	26 (100)		23 (88,5)		0,019**
Surfactant	16 (100)	26 (100)		24 (100)		0,003**

VP/E = Very Preterm/extremely; MP = Moderate Preterm; LP = Late Preterm; NIV = Non-Invasive Ventilation; IMV = Invasive Mechanical Ventilation; SD = Standard Deviation; pa = Student t-Test; pb =ANOVA; pc = Pearson's Chi-Square Test.

Table 4 - Classification of weight according to the GA at birth and at the time of discharge from the NICU in preterm groups, who were hospitalized in a level IV hospital located in the Northwest region of the *Rio Grande do Sul* State, Brazil. n=66

	Birth			Discharge		
Classification	SGA	AGA	BGA	PIG	AIG	P
		n (%)		n (%)		
Late preterm	8 (33)	16 (67)	-	18 (75)	6 (25)	0,046*
Moderate preterm	5 (20)	21 (80)	-	14 (54)	12 (46)	0,021*
Very preterm/ extremely	-	14 (82)	2 (18)	4 (18)	12 (82)	0,461
Total	**13 (19)**	**51 (77)**	**2 (3)**	**36 (54)**	**30 (45)**	**0,001**

NBirth = classification of weight according to the gestational age at birth; Discharge = classification of weight according to the gestational age at the time of discontinuation of the NICU; AGA = Appropriate for Gestational Age; BGA= Big for Gestational Age; SGA= Small for Gestational Age; Pearson's Chi-Square Test.

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Corresponding author
Simone Zeni Strassburger
Universidade Regional do Noroeste do Estado do Rio Grande do Sul/UNIJUI
Endereço: Rua do Comércio, 3000, Bairro Universitário
Ijuí/RS, Brazil
Zip code: 98700-000
Email address: simone.s@unijui.edu.br
Telephone numbers: +55 (55) 3332-0461/98111-7282
ORCID: http://orcid.org/0000-0001-9655-8807

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