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ORIGINAL ARTICLE

Hypoglycemia and associated factors in neonates: A single center observational study

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Resume

Introduction: Neonatal hypoglycemia (NH) is one of the most frequent metabolic pathologies in the neonatal period. It increases morbidity and mortality in the newborn and can leave permanent sequelae; however, itcan be prevented, diagnosed, and treated early. This studyaimed to determine the factors associated with neonatal hypoglycemia in newborns from the neonatology service at a Vicente Corral Moscoso public hospital in Cuenca-Ecuador.

Methods: This case control study was conducted from January 2018 to December 2019. Matched by gestational age, sex, and maternal residence. Patients with NH entered the study during the first seven days of life, and the controls did not present NH. The sample was taken for convenience. The variables weregestational diabetes, uncontrolled type II diabetes mellitus, small for gestational age, macrosomal, respiratorydistress syndrome, and intrauterinegrowth restriction. The association was quantified using theodds ratio with a confidence intervalof 95%.

Results: A total of 101 cases and 202 controlswere homogeneous in gestational age, sex, and maternal residence ($P>0.05$). The factors associated with statistically significant neonatal hypoglycemia were small for gestational age (OR 2.54; CI1.54-4.20;$P<0.001$) and intrauterine growth restriction (OR 2.1; CI 1.29.54;$P= 0.003$) while gestational diabetes (OR 1.2; IC 0.374.88;$P=0.649$), macrosomia (OR 1.2; IC 0.285.1;$P=0.800$) and respiratory distress syndrome (OR 0.89; IC 0.541.47;$P=0.672$) were not statistically significant.

Conclusion: Neonatalhypoglycemiais associated with factors such as intrauterine growth restriction and small for gestational age.

Keywords: MESH: Hypoglycemia; Glucose; Newborn; Risk factors.

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Introduction

Neonatal hypoglycemia (NH) is considered a clinical-metabolic pathology related to carbohydrate metabolism, whichto date has been controversial worldwide regarding its definition, clinical importance, and optimal therapeutic management [1–3]. It is a decrease in plasma glucose concentration of less than 47 mg/ld [4–6].

The rate of symptomatic NH in firstworld countries is between 1.3and 3 per 1000 live births, unlikein Latin America, where it occurs between 10and 20 per 1000 live births, according to data from the World Health Organization [7].

Glucose is an essential substrate for fetal development. During the gestational period, the fetus receives a constant supply of glucose from its mother through facilitated diffusion and producesinsulin to remain euglycemic. In the postnatal period, the constant supply of glucose ceases, and neonatal insulin concentrations must be regulated. During this period, the newborn (NB) may fail in the normal metabolic adaptation process, thus producing NH [8]. It is essential to know that maintaining glucose balance is extremely difficult in all newborns, but even more so in those with some associated risk factor [1]. On the other hand, the extreme sensitivity to changes in glycemia levels, added to the difficulty in maintaining them, allows any stimulus unrelated to metabolism (infections, respiratory distress) to be associated with significant changes in these metabolic processes [1,7].

This pathology can be prevented, diagnosed, and treated promptly. However, NH to date is difficult to control, especially in thirdworld countries; some cases range from a variety of symptoms, which can disappear when the cause is treated without leavingany complications, topermanent sequelae, mainly at the neurological level.

Perinatal morbidity and mortality are the expressions of the inequity gaps in access to health services and evidence of the inequality conditions that mainly affect risk groups, especially newborns; therefore, it is a public health problem as well as human rights and social justice.

There are no data on the study of factors associated with NH that may affect NBs in our region. Therefore, it is clinically relevant to preventhte appearance of this pathology, and it should be studied in all newborns at risk of developing it. This study aimed todetermine the factors associated with NH in neonates born in a public hospital in Cuenca, Ecuador.

Materials and methods

Design of the investigation

This design is an observational, case control study, and the source was retrospective.

Scenery

The study was carried out at the Vicente Corral Moscoso Hospital of the Ministry of Public Health in Cuenca-Ecuador. The study period was from January 1, 2018, to December 31, 2019.

Inclusion criteria

Patients with a diagnosis of hypoglycemia due to capillary glycemia or central glycemia recorded in the clinical history of less than 47 mg/dl during the first seven days of life were admitted to the case group. Controls: hospitalized patients with similar characteristics to the cases and who did not experience hypo - glycemia in the first seven days of life.

Study size

The sample was taken for convenience and was calculated with a confidence level of 95%, power of 80%, OR 2.1,prevalence of exposure in the cases of 76% exposure prevalence among controls of 60% (based on "intrauterine growth restriction" (IUGR), which was the variable with the lowest prevalence of risk factors for neonatal hypoglycemia), and a ratio of 1 case to 2 controls. Cases 101, control 202.

Variables

The dependent variable was neonatal hypoglycemia . The independent variables were gestational diabetes, type II diabetes mellituswithout disease control,small for gestational age, macrosomal, respiratory distress syndrome, and intrauterine growth restriction. Moderating variables: gestational age, sex, and maternal residence.

Data sources/measurement

Data were collected from the institutional clinical history using a form designed for this purpose. The records of the neonatology service were consulted and

compared with the complete clinical history of the institution's statistics departmetn.

Avoidance of bias

To guarantee the reliability of the information, the researchers were trained in data collection. A double checklist was used to include all cases. The datawere validated and curated by the principal investigators. To avoid possible interviewer, information, and memory biases, the leading investigator kept the data at all times with a guide and appropriate records. Observation and selection bias was avoided by applying the participant selection criteria.

Statistical method

Once the information was collected, it was tabulated in the statistical program SPSS version 15.0 (SPSS Inc. Released 2006. SPSS for Windows). Chicago, SPSS Inc. Information is presented in associationtablesFor data analysis, descriptive statistics were performed for the qualitative variables (gestational age, sex, and maternal residence), frequencies, and percentages. To see the degree of homogeneity of the groups and determine the association, chi2 was usedTo determine the magnitude of risk exposure, it was calculated by OR, with a 95% confidence interval, with a significance of $P<0.05$. For the interpretation of the OR, a value > 1 was considered "risk", and a value <1was considered a "protective" factor.

Results

The study included 101 cases and 202 controls.

General characteristics

The cases and controls were comparable regarding gestational age, sex, and maternal residence ($P>0.05$). These three variables were used to match the groups (Table 1). The majority of the group belongs to the urban zone, with a slight predominance of themale sex and with gestational age at term in 66 and 63% of the cases and controls, respectively.

Table 1.Matching of cases and controls.

	CASES		CONTROLS		P
	F	%	F	%	
Gestational age					
Term	67	66.34%	134	66.34%	1.0
Late Preterm	19	18.81%	38	18.81%	
Moderate Premature	1	0.99%	2	0.99%	
Very premature	10	9.9%	20	9.9%	
Extreme Pre-	4	3.96%	8	3.96%	
Sex					
Male	59	58.42%	101	50.0%	0.26
Female	42	41.58%	99	49.0%	
Indeterminate	0	0%	2	1.0%	
Maternal residence					
Rural	35	34.65%	75	37.13%	0.67
Urban	66	65.35%	127	62.87%	

Bivariate analysis

All the variables were compared between the groups, and small sizes for gestational age and the presence of IUGR were established as risk factors for developing neonatal hypoglycemia. There was no association between macrosomia and RDS (Table 2).

Table 2. Risk factors for neonatal hypoglycemia

	Cases n=101	Controls n=202	OR	95% CI	P
Gestational diabetes	4 (3.96%)	6 (2.48%)	1.34	0.37-4.88	0.649
SGA	48 (47.5%)	53 (26.24%)	2.54	1.54-4.20	<0.0001
Macrosomal	3 (2.97%)	5 (2.48%)	1.20	0.28-5.15	0.800
RDS	63 (62.38%)	131 (64.85%)	0.89	0.54-1.47	0.672
ICRU	43 (42.57%)	52 (25.74%)	2.13	1.29-3.54	0.003

OR: odds ratio. CI: confidence interval. SGA: small for gestational age RDS: respiratory distress syndrome.

Discussion

NH is a clinical-metabolic disease produced by an alteration in the glucose balance related to factors associated with the mother and the newborn 1[]. However, it can be prevented, diagnosed, and treated promptly, thus avoiding complications such as neurological sequelae [7]. In the present investigation,

we worked with 101 cases and 202 controls. The analyses showed a statistically significant association between SGA and IUGR factors.

In this study, it was observed that being SGA increases the risk of presenting hypoglycemia 2.54 times, which coincides with the reported literature, such as the case of Mulul [9]. (2013), in their research in which they included 352 NBs, 26 NBs presented the SGA and NH factor with an ORof 5.75 (95% CI 2.91-11.12) (P <0.05). In the same way, Mejia [10] (2017), in his study carried out on 131 NBs, found an OR of 309 (P=0.007), and Alor [11] (2019) showed an ORof 6.63 (95% CI 2.52-17.45); P< 0.001.

SGA newborns present a delay in the gluconeogenesis cycle and limitations in glycogen storage, predisposing them to present NH1[]. IUGR is a disorder in which the fetus is smaller than expected for gestational age; according to Medina [12] (2019), newborns with IUGR are more vulnerable to NH. In this investigation, it was observed that these patientshad twice the risk of presenting hypoglycemia, and this relationship was statistically significant. These results agree with those reported in the research carried out by Alor [11] (2019), where having IUGR increases the risk of presenting hypoglycemia 4.05 times (OR 4.05 CI 1.66- 9.86; P<0.004). However, they differ from the study carried out by Flores [3] (2019), who studied 116 NBs and found no such association (OR 2.1; CI 0.-76.0; P=0.1). The presence of hypoglycemia in patients with IUGR is most likely due to their hormonal and enzymatic immaturity, reduced hydration and energy, and feeding difficulties [5].

GD, known as hyperglycemia due to reduced tolerance to carbohydrates, is diagnosed for the first time during pregnancy; in this study, no statistically significant association with NH was evidenced, which agrees with Mulul's research [9] (2013), who reported that DG is not a factor associated with NH (OR 2.30, CI 0.14-37.07). Unlike what was found by Rodríguez[4] (2018), who reported that having DG increases the risk of presenting neonatalhypoglycemia 4 times (OR 4.6; CI 2.34-8.72; P<0.05). The results of this study could be explained because adequate control of high-risk mothers is carried out in the institution. Presenting macrosomia was not identified as a risk factor for neonatal hypoglycemia; this result is similar to that made by Montalvo [15] (2020), who stated that macrosomia was not a statistically significant factor in NH (OR 0.76; CI 0.14-3.9; P=0.74).In contrast,Bazán et al. [16] (2019) determined that the presence of macrosomia was statistically significant for developing NH (OR 6.40; CI 1.86-22.19;P=0.003). The RDS did not have a statistically significant association either. In contrast, Bellido [17] (2014) and Yupanqui [18] (2018) did find such an association (OR 4.43, CI 1.72-11.73, P<0.001 and OR 2.34, CI 1.25-4.37, P<0.05, respectively). However, this difference in results should be corroborated with more research that includes a more extensive study population. The timely identification of factors such as SGA and IUGR are critical indicators in the prevention and control of NH. As limitations of this research, we can report the incomplete record of clinical histories and that no patients born to mothers with poorly controlled type II diabetes mellitus were found.

Conclusions

The risk factors associated with NH that were statistically significantwere SGA and IUGR.

Abbreviations

GD: gestational diabetes.
NH: neonatal hypoglycemia.
SGA: small for gestational age.
IUGR: Intrauterine growth restriction.
RDS: Respiratory distress syndrome.

Supplementary information

No supplementary materials are declared.

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Author contributions

Sandy Lisseth Vera Morales: Conceptualization, Data Curation, Fundraising, Research, Resources, Software, Writing- original draft.
Paola Daniela Santacruz Pérez: Conceptualization, Data conservation, Supervision, Acquisition of funds, Research, Resources.
Ximena Margoth Bermeo Guartambel: Conceptualization, Supervision, Acquisition of funds, Research, Resources.
All authors read and approved the final version of the manuscript.

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Availability of data and materials

The data sets generated and analyzed during the current study are not publicly available due to participant confidentiality but are available through the corresponding author upon reasonable scholarly request.

Statements

Ethics committee approval and consent to participate

The Research Bioethics Commission of the University of Cuenca and the Teaching and Research Unit of the Vicente Corral Moscoso Hospital approved this study. This research did not require informed consent as it was a data-base study.

Publication Consent

This publication consent does not apply to studies that do not publish MRI/CT/Rx images or physical examination photographs.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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