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Original Article

Frequency of Hypoglycemia in Neonates with Intrauterine Growth Restriction Presenting to Pak-Emirates Military Hospital Neonatal Intensive Care Unit

Aqsa Zafar, Muhammad Tariq Nadeem, Tamoor Afzal*, Hira Ahmed, Amina Pirzada, Maryam Waheed

Department of Pediatrics, Combined Military Hospital/National University of Medical Sciences (NUMS), Rawalpindi Pakistan,
*Department of Pediatric Surgery, Pak Emirates Military Hospital/National University of Medical Sciences (NUMS), Rawalpindi Pakistan

ABSTRACT

***Objectives*:** To determine the frequency of hypoglycemia in neonates born with intra-uterine growth restriction.
Study Design: Cross-sectional study.
***Place and Duration of Study*:** Department of Paediatrics, Pak-Emirates Military Hospital, Rawalpindi, Jan to Sep 2022.
***Methodology*:** This study was conducted on 127 neonates diagnosed with intrauterine growth restriction. Neonates with IUGR who were born at term were included in the study. Those born to diabetic mothers, with chronic disorders, or were born with birth asphyxia or meconium aspiration were excluded. Neonates were tested for blood glucose levels at birth and then at hourly intervals for five hours post-birth.
***Results*:** We studied a sample with a mean gestational age at birth of 38.56±1.48, of whom 72(56.7%) were female. The sample had the lowest mean blood glucose levels at three- and four hours after birth. A total of 52(40.9%) neonates developed hypoglycemia at least once during the five-hour observation period. Neonates who were delivered via cesarean section had a significantly lower frequency of development of hypoglycemia compared to those delivered per vaginum (p=0.012). Other factors such as neonatal gender, gestational age at birth, maternal history of smoke exposure, abortions or previous neonatal death, and antenatal care receipt were not associated with an increase in the frequency of hypoglycemia (p>0.05).
***Conclusion*:** Hypoglycaemia is common in neonates suffering from intrauterine growth retardation and requires adequate monitoring in this population.

Keywords: Hypoglycaemia, Intrauterine Growth Restriction, Neonates.

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INTRODUCTION

Intrauterine growth restriction (IUGR) is defined as a fetal growth rate that is less than the growth potential of a normal fetus at that gestational age.[1] It is a commonly encountered complication in pregnancy that can affect anywhere between 10% and 23% of gestations or an estimated 30 million cases per annum.[1,2] Depending on its severity, IUGR is associated with a vast array of complications: in the short term, neonates are at increased risk of developing respiratory distress syndrome, birth asphyxia, meconium aspiration syndrome, pathological jaundice, hypocalcemia, hypothermia, increased susceptibility to infections, and being born prematurely.[3,4] Long-term complications include the inability to attain full height, even through adolescence, poor cognition, behavioral and hyper-activity disorders, and cerebral palsy. In addition, patients have an increased risk for the development of renal disorders, metabolic syndrome, ischaemic heart disease, diabetes mellitus, and dyslipidaemias.[3-5]

Hypoglycaemia in the neonatal period is defined as a serum glucose level of less than 47 mg/dL.[6] It can manifest in a wide variety of ways in the neonate including, but not limited to, sweating, hypothermia, weak cry, poor sucking reflex, irritability, lethargy, stupor, breathing difficulties including apnoea and cyanosis, seizures or coma, however, it is pertinent to note here that a majority of neonates with hypoglycemia do not manifest any symptoms, despite severity.[6-8] Complications of hypoglycemia are mainly neurological and include short- and long-term impairment of motor and sensory function, cognitive and behavioral deficiencies, neurodevelopmental delays, as well as the risk of developing cerebral palsy and even death.[7-10] Thus, the combination of IUGR and hypoglycemia can result in severe short- and long-term risks for the neonate.[9,10]

We conducted this study on neonates suffering from IUGR to determine the frequency of occurrence of hypoglycemia in these patients. Since most neonates

Correspondence: Dr Aqsa Zafar, Department of Pediatrics, Combined Military Hospital, Rawalpindi Pakistan
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do not manifest symptoms with hypoglycemia, sometimes, despite severity, the establishment of a frequency of this complication is paramount in recognizing the size of the problem. This will help determine whether there is a requirement for frequent and more intensive surveillance of blood glucose levels in these neonates, regardless of their clinical appearance. This, in turn, will help detect neonates with the disorder earlier, allowing for the early institution of management and the limitation of both short- and long-term complications, which will reduce morbidity and mortality in this population.

METHODOLOGY

The cross-sectional study was conducted from January to September 2022 in the Department of Paediatrics, Pak Emirates Military Hospital, Rawalpindi Pakistan, on 127 neonates born with IUGR after obtaining consent from their parents or guardians. The study participants were selected using non-probability, consecutive sampling after obtaining permission from the Ethics Review Board (A/28/EC/377/2021). The WHO sample size calculator was used to calculate the sample size.[11]

Inclusion Criteria: Neonates diagnosed with IUGR of both genders, born between the start of 37 weeks of gestation and before the end of 42 weeks of gestation, were included.

Exclusion Criteria: Neonates born to mothers with diabetes mellitus (gestational or otherwise), those with severe neonatal hepatic, renal, or other metabolic disorders, birth asphyxia, or meconium aspiration syndrome were excluded.

Intrauterine growth restriction was defined as an estimated fetal weight less than the 10^{th} percentile for gestational age, as determined by prenatal ultrasound performed at the time of delivery.[3] All mothers received an abdominopelvic ultrasound (Voluson E10 Ultrasound Machine, General Electric; Boston, USA) at the time of delivery to confirm the diagnosis of IUGR. Demographic data, including details of mother and pregnancy, were also documented. Mothers underwent delivery as per hospital protocols. All neonates underwent testing for blood glucose levels at birth and then at hourly intervals for five hours. All blood sugar testing was conducted using a calibrated and control-tested glucometer (Evocheck GM700S Blood Glucose Monitoring System, PharmEvo; Karachi, Pakistan). Hypoglycaemia was defined as a blood glucose level of less than 47mg/dL.[12] All patients were breast-fed at one-hourly intervals. Neonates with hypoglycemia received a bolus of 10% dextrose water at 2mL/kg intravenously for correction.

Data was analyzed using the Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows version 26, IBM Corp; Armonk, USA). The mean and standard deviation were calculated for the quantitative variables. Qualitative variables were recorded in terms of frequency and percentage. Patients were divided into two groups: one with hypoglycemia and the other without. Quantitative variables were compared across groups using the independent samples *t*-test, while the chi-square test was used for qualitative variables. The *p*-value of ≤0.05 was considered statistically significant.

RESULTS

Our study sample consisted of 127 neonates, with a mean age of 38.56±1.48 weeks and a total of 72(56.7%) females. The mean age of the mothers at the time of birth was 30.15±4.71 years, with a mean gravidity and parity of 3.06±1.40 and 1.68±1.19, respectively. A total of 22(17.3%) had a history of smoking/secondary smoking/biomass exposure, while 18(14.2%) did not receive any antenatal care. The majority of patients, i.e., 71(55.9%), were delivered vaginally, while the remaining 56(44.1%) were delivered by caesarean section. Table-I presents the characteristics of the neonates and their mothers, distributed according to neonatal gender. Table-II presents data on the blood glucose levels of the neonates in the sample. Blood glucose levels were observed to dip around three to four hours post-birth and were significantly lower in males at the four-hour mark ($p=0.045$). A total of 52(40.9%) neonates suffered from hypoglycemia at least once during the study period.

Table-I: Patient/Maternal Characteristics according to Neonatal Gender (n=127)

Variable	Male (n=55)	Female (n=72)
Gender	55(43.3%)	72(56.7%)
Gestational Age at Birth (weeks)	38.45±1.46	38.64±1.50
Maternal Age (years)	30.18±4.51	30.13±4.90
Gravidity	3.02±1.33	3.08±1.46
Parity	1.62±1.19	1.72±1.18
Maternal History of Abortions	23(41.8%)	27(37.5%)
Maternal History of Neonatal Death	7(12.7%)	12(16.7%)
Smoking / Secondary Smoking / Biomass Exposure	10(18.2%)	12(16.7%)
Antenatal Care	9(16.4%)	9(12.5%)
Mode of Delivery		
Caesarean Section	23(41.8%)	33(45.8%)
Per Vaginum	32(58.2%)	39(45.2%)

Table-II: Blood Glucose Characteristics according to Gender (n=127)

Variables	Male (n=55)	Female (n=72)	*p*-value
Blood Glucose Level (mg/dL) at Birth	72.87±24.46	76.94±25.35	0.364
Blood Glucose Level (mg/dL) at One Hour	83.22±28.73	85.10±24.22	0.690
Blood Glucose Level (mg/dL) at Two Hours	74.00±25.06	79.18±24.83	0.248
Blood Glucose Level (mg/dL) at Three Hours	69.51±19.33	69.18±18.75	0.923
Blood Glucose Level (mg/dL) at Four Hours	68.71±23.49	77.60±25.35	0.045
Blood Glucose Level (mg/dL) at Five Hours	77.18±25.70	77.44±25.41	0.954
Hypoglycaemia	27(49.1%)	25(34.7%)	0.103

Table-III: Association of Maternal/Neonatal/Pregnancy Factors with Hypoglycaemia (n=127)

Variables	Hypoglycaemia (n=52)	No Hypoglycaemia (n=75)	*p*-value
Gender			
Male	27(55.3%)	28(52.2%)	0.103
Female	25(44.7%)	47(47.8%)	
Gestational Age	38.44±1.53	38.64±1.45	0.461
Maternal Age (years)	29.88±4.69	30.33±4.76	0.600
Gravidity	3.04±1.40	3.07±1.41	0.912
Parity	1.62±1.30	1.72±1.11	0.627
Maternal History of Abortions	21(40.4%)	29(38.7%)	0.846
Maternal History of Neonatal Death	9(17.3%)	10(13.3%)	0.537
Smoking / Secondary Smoking / Biomass Exposure	10(19.2%)	12(16.0%)	0.636
Antenatal Care Not Received	9(17.3%)	9(12.0%)	0.399
Mode of Delivery			
Caesarean Section	16(30.8%)	40(53.3%)	0.012
Per Vaginum	36(69.2%)	35(46.7%)	

DISCUSSION

Neonates afflicted by IUGR are prone to the development of several complications that are associated with a significant degree of both short- and long-term morbidity and even mortality. Hypoglycaemia is a potential complication that can occur in such patients, is potentially preventable, and is easily treatable if recognized early; this study was conducted to determine the frequency of this complication in IUGR-affected neonates in our population.

A total of 40.9% of neonates with IUGR developed hypoglycemia in our study. This finding was similar to that of Taranushenko *et al.,* who reported a frequency of 41.0% in neonates with IUGR in their study.[13] Doctor *et al.,* noted that only 5.0% of neonates with IUGR developed hypoglycemia in their research.[11] Mejri *et al.,* noted a frequency of 26.0% in such patients,[14] while Sadat-Tabatabaie *et al.,* noted a frequency of 14.0%.[15] While a certain degree of variability is expected across diverse populations, we believe the grossly different results are primarily due to the way hypoglycemia was defined: some studies, such as Sadat-Tabatabaie *et al.,* had very low thresholds of <30mg/dL, and thus reported fewer cases, as opposed to our study were we had a cut-off of 47mg/dL.[15]

Neonates had the lowest blood glucose levels around the four hours post-birth mark in our study. Mukunya *et al.,* reported that neonatal hypoglycemia is most frequently seen in the first few hours post-birth.[16] Meanwhile, Edwards *et al.,* noted that blood glucose monitoring in neonates should be initiated between one and four hours after birth, as this is the most at-risk period for the development of hypoglycemia.[17]

The mean gestational age at birth for our entire study sample was 38.56±1.48 weeks; gestational age did not appear to affect the development of hypoglycemia (p=*0.461*). Mitchell *et al.,* reported that neonates born before the gestational age of fewer than 33 weeks had a high incidence of hypoglycemia compared to older neonates.[18] Conversely, Butorac-Ahel *et al.,* noted that premature neonates born ≥34 weeks of gestation had a higher incidence of hypoglycemia as compared to neonates who were born with shorter gestations.[19] We believe this heterogeneity is due to two reasons: 1) Our study looked at infants at term who were suffering from IUGR, and while preterm infants suffer from varying degrees of metabolic immaturity depending on gestational age, term infants are largely similar in this aspect to each other, and 2) the occurrence of lower rates of hypoglycemia in very pre-term neonates may be iatrogenic; very premature infants are managed using parenteral glucose, which is more likely more effective in managing blood glucose levels, while those born close to term are primarily fed orally, which may not be as effective.[18,19]

A majority of 56.7% of our patients were female, and there did not appear to be a higher proclivity for any gender to develop hypoglycemia (p=0.103). Taranushenko *et al.,* also reported that there was no difference between genders when it came to the development of hypoglycemia with IUGR,[13] a conclusion that was shared by Mejri *et al*.[14]

Mothers in our study had a mean age of 30.15±4.71 years, with maternal age not having a significant effect on the development of hypoglycemia (*p=0.600*). While advancing maternal age is a risk factor for the development of IUGR, our study did not show a statistically significant relationship with the development of hypoglycemia in neonates with IUGR. However, a comparable study examining this aspect was not available despite an exhaustive literature search, and further study is required before adequate conclusions can be drawn.[20]

A history of the total of smoking/secondary smoking/biomass exposure was seen in 17.3% of mothers in our study, which did not appear to have a statistically significant association with the development of hypoglycemia in our study, which was in keeping with existing literature such as Fang *et al*., who noted that there was no difference in the blood glucose levels of neonates born to smoking mothers versus those who were non-smokers.[21]

Lastly, A total of 55.9% of patients were delivered vaginally, while the remaining 44.1% were delivered by cesarean section, with hypoglycemia manifesting more frequently in neonates born via vaginal delivery (*p*=0.012). Mitchell *et al.,* reported that vaginal delivery was associated with a significantly increased risk for the development of hypoglycemia on univariate analysis (OR 2.17, 95%CI 0.96–5.43),[18] while Turner *et al.,* reported the converse, neonates under cesarean section had a higher incidence of hypoglycemia requiring intravenous intervention (OR 1.4, 95% CI 1.1–1.9).[22] This aspect of our study requires further research before we can draw concrete conclusions. However, we believe that vaginal delivery is associated with greater stress to the neonate, which requires the greater utilization of glucose and a consequent drop in blood glucose levels.[23]

LIMITATION OF STUDY

This was a descriptive cross-sectional study that lacked a control arm; a better determination of the association between various maternal, neonatal/fetal, and pregnancy factors could be obtained by comparing patients with IUGR to controls. Lastly, breastfeeding was performed on an hourly basis in this study; however, the breast milk produced by each mother was not quantified, which may have been variable and may have introduced some degree of confounding into the results.

CONCLUSION

Hypoglycaemia is a frequently encountered phenomenon in neonates suffering from intrauterine growth retardation and requires intensive vigilance if it is to be prevented. Such neonates are particularly at risk for the development of this complication three to four hours after birth, and surveillance of blood glucose levels during this period and the institution of timely and appropriate management can result in a reduction in both short- and long-term morbidity. Labor room and neonatal intensive care staff should be sensitized to exercise caution when treating such patients, and future research should focus on identifying further factors that influence the development of hypoglycemia in growth-restricted neonates using control groups.

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Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

AZ & MTN: Conception, study design, drafting the manuscript, approval of the final version to be published.

TA & HA: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

AP & MW: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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