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Original Article

Biochemistry Section

Blood Glucose Level and Risk Factor Affecting Glucose Homeostasis in Premature Newborns: A Retrospective Study

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ABSTRACT

Introduction: Neonatal blood glucose levels are affected by pregnancy outcomes. Preterm infants are more prone to hypo- and hyperglycaemia compared to full-term newborns. Understanding glucose fluctuation in these infants is important for improving early diagnostic accuracy and neonatal survival rate.

Aim: To explore the glucose levels and risk factors affecting glucose homeostasis among premature neonates.

Materials and Methods: A retrospective study was conducted from January 1 to March 31, 2017, at the Maternity Teaching Hospital affiliated with Hawler Medical University in Erbil city, Iraq. A total of 212 preterm newborns treated in the Neonatal Intensive Care Unit (NICU) were included. Information concerning premature neonates (glucose status, birth weight, and health status) of 24-hour-old newborns and maternal data (ages and gestation) were collected. Statistical analysis was conducted using Statistical Package for the Social Sciences (SPSS) software; methods used are descriptive statistics and inferential tests.

Results: Mean maternal age was 26.7±6.9 years and 113 (53.3%) of women were in young age (20-29 years). A total of 179 (84.4%) of the neonates had normal random blood glucose levels. Highest percentage of maternal 139 (65.6%) were in the group of 33 to 36 weeks of Gestational Age (GA). More than half 135 of premature newborns (63.7%), were in Low Birth Weight (LBW) group. Negative significant correlation found between random blood glucose with GA (unstandardised coefficient β= -1.3; 95% CI: -2.5 to -0.196) and with birth weight of newborns unstandardised coefficient β=-8.5; 95% CI: -14.3 to -2.7). Apgar moderate scores of 4-6 at five minutes increased with increase random blood glucose levels. While Apgar good 7-10 scores group at 10 minutes inversely associated with random blood glucose, (r=-0.196, p-value=0.021).

Conclusion: Most neonates demonstrated normal blood glucose levels. However, lower GA and birth weight were associated with a higher level of glucose, likely due to physiological stress and metabolic immaturity. This may be reflected in Apgar scores, as these infants require more time to adapt to extrauterine life.

Keywords: Apgar scores, Birthweight, Gestational age, Hyperglycaemia

INTRODUCTION

Glucose is the primary energy source for all living organisms, especially the fetus and neonate [1]. It is essential for energy production in organs such as the brain, renal medulla, and erythrocytes, and it is utilised by the muscles, liver, heart, kidneys, and digestive system [2]. Extremely LBW (ELBW) infants consume significantly more glucose per kilogram than adults due to their higher brain-to-body ratio [2]. Akmal DM et al., reported that neonatal blood glucose is influenced by factors such as GA, birth weight, hypoxia, and the severity of sepsis. Furthermore, interventions rapid dextrose infusions, intra-lipid solutions, contribute to the development of neonatal hyperglycaemia [3].

Premature infants are particularly vulnerable to various health challenges that can significantly affect their immediate and long-term wellbeing [4]. Regulation of glucose homeostasis is critical as noted that both hypoglycaemia and hyperglycaemias can lead to severe complications, such as neurological impairment and increased morbidity [5].

Preterm infants often have limited stores of energy and their organs, including the liver, pancreas, brain, and endocrine glands, are still developing. Consequently, they are more susceptible to hypo- and hyperglycaemia compared to full-term neonates [6]. Prematurity is a significant risk factor for hyperglycaemia, influenced by increased levels of inflammatory mediators, catecholamines, and cytokines that contribute to insulin resistance. The underdeveloped beta cells in the pancreas are unable to produce enough insulin, resulting in a relative insulin deficiency [3].

In the first week of life, preterm infants often face disruptions in placental function and impaired glucose regulation, including incomplete processing of pro-insulin by β-islet cells requiring glucose infusion and the inability to suppress glucose production during parenteral glucose administration and hyperglycaemia can occur [7]. Hyperglycaemia occurs more frequently under conditions of excess glucose and lipid infusion, as well as under stressful conditions such as mechanical ventilation and hypoxia [8].

Infections, particularly sepsis, further complicate glucose regulation, often precipitating episodes of hypoglycaemia or hyperglycaemia [9]. Finally, hyperglycaemia is frequently observed in critically-ill premature infants, where stress responses and excessive nutritional intake can exacerbate the condition [10]. Complications of hyperglycaemia include intraventricular haemorrhage, retinopathy of prematurity, and bronchopulmonary dysplasia [6].

Premature birth itself is a primary risk factor for hypoglycaemia, as these infants typically have reduced glycogen stores and a limited capacity to mobilise glucose in response to metabolic demands [11]. Morbidity of hypoglycaemia in neonates is linked to long-term neurological issues, including visual impairments, localisation-related epilepsy, and cognitive dysfunction [11]. Neonatal deaths account for approximately one-third of all infant deaths. Preterm births have been strongly linked to an increased risk of early neonatal mortality [12]. It is crucial to monitor blood glucose levels in preterm infants, especially in those who are small for their GA or have low Apgar scores [6].

Neonatal hypoglycaemia is a known risk factor for higher neonatal morbidity and mortality rates in Iraq [13,14]. Both hypoglycaemia

and hyperglycaemia are significant contributors to the risk of neonatal death, particularly among premature infants in Iraq. Early feeding may help prevent both hypo- and hyperglycaemia [6]. Additionally, exogenous insulin infusion has been shown to partially reduce endogenous glucose production in preterm infants [15].

Blood sugar fluctuations are common during the first week of life in preterm neonates [16,17]. Further research is essential to understand glucose regulation in this population, as early detection and intervention are critical for improving clinical outcomes. The aim of the present study was to measure blood glucose levels and the primary risk factors influencing glucose homeostasis, as well as their impact on the health status of premature neonates.

MATERIALS AND METHODS

This retrospective study was conducted analysing data collected during three months, from January 1 to March 31, 2017, at the NICU/Maternity Teaching Hospital in Erbil city/Iraq. Ethical approval was obtained from the Ethical Committee of the College of Health science (Ref. Number: HSB-002) and the Health Directorate in Erbil. Administrative permission was granted by the Maternity Teaching Hospital to access patient records, rather than directly from the parents, as the hospital was responsible for the premature newborn care.

Inclusion criteria: Preterm newborns (<37 weeks gestation) admitted to Erbil maternity hospitals during the study period (Jan-Mar 2017), with at least one recorded blood glucose measurement, vital signs data (Heart Rate (HR), Respiratory Rate (RR), blood pressure, Apgar score) needed for analysis were included in the study.

Exclusion criteria: Newborns with missing or incomplete blood glucose data, as well as those with incomplete health status information were excluded. Furthermore, infants presenting with major congenital anomalies affecting glucose metabolism were excluded, along with infants born to mothers with pre-existing or gestational thyroid dysfunction, or those affected by maternal pregnancy complications such as Gestational Diabetes Mellitus (GDM), preeclampsia, or eclampsia were excluded from the study.

Sample size: Since this was a retrospective study, the sample size was determined by the number of available medical records (all the subjects who presented within the defined period were enrolled in the study by purposive sampling). Blood glucose values were recorded mostly for all infants 212, however, complete data on health status were available for only 139 infants from recorded document.

Data collection: Data were collected from medical document records by using a questionnaire comprising of two parts:

Part A: Information concerning premature neonates (24-hour-old), specifically birth weight. It is categorised to four groups according to World Health Organisation (WHO) Statistical Information Systems [18], by weight, independent of GA. Normal Birth Weight (NBW) ≥2500-4000 g, LBW=1500-2499 g, very LBW=1000-1499 g, and ELBW ≤999 g, gender, health status, indicators of prematurity, and random blood glucose levels measured using a glucometer (Accu-check, enzymatic method). Samples were regarded as hyperglycaemic if serum glucose was greater than 150 mg/dL (8.3 mmol/L) or whole blood glucose was greater than 125 mg/dL. Plasma glucose value of 47 mg/dL is defined as hypoglycaemia in neonates [19].

The health status of premature neonates was measured using several clinical indicators. Bilirubin, Packed Cell Volume (PCV), RR, HR, peripheral Oxygen Saturation (SpO_2), and Apgar scores. The normal range of bilirubin for premature infants is generally considered to be up to 5 to 14 mg/dL within the first week of life [20]. For premature infants, the PCV typically ranges from 40% to 60% [21]. The normal RR for premature neonates is generally between 40 to 60 breaths per minute [22]. HR for premature neonates typically falls between 120 to 180 beats per minute [23]. Finally, the SpO_2 range was 90-95% for preterm infants [24]. Apgar scores were categorised to 3 groups (0-3) first which needs immediate medical intervention, second (4-6) needs medical assistance or monitoring, third group (7-10) no intervention [25].

Part B: Maternal information, specifically: age, and GA.

STATISTICAL ANALYSIS

SPSS, software version 22.0 was used for all data analysis, methods used included descriptive analysis, for calculation of; means and standard deviation for continuous variables. Inferential statistics, including Spearman correlation for relationships between continuous variables, were used. A p-value ≤0.05 was considered statistically significant. B-coefficient and Confidence Interval (CI) are for measuring strength and direction of correlation.

RESULTS

Maternal age ranged from 15 to 46 years, with a mean value of 26.7±6.9. The ages were grouped into six categories, and the highest percentage 60 (28.3%) was in the age group of 20-24 years. GA ranged between (<28-36) weeks with mean value (33±3.5) week, was divided to three groups. The highest value 139 (65.6%) was in the group (33-36) week [Table/Fig-1].

Categories of maternal age (years)	n (%)
≤19	25 (11.8)
20-24	60 (28.3)
25-29	53 (25)
30-34	41 (19.3)
35-39	24 (11.3)
≥40	9 (4.2)
Categories of Gestational Age (GA) (weeks)	
≤28	17 (8.0)
29-32	56 (26.4)
33-36	139 (65.6)

[Table/Fig-1]: Maternal parameter.

Blood glucose ranged between 20 to 240 mg/dL, with a mean value of 73.9±27.9 mg/dL. The samples were categorised into three groups. 179 (84.4%) of the neonates had normal random blood glucose levels. Birth weight of premature newborns mean value was 2.12±0.5 kg. It is categorised to 4 groups. LBW had highest percentage 63.7% [Table/Fig-2].

Categories of random blood glucose (mg/dL)		n (%)
Random blood sugar	≤47	24 (11.3)
	48-125	179 (84.4)
	>125	9 (4.2)
Categories of birth weight (kg)		
Extremely Low Birth Weight (ELBW) ≤0.99		4 (2.0)
Very Low Birth Weight (VLBW) 1.0-1.49		27 (12.7)
Low Birth Weight (LBW) 1.50-2.49		135 (63.7)
Normal ≥2.500		46 (21.6)

[Table/Fig-2]: Premature neonate parameter (Random Blood glucose and birth weight).

The health status indicators were available among 139 newborns. The majority of the subjects had normal levels of bilirubin, while majority had upper limit of PCV and correlate negatively with Apgar score at ten minutes. According to RR, HR and SpO_2 were normal in majority of premature. Apgar score ranged between (1-10) score and had been taken in the first five minutes and 10 minutes of delivery. The highest percentage 44.6% had moderate 4-6 scores taken in five minutes. Apgar scores at ten minutes were good scores in 84.2% and 12.2% of neonates scores was 0-3 taken in five minutes [Table/Fig-3].

Categories of indicators		F.+	%	r+	p-v+
Bilirubin	<5	64	46.0	0.048	0.66
	5-14	75	54.0		
PCV	<40	2	1.4	-0.28	0.008*
	40-60	49	35.3		
	>60	88	63.3		
RR	<40	20	14.4	0.029	0.76
	40-60	80	57.6		
	>60	39	28.0		
HR	<120	34	24.5	-0.11	0.28
	120-180	105	75.5		
	>180	0	0.0		
SpO_2	<90	34	24.5	0.035	0.7
	90-95	103	74.1		
	>95	2	1.4		
		5 minutes	10 minutes		
Apgar scores	0.-3	17 (12.2)	5 (3.6)	-	
	4-6	62 (44.6)	17 (12.2)		
	7-10	60 (43.2)	117 (84.2)		
	Total	139 (100)	139 (100)		

[Table/Fig-3]: Health status indicators of premature neonates and correlation of PCV with 10 min score of Apgar.
r+=Spearman correlation, p-v+=p-value

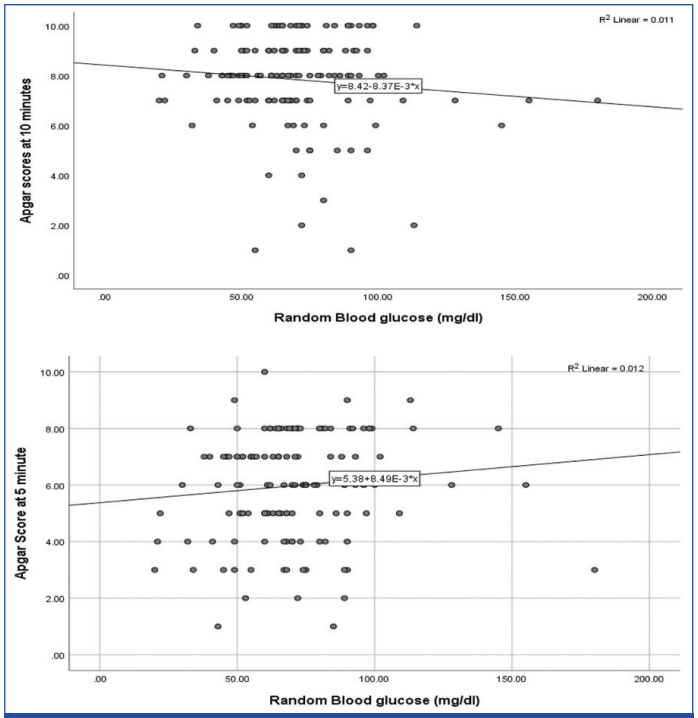
PCV correlation with Apgar score at ten minutes was assessed as they serve an indirect indicator of glucose homeostasis by reflecting a state of tissue hypoxia that accelerates systemic glucose consumption. We assessed the correlation for other health status indicator but the result was not significant.

Maternal age correlate negatively although non significantly with premature neonates blood glucose, while GA and birth weight were associated negatively significantly with blood glucose levels, there was decrease in GA and birth weight in high blood sugar levels. Scores of Apgar after 10 minutes of delivery correlate negatively with blood glucose levels and 10 minute high score decrease by increase of blood glucose level [Table/Fig-4].

Parameters of premature	Correlation r+	p-value	B-c+	95% CI
Maternal age	-0.115	0.096		
Gestational Ages (GA) (weeks)	-0.17	0.022*	-1.3	-2.5 to -0.196
Birth weight (Kg)	-0.17	0.014*	-8.5*	-14.3 to -2.7
10 minute score	-0.196	0.021*	OR=0.97	0.95-0.99
Apgar 5 min score	0.01	0.905		

[Table/Fig-4]: Correlation of blood glucose of premature neonates with maternal and neonates risk factors.
*significant, B-C+=B coefficient, r+=Spearman correlation, p-v+=p-value. OR: Odds ratio

While high blood glucose positively correlate with moderate scores at five minutes and negatively correlate with Apgar score at 10 minutes. The high portion of scores remained in the moderate range (4-6) scores at five minute [Table/Fig-5].



[Table/Fig-5]: Correlation between Random Blood glucose and Apgar Score at 5-Minute Scores (n=139).

DISCUSSION

Majority of premature neonates had normal blood glucose levels, which was consistent with the findings in previous study which concluded that during the first two hours after birth, only a small percentage of preterm infants (12.8%) were with hypoglycaemia and 1.4% with hyperglycaemia) exhibited glucose imbalances [26]. Also, the result of a study conducted in Erbil Maternity Teaching Hospital found that hypoglycaemia was 16.25% of neonates during the first three hours of life [13]. These results indicate that glucose disturbances were not a widespread among the sample and severe form may not be common in all preterm infants, especially when early feeding and close monitoring and management are implemented.

In present study, majority of women 53.3% were in young; age (20-29) year and correlated inversely with blood glucose. This result indicates that young age protects them from pregnancy complications like GDM [27] and their infant maintained normal or healthy high blood glucose levels. The risk for preterm delivery may be driven by limited access to prenatal care [12,27].

The high levels of glucose were found to increase for infants born at younger preterm ages. This result attributed to the immaturity of pancreatic beta cell and shortage of insulin and stress hormones. Literature found the highest blood glucose levels in the GA, less than 28 weeks [6,28]. Additionally, physiological stress as a result of immature organ systems can lead to increased production of stress hormones, such as cortisol, which elevate blood glucose levels [26,29].

LBW and increasing with high blood glucose indicates to limited glycogen and fat stores which affect their ability to produce glucose through gluconeogenesis, especially during periods of stress or illness when energy demands increase [30]. As a result, they may experience fluctuations in blood glucose levels leading to high level of glucose.

All health status indicates normal in majority as consequence of normal blood glucose except a high PCV which correlated negatively with Apgar at ten minutes. This indicates that the infant blood was thick with too many red blood cells, derived from stress-catecholamine link which cause hyperglycaemia and stimulate bone marrow to more production of red blood cell which affect blood flow in capillaries and hypoxia. A previous study reported that stress in preterm neonates cause block of insulin, and hyperglycaemia. This combined with thick blood and makes harder for the baby's body to circulate energy and stay stable [31].

Stabilising Apgar score among majority of preterm neonates at good score in ten minute suggest that preterm needs more than five minutes after birth for response to the environment. This conform to Zamir I findings who suggest that newborns take longer than five minutes to adapt [2]. Specifically, an Apgar score below six at the 5-minute and linked to an increased risk of neonatal hyperglycaemia.

A positive correlation between moderate Apgar scores (4-6) and high glucose levels, indicates to transitional physiological stress (hypoxia,

cold stress, separation from placenta) which enhance the release of catecholamines hormones and increasing blood glucose levels by encouraging the breakdown of glycogen and diminishing the effectiveness of insulin. It is consistence with previous studies, which indicates that decreased Apgar scores are associated with increased blood glucose levels as a key sign of neonatal stress [32].

However, this condition appears to be transient, as evidenced by the significant negative correlation between improved Apgar scores at 10 minutes and lower, blood glucose levels. This may be caused by diminished level of stress hormone (half-life is 1-2 minutes). A previous study reported that catecholamine hormone at five minutes reach their peak, causing a significant increase in blood glucose to provide energy for birth [3]. At 10 minutes, as neonatal stress subsides and counter regulatory hormone levels diminish, infants with improving Apgar scores exhibit a corresponding decrease in blood glucose levels [33].

Additionally, oxygen ventilation for infants who had bad and moderate scores initiated within the first one minute of life, after birth that shift the body from anaerobic to aerobic metabolism [34,35]. It is consistent with the findings of Sharma A et al., who reported that oxygen ventilation enables the infant to effectively "burn" and utilise the available glucose in the bloodstream for energy and decrease it [1]. Paulsen ME and Rao RB, point out that when ventilation normalises blood pH, and the cells in the infant become more sensitive to insulin [36].

The Key Finding

These results indicate that if the baby is approximately mature, their organs work well, their 10-minute Apgar score goes up, and they quickly clear that excess glucose out of their blood within one to two till 12 hours. But if the baby is immature or has a LBW <1.5 kg, their body cannot clear their blood glucose and remains high. Additionally, the percentage of neonates with good scores 84.2% at 10 minutes approximately matches the percentages of birth weight neonates >1.5 kg and normal blood glucose levels (84%) in present study.

Limitation(s)

1- The result cannot be generalised, because the samples were taken from one hospital;

2- Samples were taken from a medical record because the hospital did not allow entry to the intensive care unit and taking samples from the infant in intensive care. This led to the deletion of some samples due to missing information.

CONCLUSION(S)

Normal glucose levels were abundant. Low GA and birth weight increase high levels of glucose as a result of immaturity of organs, metabolic stress. Glucose homeostasis fluctuate and link to metabolic and stress change and they need more time to response to change in environment. This study indicates that antenatal care, early detection of blood glucose levels, and timely management via early feeding and oxygen ventilation are essential for preterm neonates to minimise glucose disturbances.

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