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Prevalence of Hypoglycemia and Hypocalcemia Among High-Risk Infants in the Neonatal Ward of Fatemieh Hospital of Hamadan in 2016 - 2017

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Abstract

Background: Hypoglycemia and hypocalcemia are common metabolic disorders in high-risk infants that may cause serious complications in case of late diagnosis.
Objectives: This study intended to determine the prevalence of hypoglycemia and hypocalcemia among high-risk infants.
Methods: A cross-sectional study was conducted on all the infants prone to hypoglycemia and hypocalcemia admitted to the neonatal ward of Fatemieh Hospital in Hamadan from September 2016 to October 2017. If infants' blood glucose was less than 40 mg/dL within the first four hours after birth and less than 45 mg/dL within 4 - 24 hours after birth, they were diagnosed with hypoglycemi. If their blood calcium was less than 7 and 8 mg/dL in preterm and full-term infants, respectively, within 12 - 24 hours after birth, they were diagnosed with hypocalcemia.
Results: A total of 883 infants participated in this study. The prevalence of hypoglycemia and hypocalcemia was 39.1% and 1.8%, respectively. The mean birth weight was 2124.1 ± 272.8 g, and the gestational age was 35 ± 1.88 weeks. Hypoglycemia had a significant relationship with preterm birth ($P = 0.002$), lower mean birth weight ($P = 0.001$), and low Apgar score at 1 and 5 minutes after birth ($P < 0.05$). Hypocalcemia had a significant relationship with small for gestational age (SGA) ($P = 0.007$), lower mean birth weight ($P = 0.025$), and low Apgar score at one and five minutes after birth ($P < 0.05$).
Conclusions: It is recommended to measure blood glucose and blood calcium in high-risk infants, including infants of diabetic mothers (IDMs), preterm infants, and infants with lower birth weight (LBW), SGA, and low Apgar score at one and five minutes after birth.

Keywords: Hypoglycemia, Hypocalcemia, Infants, Risk Factors

1. Background

Hypoglycemia is a common neonatal metabolic disorder that is more prevalent in high-risk infants including IDMs, Small for gestational age (SGA) infants, asphyxia, and preterm infants. Infants with hypoglycemia are often asymptomatic or have nonspecific symptoms that are difficult to diagnose.

The plasma glucose level in the umbilical vein consists of 80% of mothers' blood sugar. After cutting the umbilical cord, the transfer of glucose and other nutrients to the infant suddenly stops. Subsequently, glucose drops to its nadir level in infants within 1 - 3 hours after birth, however, it spontaneously increases and reaches a steady state 3 - 4 hours after birth (1-5).

Hypoglycemia may be considered a metabolic disorder associated with many severe neonatal diseases. Glycogen depletion, impaired gluconeogenesis, and increased peripheral use of glucose may also be among the risk factors for hypoglycemia. There is no consensus about the long-term complications caused by transient hypoglycemia. However, severe recurrent hypoglycemia may cause sustained neurological problems such as seizures and mental retardation (6-9).

Calcium is one of the body electrolytes that plays a

critical role in enzyme regulation, muscle contractions, nerve impulses and neural interactions, and metabolic activities. It is also an integral component of the skeletal system (10, 11). Infants may develop hypocalcemia in two forms, namely early-onset and late-onset hypocalcemia. Reduced serum calcium level within the first three days of birth is called early-onset hypocalcemia; if it lasts more than three days, it is referred to as late-onset hypocalcemia (12). The early-onset hypocalcemia is more common and its difference from the late-onset hypocalcemia lies with its etiology and treatment (13). Several factors affect neonatal hypocalcemia. The early-onset hypocalcemia is more prevalent in infants with intrauterine growth retardation or dystocia, IDMs, and preterm infants. Symptoms of neonatal hypocalcemia range from asymptomatic hypocalcemia to mimic symptoms of disseminated infections (14, 15). Hypocalcemia has got considerable importance since it lays the groundwork for many neonatal disorders and long-term complications including mental disability, academic failure, and physical disability (16-19).

2. Objectives

Therefore, the present study aims to determine the prevalence and risk factors of hypoglycemia and hypocalcemia in low birth weight (LBW) infants in order to prevent their consequences and reduce infant mortality by facilitating early diagnosis and treatment of these disorders.

3. Methods

A cross-sectional study was conducted on all the infants prone to hypoglycemia and hypocalcemia admitted to the neonatal ward of Fatemieh Hospital in Hamadan from September 2016 to October 2017. This study was conducted according to the 2011 AAP guidelines (20).

Inclusion criteria:

- Low-birth-weight infant (LBW): birth weight $\leq$ 2500 g.
- SGA infants: birth weight $\leq$ 10 percentile.
- IDMs: maternal diabetes mellitus or gestational diabetes mellitus.
- Late preterm infant (LPI): a premature infant born at a gestational age of 34 0/7 and 36 6/7 weeks.

Exclusion criteria:

- Healthy term infants.
- Infants with congenital malformations.
- Infants suffering from perinatal asphyxia.
- Infants who were not ready for enteral feeding in the first hour.
- Infants with sepsis.

The relative frequency and the risk factors for neonatal hypoglycemia and hypocalcemia, including weight, gender, Apgar score, and maternal diseases during pregnancy (e.g. diabetes mellitus), were examined. Data were collected using a registration form and infants' dossiers. The frequency of the intended risk factors affecting hypoglycemia and hypocalcemia was reported at the 95% level of confidence. A chi-square test was used to investigate the relationship between the variables. All statistical analyses were performed in SPSS V. 20 at the 0.05 level of significance ($P < 0.05$).

In this study, if infants' blood glucose was less than 40 mg/dL within the first 4 hours after birth and less than 45 mg/dL within 4 - 24 hours after birth, they were diagnosed with hypoglycemia; if their blood calcium was less than 7 and 8 mg/dL in preterm and full-term infants, respectively, within 12 - 24 hours after birth, they were diagnosed with hypocalcemia (6, 7).

Diabetes mellitus was diagnosed by reviewing mothers' dossiers. If the blood glucose of the mothers after 8 hours of overnight fasting, 1 and 2 hours after oral administration of 75 g of glucose solution (OGTT) was equal to or greater than 92, 180, and 153 mg/dL, respectively, they were diagnosed with gestational diabetes mellitus (GDM).

Preeclampsia (PE) is a disorder of pregnancy characterized by the onset of high blood pressure (defined as a BP $\geq$ 140 mmHg systolic and/or $\geq$ 90 mmHg diastolic, based on at least two measurements taken at least 4 hours apart) and often a significant amount of protein in the urine.

4. Results

A total of 883 infants participated in the study. The data showed that 441 participants (49.9%) were male and 595 of them (67.4%) were singleton-delivered. In addition, 798 infants (90.4%) were preterm and 726 of them (82.2%) were cesarean-delivered. The prevalence of diabetes mellitus and Pre-eclampsia (PE) among their mothers was 1.4% (12 cases) and 0.3% (3 cases), respectively. The mean (SD) infant weight was 2124.16 $\pm$ 272.80 g, one-minute Apgar score was 7.6 $\pm$ 1.18, five-minute Apgar score was 8.79 $\pm$ 0.93, blood glucose was 47.27 $\pm$ 24.05, blood calcium was 9.18 $\pm$ 2.8, and gestational age was 35 $\pm$ 1.88 weeks. The prevalence of hypocalcemia and hypoglycemia among the infants was 1.8% and 39.1%, respectively (Table 1).

The prevalence of hypocalcemia was 3% in male infants and 9% in female infants, indicating a significant difference ($P = 0.044$). Hypocalcemia was only observed in cesarean-delivered infants, but there was no significant difference between males and females in this regard ($P = 0.091$). There was no significant relationship between neonatal hypocalcemia and history of diabetes mellitus ($P = 0.802$) as well as between hypocalcemia and history of PE ($P = 0.947$). On the contrary, neonatal hypocalcemia had a

Table 1. Frequency Distribution of Demographic Features of the Infants Under Study

Variable	No. (%)
Number of offspring in pregnancy	
Singleton	595 (67.4)
Twin	257 (29.1)
Triplets	27 (3.1)
Quadruplets	4 (0.5)
Offspring	
First	734 (83.1)
Second	138 (15.6)
Third	10 (1.1)
Fourth	1 (0.1)
Sex	
Male	441 (49.9)
Female	442 (50.1)
SGA	
Yes	141 (16)
No	742 (84)
Preterm	
Yes	798 (90.4)
No	85 (9.6)
Hypocalcemia	
Yes	16 (1.8)
No	867 (98.2)
Hypoglycemia	
Yes	345 (39.1)
No	538 (60.9)
Total	883 (100)

Abbreviation: SGA, small for gestational age.

Table 2. Relationship Between Hypocalcemia and Intended Variables[a]

Variable	Hypocalcemia		P Value
	Yes, 16 (1.8)	No, 867 (98.2)	
Female	4 (25)	437 (50.4)	0.044[b]
Preterm	2 (12.5)	796 (91.8)	0.661[c]
Caesarean delivery	0 (0)	157 (18.1)	0.091[c]
Maternal diabetes	0 (0)	12 (1.4)	0.636[c]
Preeclampsia	0 (0)	3 (0.3)	0.814[c]
SGA	7 (43.8)	134 (15.5)	0.007[b]
Birth weight, g	1971.12 ± 339.60	2126.95 ± 270.86	0.025[d]
Apgar score at 1 minute	6.56 ± 1.67	7.56 ± 1.68	0.028[d]
Apgar score at 5 minutes	8.00 ± 1.03	8.81 ± 0.92	0.007[d]

[a]Values are expressed as No. (%) or mean ± SD.
[b]Chi-square test and significant.
[c]Chi-square test and not significant.
[d]Independent *t*-test and significant.

Table 3. Relationship Between Hypoglycemia and Intended Variables[a]

Variable	Hypoglycemia		P Value
	Yes, 345 (39.1)	No, 538 (60.9)	
Female	166 (48.1)	275 (51.1)	0.384[c]
Preterm	325 (94.2)	473 (87.9)	0.002[b]
Caesarean delivery	291 (84.3)	435 (80.9)	0.185[c]
Maternal diabetes	5 (1.4)	7 (1.3)	0.853[c]
Preeclampsia	1 (0.3)	3 (0.4)	0.838[c]
SGA	54 (15.7)	87 (16.2)	0.851[c]
Birth weight, g	2067.97 ± 308.13	2160.20 ± 240.99	< 0.001[d]
Apgar score at 1 minute	7.43 ± 1.22	7.64 ± 1.14	0.009[d]
Apgar score at 5 minutes	8.61 ± 1.08	8.91 ± 0.79	< 0.001[d]

[a]Values are expressed as No. (%) or mean ± SD.
[b]Chi-square test and significant.
[c]Chi-square test and not significant.
[d]Independent *t*-test and significant.

significant relationship with SGA (P = 0.007), lower mean birth weight (P = 0.025), and low Apgar score at 1 and 5 minutes after birth (P < 0.05) (Table 2).

The prevalence of hypoglycemia was 38% in female infants and 40% in male infants, indicating an insignificant difference (P = 0.384). There was no significant relationship between neonatal hypoglycemia and type of delivery (P = 0.185), history of diabetes mellitus (P = 0.853), history of PE (P = 0.838), and SGA (P = 0.851). On the contrary, neonatal hypoglycemia exhibited a significant relationship with preterm birth (P = 0.002), lower mean birth weight (P = 0.001), and low Apgar score at 1 and 5 minutes after birth (P < 0.05) (Table 3).

According to Table 4, which shows the effect of variables on hypoglycemia based on logistic regression analysis, it can be concluded that preterm labor and birth weight had substantial effects on hypoglycemia, regardless of the effect of other variables.

5. Discussion

The prevalence of hypoglycemia in high-risk infants was 39.1%, which was higher than the results of the studies conducted by Hosagasi et al. (17.8%) and Stark et al. (27%) (21, 22), however, it was almost similar to the figure obtained

Table 4. Effect of Intended Variables on Hypoglycemia Based on Logistic Regression Analysis

Variable	Regression Coefficient	Standard Error	Odds Ratio	Wald Test Value	P Value
Intercept	2.31	0.68	10.07	11.4	0.001
Diabetes	0.056	0.6	1.06	0.009	0.926
Preterm	0.627	0.33	1.87	3.53	0.016
SGA	0.05	0.25	1.05	0.038	0.845
Vaginal delivery	-0.127	0.194	0.88	0.425	0.514
Apgar score at 1 minute	-0.064	0.063	0.93	1	0.317
Birth weight, g	-0.001	0.00003	0.99	12.74	< 0.001

Abbreviation: SGA, small for gestational age.

by Thinesh Kumar et al. (33.3%) (23). The prevalence of hypoglycemia varies depending on the definition of hypoglycemia, the feeding status, and the timing of blood glucose measurement in different studies (21).

The study results indicated that the mean birth weight of hypoglycemic infants was lower than healthy infants. In this regard, Singh et al. and Thornton et al. found that the prevalence of hypoglycemia was higher in LBW infants (24, 25). There is a direct relationship between blood glucose level and low birth weight, which is due to low glycogen storage and the relatively high prevalence of other factors that contributes to hypoglycemia in such infants.

There was no significant difference between male and female infants in terms of the prevalence of hypoglycemia in this study. However, Singh et al. found that hypoglycemia was more prevalent in male infants (24). Sadi-Nezhad indicated that the prevalence of hypoglycemia in male infants hospitalized with the initial diagnosis of sepsis was seven times higher than in female ones, whereas it has been mentioned to be twofold in reference books (26).

The study findings also demonstrated that there was no significant difference between IDMs and infants of non-diabetic mothers in the prevalence of hypoglycemia. This is consistent with the results of Hernandez-Herrera et al. (27) but inconsistent with the findings of Ramos et al. (28). Early diagnosis and treatment of gestational diabetes can prevent the incidence of macrosomia, hypoglycemia, and hypocalcemia in these infants.

Based on the study findings, there was no significant difference between SGA infants and non-SGA infants in terms of the prevalence of hypoglycemia. In contrast, Singh et al. found that hypoglycemia was more prevalent in SGA infants (24). However, an increase in the prevalence of hypoglycemia in SGA infants may be due to the decreased liver glycogen stores, discrepancy in the size of the utilizer (brain) and provider (liver glycogen) of glucose, impaired gluconeogenesis, and hyperinsulinism in these infants that lead to hypoglycemia (29).

Hypoglycemic infants gained lower mean Apgar scores at 1 and 5 minutes after birth. The difference between their one-minute and five-minute Apgar scores was statistically significant. Yoon et al. reported that a low Apgar score at 1 and 5 minutes after birth was a risk factor for neonatal hypoglycemia; hypoglycemic infants had lower mean Apgar scores (30).

The results demonstrated that there was a significant difference between preterm and full-term infants in the prevalence of hypoglycemia. Hossein-Nezhad et al. and Singh et al., respectively, found that about 34.3% and 19.5% of infants were preterm (24, 31) due to liver glycogen depletion.

The results also showed that hypocalcemia was significantly more prevalent in male infants than females. Behjati et al. reported that gender had no significant effect on the prevalence of early-onset and late-onset hypocalcemia (32). On the contrary, Thomas et al. introduced gender as a risk factor affecting the prevalence of hypocalcemia and found that transient hypocalcemia was more prevalent among male infants (12).

In this study, one-minute and five-minute Apgar scores were significantly lower in infants with hypocalcemia than healthy infants. Khalesi et al. and Jain et al. found that hypocalcemia was more prevalent in infants with an Apgar score lower than five (33, 34). Asphyxia and low Apgar score can reduce the absorption of calcium and oral intake while increasing endogenous phosphorus and concentration of serum calcitonin. This subsequently increases the likelihood of neonatal hypocalcemia. In infants with asphyxia, the response of parathyroid hormone (PTH) to hypocalcemia decreases.

In this study, hypocalcemia was significantly more prevalent in SGA infants than non-SGA infants, and according to the results, the birth weight of infants with hypocalcemia was significantly lower than healthy infants. Blaga et al. found that hypocalcemia was more prevalent in infants with severe SGA and a birth weight of 2500 g or less

(35).

The results indicated that all of the infants of non-diabetic mothers developed hypocalcemia. However, there was no significant difference between IDMs and infants of non-diabetic mothers in the prevalence of hypocalcemia. Jain et al. and Abdul Tawab et al. reported that hypocalcemia was more prevalent in IDMs (34, 36). Behjati et al. found that gestational diabetes, along with insulin intake, significantly increased the relative prevalence of hypocalcemia in hospitalized infants (32). Early-onset hypocalcemia occurred in 50% of the infants of non-insulin dependent diabetic mothers. It is assumed that hypocalcemia in patients with non-insulin dependent diabetes is associated with hypomagnesemia. Urinary magnesium depletion in diabetic mothers is followed by magnesium deficiency in fetuses and results in secondary hypoparathyroidism in the fetus and the infant.

Furthermore, neonatal hypocalcemia was only observed in cesarean-delivered infants; none of the vaginal-delivered infants had hypocalcemia, indicating a significant difference. Khalesi et al. reported that about 63% of infants were delivered by cesarean, however, there was no significant relationship between the delivery type and hypocalcemia (33).

5.1. Conclusions

Hypoglycemia and hypocalcemia are more prevalent in high-risk infants; therefore, early diagnosis and treatment can prevent the occurrence of their serious complications. Consequently, it is recommended to measure blood glucose and blood calcium in high-risk infants, including IDMs, preterm infants, and infants with LBW, SGA, and low Apgar score at one and five minutes after birth.

Supplementary Material

Supplementary material(s) is available here [To read supplementary materials, please refer to the journal website and open PDF/HTML].

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Footnotes

Authors' Contribution: Mohammad Kazem Sabzehei and Marzeyeh Otogara designed and coordinated the study and participated in most of the experiments. Samira Ahmadi, Fariba Daneshvar, Maryam Shabani, Saeedeh Samavati, Someyeh Hosseinirad, and Nasrin Shirmohammadi-Khorram coordinated and carried out all the experiments, analyzed the data, and participated in manuscript preparation. All authors read and approved the content of the manuscript.

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