

Neonatal Glycemic Status of Infants of Diabetic Mothers in a Tertiary Care Hospital

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Abstract

Background: Diabetes is a common medical complication during pregnancy that results in significant neonatal morbidities. In infants of diabetic mothers (IDMs), hypoglycemia is a common complication. **Objective:** To study the neonatal hypoglycemia in IDMs in a tertiary care hospital. **Settings and Design:** A cross-sectional study was done in postnatal ward in Bangladesh Institute of Research and Rehabilitation in Diabetic, Endocrine and Metabolic Disorders from January to December 2009. **Subjects and Methods:** The data of IDMs were collected from postnatal ward. All IDMs delivered during this period staying in postnatal ward were included in this study. The outcomes were compared between the hypoglycemic and normoglycemic IDMs and between gestational diabetes mellitus (GDM) and pre-GDM in hypoglycemic group using Chi-square test and Fisher's exact test. The data analysis was performed with Epi-info7 software. Statistical significance was set at $P < 0.05$. **Results:** A total of 363 IDMs were included in this study. Hypoglycemia developed in 38.3% IDMs and 43.2% mothers of hypoglycemic IDMs had GDM and 56.8% had pre-GDM. Duration of maternal diabetes ($P = 0.04$) and large for gestational age ($P = 0.0001$) were associated with hypoglycemia. Multigravidae (82.2% vs 68.3%, $P = 0.03$), prolonged duration of maternal diabetes (45.46 weeks vs 3.23 weeks, $P = 0.00001$), preterm babies (48.1% vs 28.3% $P = 0.009$), and control of diabetes by insulin (81% vs 46.7%, $P = 0.001$) were more in pre-GDM, and statistically significant. About 85% IDMs developed hypoglycemia within 6 h of birth (P -value 0.00001) and majority (68%) were at 2 h of age. Forty percent of hypoglycemic IDMs from postnatal ward were admitted in special care baby unit. **Conclusion:** Hypoglycemia observed in 38.3% IDMs and developed within 6 h of age and maximum were at 2 h. Early recognition and appropriate intervention are needed in IDMs.

Keywords: Gestational diabetes mellitus, hypoglycemia, infants of diabetic mothers, pre-gestational diabetes mellitus

INTRODUCTION

Diabetes is a common medical complication in pregnancy. The prevalence of diabetes mellitus (DM) in pregnancy ranges from 1 to 14%.^[1] It may be pre-gestational diabetes mellitus (pre-GDM) or may be gestational diabetes mellitus (GDM).^[2] The World Health Organization (WHO) has predicted that between 1995 and 2025, there will be a 35% increase in the worldwide prevalence of diabetes.^[3] Moreover, women born in Asian countries shows the highest prevalence of GDM, with up to 17% of women likely to develop GDM.^[4,5] As the incidence of diabetes continues to rise and increasingly affects individuals of all ages, including young adults and children, women of childbearing age are at increased risk of diabetes during pregnancy. The prevalence of diabetes in Bangladesh is 8.1% in urban and 2.3% in rural area.^[6] The prevalence of GDM in urban Bangladeshi population is about 7.5%.^[7]

Glucose is essential for normal brain cell function. Normal blood glucose (BG) levels in the newborn period ensure proper neurological development.^[8] Therefore early detection of hypoglycemia in neonate at risk is of utmost value to prevent the complication arising from neonatal hypoglycemia.^[9] Various factors influence newborn BG concentrations even in healthy term newborns, such as birth weight, gestational age, presence or absence of disease, perinatal complications, mode of delivery, and feeding behavior.^[10] Most IDMs are prone to hypoglycemia during the first postnatal hours.^[5] The incidence of hypoglycemia is highest at 1–4 h of age when there is fall in plasma glucose, following the cessation of maternal glucose infusion.^[11,12]

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Access this article online

Quick Response Code:



Website:
www.ijem.in

DOI:
10.4103/ijem.IJEM_689_17

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How to cite this article: Begum S, Dey SK, Fatema K. Neonatal glycemic status of infants of diabetic mothers in a tertiary care hospital. Indian J Endocr Metab 2018;22:621-6.

Uncontrolled maternal glycaemia causes neonatal hypoglycaemia as well as transient hyperinsulinemia.^[13] *In utero*, maternal hyperglycaemia increases placental glucose transport and results in fetal hyperglycaemia, which stimulates fetal pancreatic insulin production. After delivery, maternal glucose supply ceases even though newborn insulin production continues and results in hypoglycaemia. Hypoglycaemia may continue for 24–72 h until insulin secretion returns to normal.^[14] Newborn glucose levels fall to a low point in the first 1–2 h of life and then increased and stabilize gradually. It is clear that the IDM must be screened carefully in the early hours of life for this possible complication.^[15]

High insulin, low glucagon, and epinephrine were observed in IDMs. As a consequence of this abnormal hormone profile, endogenous glucose production is significantly inhibited compared with that in normal infants, thus predisposing them to hypoglycaemia.^[16] Neonatal hypoglycaemia is associated with poor neurological outcome. To ensure normal neural function in infants irrespective of the presence or absence of abnormal clinical signs, BG should be maintained within normal limit. Rapid diagnosis and prompt management of patients with hypoglycaemia is essential so that brain damage is to be avoided.^[17]

The present study attempts to assess the BG levels in IDMs to observe frequency of hypoglycaemia in IDMs and factors influencing it. The results of this study may broaden our knowledge with regard to BG assessment and its risk factor in IDMs.

MATERIALS AND METHODS

A cross-sectional study was done in postnatal ward in Bangladesh Institute of Research and Rehabilitation in Diabetic, Endocrine, and Metabolic Disorders (BIRDEM) from January to December 2009. BIRDEM is a tertiary care hospital, serves diabetic and other endocrine patients, so majority neonates are IDMs. Approval from Ethical Committee was obtained and written informed consent for the study was taken from all the patients. The data of IDMs were collected from postnatal ward. The infants were subjected to glucose estimation at predetermined intervals as per protocol. All IDMs delivered during this period staying in postnatal ward were included in this study. IDMs with very low birth weight (LBW), extremely LBW, birth asphyxia, respiratory distress, sepsis, congenital anomalies, and those admitted in special care baby unit (SCABU) after birth due to any other reasons were excluded from this study.

IDMs is a term used to refer to infants born to mothers with either pre-GDM or GDM. For the study purpose hypoglycaemia was defined as blood sugar <2.6 mmol/l. Blood sugar was estimated by glucometer at 0, 2, 4, 6, 8, 12, 18, and 24 h of life. All IDMs were fed by milk initially. Those developed hypoglycaemia were managed by standard protocol. GDM has been defined as onset of glucose intolerance during pregnancy. Pre-GDM was defined as onset of glucose intolerance before

pregnancy. According to WHO criteria, diagnosis of GDM was made if there was at least one (5.1, 10, and 8.5 mmol/l for fasting, 1-h, and 2-h plasma glucose concentration, respectively) abnormal value after a 75 g oral glucose tolerance test.

Bed-side BG was measured by On-Call Plus BG meter, where whole BG concentration was measured through a quantitative amperometric assay (glucose oxidase). The On-Call Plus BG monitoring system is an electrochemical enzymatic assay for the quantitative detection of glucose in capillary whole blood. It was one-touch ultrablood glucose monitoring system (K002134) similarities measurement that range from 20 to 600 mg/dl (1.1–33.3 mmol/l).

IDMs who developed hypoglycaemia at any time during the first 24 h of age were included in hypoglycemic IDMs and who did not develop hypoglycaemia during the first 24 h were included in normoglycemic IDMs. Mother of hypoglycemic IDMs was categorized into GDM and pre-GDM according to onset of DM.

Statistical Analysis

The data analysis was performed with Epi Info 7 software (Atlanta, Georgia). Statistical significance was set at $P < 0.05$. The outcomes were compared between the hypoglycemic and normoglycemic IDMs and between GDM and pre-GDM in hypoglycemic group using Chi-square test and Fisher's exact test.

RESULTS

In this study IDMs were 363, hypoglycaemia developed in 139 (38.3%) IDMs. There was no significant different maternal demographical characteristics between hypoglycemic and normoglycemic IDMs. In majority of cases, age of the mothers was between 21 and 40 years and multigravidae. Maternal antenatal problems such as hypertension, pregnancy-induced hypertension (PIH), and preeclamptic toxemia (PET) and obstetrical complications such as abortion, intrauterine death (IUD), and neonatal death were equal in both normoglycemic and hypoglycemic group.

Duration of maternal diabetes was 1–216 (mean 27.1 ± 33.44) months in hypoglycemic group and 1–156 (mean 21.3 ± 27.83) months in normoglycemic group ($P = 0.04$). Control of maternal diabetes during pregnancy by diet were 33.8 and 66.2% and by drug (Inj. insulin) in 40.2 and 59.8% in hypoglycemic and normoglycemic groups, respectively ($P = 0.11$) [Table 1].

Demographical characteristics of IDMs between hypoglycemic and normoglycemic group were not different significantly. About 96% babies were delivered by cesarean section, mean gestational age was about 36.5 weeks in each group, and male and female ratio was 1:1. Birth weight was 2792 ± 537.33 g in hypoglycemic group and 2906 ± 591.75 g in normoglycemic group; term babies were more than preterm in both groups; and more than 86% baby's birth weight was normal in both groups. Appropriate for gestational

age (AGA) was more (79% vs 58.2%) in normoglycemic group, and hypoglycemia developed more in large for gestational age (LGA) (28.1% vs 12.1%, *P* value = 0.0001) and statistically significant [Table 2].

Types of maternal diabetes in hypoglycemic group were GDM in 43.2% and pre-GDM 56.8% cases. Hypoglycemia was more in infants of multigravidae in pre-GDM group (82.2% vs 68.2%) and infants of primigravidae in GDM group (31.7% vs 17.7%) and statistically significant (*P* = 0.03). Maternal complications such as HTN, PIH, and PET were observed in 8.3, 11.7, and 1.7% in GDM and 10.1, 3.8, and 3.8% in pre-GDM, respectively, but *P* value was not significant. Obstetrical complications such as abortion (20% vs 24%), IUD (10% vs 7.6%), and neonatal death (6.7 vs 11.4%) were not statistically significant between two groups.

Duration of maternal diabetes was 1–12 (mean 3.23 ± 2.13) months in GDM and 11–216 (mean 45.46 ± 34.65) months in pre-GDM, which was statistically significant (0.00001). Control of maternal diabetes during pregnancy with diet was more in GDM (53.3% vs 19%) and Inj. insulin was needed more in pre-GDM (81% vs 46.7%). *P* value was 0.001 [Table 3].

About 96% babies were delivered by cesarean section in GDM and pre-GDM group. Male and female babies were equal in both groups. Gestational age was about 36.5 weeks in each group, mean birth weight was 3021.47 ± 568.04 in GDM group, and 2934.86 ± 513.30 in pre-GDM group. Hypoglycemia was significantly higher in preterm in pre-GDM group (48.1% vs 28.3%) and in term in GDM group (71.7% vs 51.9%) and statistically significant (*P* = 0.009). Hypoglycemia was more in normal birth weight than LBW in both groups. Hypoglycemia was observed in 76.7% and 81% in AGA and 23.3% and 18.9% in LGA in GDM group and pre-GDM group, respectively (*P* = 0.32) [Table 4].

Hypoglycemia developed within 6 h of birth in 85.6% of IDMs (*P*-value = 0.00001). Hypoglycemia developed more at 2 h (92 cases), 4 h (59 cases), and 6 h (23 cases) than 0 h (9 cases), 8 h (14 cases), 12 h (17 cases), 18 h (8 cases), and 24 h (5 cases) of age. Most of the IDM developed hypoglycemia at 2–6 hours of age. Age of development of hypoglycemia were not much different between GDM and pre-GDM group [Table 5]. In this study, 56 (40.3%) hypoglycemic IDMs were admitted in SCABU.

DISCUSSION

Neonatal hypoglycemia occurs in IDMs with impaired gluconeogenesis, brought about by excess insulin production, an inadequate substrate supply, decreased glucagon, and catecholamine secretion, which suggests altered counter-regulatory hormone production.^[18-20]

Pedersen’s hypothesis states that maternal hyperglycemia leads to fetal hyperglycemia, which leads to overstimulation

Table 1: Characteristics of mothers in relation to hypoglycemic and normoglycemic IDMs

	Hypoglycemia (n=139)	Normoglycemia (n=224)	<i>P</i>
Maternal age (years)			
≤20	3 (2.2)	5 (2.2)	0.30
21-30	72 (51.8)	140 (62.5)	
31-40	62 (44.6)	78 (34.8)	
>40	2 (1.4)	1 (0.4)	
Gravidae (%)			
Multi	106 (76.3)	177 (79)	0.26
Primi	33 (23.7)	47 (21)	
Antenatal problems (%)			
Hypertension	13 (9.3)	22 (9.8)	0.44
PIH	10 (7.2)	24 (10.7)	0.13
PET	3 (2.2)	5 (2.2)	0.63
Obstetrical complications (%)			
Abortion	31 (22.3)	46 (17.9)	0.34
IUD	12 (8.6)	18 (8.0)	0.41
Neonatal death	13 (9.3)	22 (9.8)	0.44
Duration of diabetes			
Months	1-216	1-156	0.04
Mean (months±SD)	27.1±33.44	21.3±27.83	
Control diabetes			
Diet	47 (33.8)	90 (40.2)	0.11
Drug	92 (66.2)	134 (59.8)	

PIH: Pregnancy-induced hypertension, PET: Preeclamptic toxemia, IUD: Intrauterine death

Table 2: Characteristics of infants in relation to hypoglycemic and normoglycemic IDM

	Hypoglycemia (n=139)	Normoglycemia (n=224)	<i>P</i>
Mode of delivery (%)			
Cesarean section	134 (96.4)	208 (92.9)	0.08
Normal delivery	5 (3.6)	16 (7.1)	
Sex (%)			
Male	69 (49.6)	109 (48.7)	0.47
Female	70 (50.4)	115 (51.3)	
Gestational age (wks±SD)	36.79 (±1.07)	36.59 (±1.37)	0.14
Birth wt (gram±SD)	2792 (±537.33)	2906 (±591.75)	0.28
Gestational period (%)			
Preterm	55 (39.6)	81 (36.2)	0.25
Term	84 (60.4)	143 (63.8)	
Birth weight (%)			
Normal	120 (86.3)	192 (85.7)	0.28
LBW	19 (13.7)	32 (14.3)	
AGA	100 (71.9)	197 (87.9)	0.0001
LGA	39 (28.1)	27 (12.05)	

LBW: Low birth weight, AGA: Appropriate for gestational age, LGA: Large for gestational age

of the islet cells of the fetal pancreas and to secondary fetal hyperinsulinism. So the IDMs are at significant risk for the development of hypoglycemia.^[21]

Table 3: Characteristics of mothers in relation to type of maternal diabetes

	GDM (n=60)	Pre-GDM (n=79)	P
Maternal age (years)			
≤20	2 (3.3)	1 (1.3)	0.30
21-30	35 (58.3)	37 (46.8)	
31-40	22 (36.7)	40 (50.6)	
>40	1 (1.7)	1 (1.3)	
Gravidae (%)			
Multi	41 (68.3)	65 (82.3)	0.03
Primi	19 (31.7)	14 (17.7)	
Antenatal problems (%)			
Hypertension	5 (8.3)	8 (10.1)	0.36
PIH	7 (11.7)	3 (3.8)	0.07
PET	1 (1.7)	3 (3.8)	0.41
Obstetrical complications (%)			
Abortion	12 (20)	19 (24)	0.29
IUD	6 (10)	6 (7.6)	0.31
Neonatal death	4 (6.7)	9 (11.4)	0.18
Duration of diabetes			
Months	1-12	11-216	0.00001
Mean (months±SD)	3.23±2.1342	45.46±34.6559	
Control diabetes			
Die	32 (53.3)	15 (19)	0.001
Drug	28 (46.7)	64 (81)	

GDM: Gestational diabetes mellitus, Pre-GDM: Pre-gestational diabetes mellitus, PIH: Pregnancy-induced hypertension, PET: Preeclampsia toxemia, IUD: Intrauterine death

Table 4: Characteristics of Infants in relation to type of maternal diabetes

	GDM (n=60)	Pre-GDM (n=79)	P
Mode of delivery (%)			
Cesarean section	58 (96.7)	76 (96.2)	0.45
Normal delivery	2 (3.3)	3 (3.8)	
Sex (%)			
Male	30 (50)	39 (49.4)	0.47
Female	30 (50)	40 (50.6)	
Gestational age (wks±SD)	36.97 (±1.32)	36.66 (±0.81)	0.14
Birth wt (gram±SD)	3021.47 (±568.04)	2934.86 (±513.30)	0.34
Gestational period (%)			
Preterm	17 (28.3)	38 (48.1)	0.009
Term	43 (71.7)	41 (51.9)	
Birth weight (%)			
Normal	50 (83.3)	70 (88.6)	0.36
LBW	10 (16.7)	9 (11.4)	
AGA	46 (76.7)	64 (81.01)	0.75
LGA	14 (23.3)	15 (18.99)	
Admission 56 (40.3)	27 (45.0)	29 (36.7)	0.32

GDM: Gestational diabetes mellitus, Pre-GDM: Pre-gestational diabetes mellitus, LBW: Low birth weight, AGA: Appropriate for gestational age, LGA: Large for gestational age

Of the 363 IDMs, hypoglycemia developed in 38.3% in this study and hypoglycemia was observed in 25–48% in different studies.^[21-23]

Demographic characteristics of mother and IDMs were similar in hypoglycemic and normoglycemic groups except duration of maternal diabetes (27.1 vs 21.3 months, $P = 0.04$) and LGA [(28.1% vs 12.1%, P value = 0.0001)], which were more in hypoglycemic group. Hypoglycemic infants had significantly higher birth weight and longer duration of DM, reported by Agarwal also.^[23] Up to 50% of IDMs developed significant hypoglycemia after birth observed by Kicklighter. Hypoglycemia is more common in macrosomic IDMs than in IDMs who are of appropriate size for gestational age.^[24] Neonatal hypoglycemia in the macrosomic IDM primarily is caused by a combination of hyperinsulinemia secondary to pancreatic islet cell hyperplasia and removal of the exogenous (maternal) glucose source at the time of delivery. During pregnancy, elevated maternal serum glucose results in elevated fetal serum glucose because insulin does not cross the placenta.^[24,25]

About 43.2% infants of GDM and 56.8% infants of pre-GDM developed hypoglycemia in our study. Carlow showed 15–25% of infants of GDM and 20–25% of infants of pre-GDM developed hypoglycemia. Hypoglycemia was more in infants of pre-GDM, which was similar to our study.^[26] In mothers of pre-GDM, glyceamic control were better than mothers of GDM group, as they had experience to control diabetes.

Hypoglycemia was more in infants of multigravidae, which were more in pre-GDM than GDM and statistically significant (82.2% vs 68.3%, P value 0.03). Obstetrical complications such as abortion (61.3%), neonatal death (69.2%), and maternal antenatal complications such as HTN (61.5%) and PET (75%) were more in pre-GDM but not statistically significant. Prolonged duration of diabetes in mother (45.46 weeks vs 3.23 weeks, P value = 0.00001) and control of diabetes in mother by Inj. insulin (81% vs 46.7%, $P = 0.001$) was more in pre-GDM and statistically significant. Hypoglycemia was significantly higher in term infants of GDM (71.7% vs 51.9%, $P = 0.009$) and in preterm infants of pre-GDM (48.1% vs 28.3%, $P = 0.009$) and statistically significant. This was our observation in this study.

In 85.6% IDMs developed hypoglycemia within 6 h of birth (P -value = 0.00001) and majority (66.2%) were at 2 h of age. Agarwal found 47% infants developed hypoglycemia during the first 2 h of life in his study.^[23] After birth plasma glucose fall in all infants, the nadir being reached in IDMs in first 1–4 hours of life and recovery may begin 4–6 hours, reported by Agrawal, Hawdon, and Robert.^[23,27,28] Forty percent hypoglycemic IDMs were admitted in SCABU in this study. In IDMs when BG was <1.7 mmol/l in any time and/or symptomatic, IDMs were admitted in SCABU and BG was 1.7 to <2.6 mmol/l after oral feeding patients were managed in postnatal ward. Serum glucose levels should be checked and early initiation of feedings is highly recommended. Low BG levels during the first few hours of life can be prevented or treated with early and frequent oral

Table 5: Blood glucose in mmol/l in different group

Hours	Hypoglycemic group	GDM group	Pre-DM group	P
	No. (%) BG mmol/l±SD	No. (%) BG mmol/l±SD	No. (%) BG mmol/l±SD	
0 h	9 (6.4) 1-10.8±1.9	4 (6.67) 1.1-10.5±2.1	5 (6.3) 1-10.8±1.9	0.44
2 h	92 (66.2) 0.8-72±1.07	41 (68.3) 1-5.9±1.06	51 (64.6) 0.8-7.2±1.09	0.61
4 h	59 (42.4) 1.2-5.6±0.57	32 (53.3) 1.2-5.6±0.76	27 (34.2) 1.2-5.3±0.79	0.67
6 h	23 (16.5) 1.3-5.6±0.66	8 (13.3) 1.3-5.6±0.61	15 (18.9) 1.3-5.3±0.70	0.35
8 h	14 (10.1) 1.4-7.6±0.76	5 (8.3) 1.5-6.6±0.78	4 (5.1) 1.4-4.8±0.61	0.43
12 h	17 (12.2) 1.1-9.3±0.96	10 (16.7) 1.1-9.3±1.21	7 (8.9) 1.5-5.3±0.72	0.51
18 h	8 (5.8) 1.2-5.9±0.71	2 (3.3) 2.3-5.9±0.68	6 (7.6) 1.2-5.3±0.73	0.77
24 h	5 (3.6) 1.2-8.8±0.84	2 (3.3) 1.8-8.8±0.69	3 (3.8) 1.2-8.8±0.95	0.80

GDM: Gestational diabetes mellitus, Pre-GDM: Pre-gestational diabetes mellitus

feeding. In our study 46% hypoglycemic IDMs were admitted in SCABU. A large number of hypoglycemic IDMs were admitted because BG was <1.7 mmol/l within 24 h of life, symptomatic hypoglycemia and to ensure feeding with BG 1.7 to <2.6 mmol/l.

Neonatal hypoglycemia is associated with poor neurological outcome. Evidence suggests that BG should be maintained ≥ 2.6 mmol/l to ensure normal neural function in infants irrespective of the presence or absence of abnormal clinical signs.^[8]

What does study adds?

Regular monitoring of BG within first 24 h according to protocol in IDMs helps early recognition and appropriate intervention of hypoglycemia. A large number of IDMs developed hypoglycemia within 6 h in this study.

Limitation

The study population was selected from single-center and sample size was limited. Further study may be undertaken from multiple centers with large sample size.

CONCLUSION

Hypoglycemia is a common problem in IDMs. A significant number of IDMs developed hypoglycemia in postnatal ward. Majority of IDMs developed hypoglycemia within 6 h of age and most of them were at 2 h of age. Duration of diabetes in mother and LGA babies were related to hypoglycemia in IDMs. Multigravidae, prolonged duration of maternal diabetes, preterm, and control of maternal diabetes with insulin were associated with hypoglycemia in infants of pre-GDM. To assure, early recognition and appropriate intervention are needed in IDMs.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Acknowledgements

The author would like to thank all the participants who cooperated with this study.

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