



Original Article

Glucose and Calcium Profile in Infants of Diabetic and Nondiabetic mothers- A Comparative Study

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Abstract

Background: Diabetes is one of the commonest and most important metabolic disorders that affect the health of pregnant women and infants. Diabetic mellitus is one of the most common metabolic disorders complicating pregnancy. The neonatal mortality rate is over five times that of nondiabetic mothers and is higher irrespective of birth weight and gestational age. There has been significant improvement in the outcome of diabetic pregnancies largely due to better metabolic control before and during pregnancy and vigorous neonatal care in developed countries. The management in our country still poses a major challenge.

Methods: This case-control study was designed to find out the association between an infant's hypoglycemia and hypocalcemia with maternal diabetes. For the research, a total of 300 neonates were selected, where cases were selected from infants of diabetic mothers, and the control group was selected from infants of nondiabetic mothers. The mothers were interviewed by specific questionnaire, selected neonates were examined, and some biochemical tests were done to find out the outcome.

Results: The study included 300 neonates of diabetic and nondiabetic mothers. The mean age of the Mothers of these neonates was 25.36 (SD±5.50) years. Among diabetic mothers 115(76%) had GDM and 36(23.8%) had PGDM. It is revealed that 83 (55%) of 150 mothers took insulin as the treatment. Hypoglycemia in neonates of diabetic and nondiabetic mothers right after birth at their first ½ hour of age 111 (37%). Hypoglycemia was found in 94 (62.3%) of infants of the diabetic mother than only 17(11.4%) in infants of the nondiabetic mother. Where the p-value is <0.001, which explains developing hypoglycemia in the infant of a diabetic mother is higher than nondiabetic mother. The number of hypocalcemic infants of the diabetic mother was 34 (22.5%), while hypocalcemic infants of the nondiabetic mother were only 8 (5.4%), which is significantly (p-value <0.001) lower.

Conclusions: Hypoglycemia and hypocalcemia in infants were directly associated with the presence of diabetes during pregnancy. In spite of intensive management of maternal diabetes, the infants of diabetic mothers continue to be a high-risk population. Among the pregnancies complicated by diabetes, GDM continues to have a major contribution. Hypoglycemia remains the most common biochemical abnormality, followed by hypocalcemia. Therefore, this pregnancy complication will require increased re- sources to manage appropriate glycemic control during pregnancy and reduce adverse perinatal outcomes.

KeyWords: Hypoglycemia, Hypocalcemia, GDM (Gestational Diabetes Mellitus), Neonatal mortality, PGDM (Pregestational Diabetes Mellitus).

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Introduction

Diabetic mellitus is the most common metabolic disorder complicating pregnancy.¹ About 1-14% of all pregnancies are complicated by diabetes mellitus, and 90% of them are gestational diabetes mellitus (GDM).² The precise mechanisms

underlying gestational diabetes remain unknown. Diabetes has long been associated with maternal and perinatal morbidity and mortality.³ The neonatal mortality rate is over five times that of nondiabetic mothers and is higher at all gestational ages and in every birth weight for the gestational

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age category.⁴ The potential morbidities in the infant of a diabetic mother are hypoglycemia, hypocalcemia, congenital anomalies, birth injury, asphyxia, respiratory distress syndrome, growth restriction, polycythemia, and hyperbilirubinemia. Hypoglycemia is seen in 25-40% of babies born to diabetic mothers.^{5,6} Diabetes mellitus is prevalent among 2.1% people of Bangladesh.⁷ Gestational diabetes mellitus (GDM) develops among 6.7% of all pregnancies in our population.⁸ In the western world, 2 to 3% of all pregnancies are currently being diagnosed as GDM.⁹ Infants of diabetic mothers have a 47% risk of significant hypoglycemia and 22% risk of hypocalcemia.¹⁰ Among the various metabolic errors these infants suffer, hypoglycemia is the commonest and most dangerous. Infants of diabetic mothers have hyperinsulinism at birth due to increased placental transfer of glucose and other nutrients stimulating hyperplasia of islets of Langerhans in the fetus and increased insulin secretion, raised amount of C-peptide and free insulin in the cord blood.¹¹ Once the maternal supply of glucose is cut-off by clamping the cord, The excess insulin may drop the blood glucose level of the newborn precipitously and alarmingly during the first few hours of life.¹² According to recent guidelines, a blood glucose value of <40 mg /dl is hypoglycemia. Symptoms of hypoglycemia are non-specific. Mostly it is asymptomatic, but the various presenting features are lethargy, apathy, apnea, cyanosis, weak or high-pitch crying, poor feeding, vomiting, tremor, jitteriness, irritability, seizure, coma, etc.¹³ Therefore, hypoglycemia must always be confirmed biochemically and by the response to treatment.^{14,15,16} Neonatal hypoglycemia is known to be associated with brain dysfunction and neuro-motor developmental retardation in both symptomatic and asymptomatic cases.^{17,18,19} Neonatal hypocalcemia is defined as a total serum calcium concentration of less than 7 mg/dl and ionized calcium concentration of less than 4 mg/dl.²⁰ Hypocalcaemia occur may be due to diminished production of parathormone.²¹ The incidence of hypocalcemia was significantly increased in the infant of diabetic mothers, even

when gestational age and perinatal complications were taken into consideration. Serum calcium levels were higher in diabetic mothers, but lower serum calcium levels were present in the infant of diabetic mothers. It is speculated that relative maternal hyperparathyroidism may be a factor in the pathogenesis of neonatal hypocalcemia in infants of diabetic mothers.²²

Objectives

To find out the association between an infant's hypoglycemia and hypocalcemia with maternal diabetes.

Materials and Methods

This comparative case-control study of about 300 neonates, of which 150 neonates were infants of Diabetic mothers and an equal number of control from nondiabetic mothers, was done over a period of six months from January 2017 to June 2018. Purposive sampling was done; all the infants of diabetic mothers who were admitted in the pediatric ward of Rajshahi Medical College Hospital 0-72 hours of age, whether they were in or out, born taken as a case while apparently healthy infants of nondiabetic mothers were taken as control. Patients having emergency medical and surgical abnormalities, and syndromic babies were excluded from the study. A semi-structured questionnaire was developed using the selected variables according to the objectives. Medical records, demographic profiles, and clinical and laboratory records of the subjects were recorded in the data collection sheet. All the data were checked after collection. Data analysis was proposed by using the 'Statistical Package for Social Science'. The independent t-test and χ^2 test were done to determine the level of significance. A p-value of <0.05 was considered significant (p<0.05).

Informed consent was taken from each baby's mother before enrolling in the study. There was minimal ethical binding due to minimum invasive procedures and investigation costs were relatively low, and confidentiality of the babies and parents was maintained strictly.

Results

This Case-control study was carried out at the inpatient department of pediatrics, RMCH, Rajshahi, from January 2017 to June 2018. For the research total of 300 subjects were selected along with a control group. Their parents were interviewed by specific questionnaires, and infants underwent some clinical examinations and investigations to find out the association between infant hypoglycemia and hypocalcemia with maternal diabetes.

Presence of Gestational Diabetes:

The 150 cases of this study were taken from the population who had Diabetes mellitus. The presence of diabetes in selected mothers of cases was classified into Gestational diabetes and Pre-gestational diabetes according to their detection. According to this study, the majority had Gestational Diabetes Mellitus (GDM), 114 (76%), and the rest, 36 (24%), had Pre-gestational Diabetes (Pre-GDM). In this study, the respondents were taken from the neonate group, irrespective of sex.

Fig 1: Presence of Gestational diabetes

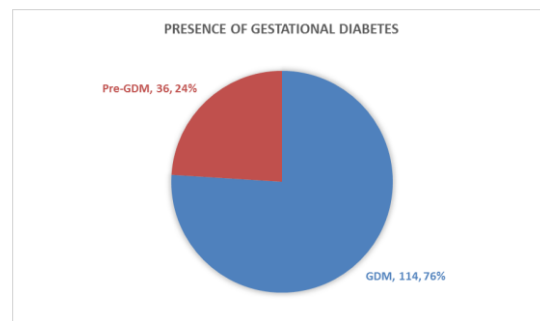


Fig. 1 (Pie chart) showing selected mothers of GDM and Pre-GDM (n=150)

Maternal drug history

The selected mothers were taken into account for having Diabetes during pregnancy; in this study, it is identified who took the medication for diabetes. It is revealed that 82 (55%) of 150 mothers took insulin as the treatment, and 68 (45%) did not take insulin or any medicine as treatment.

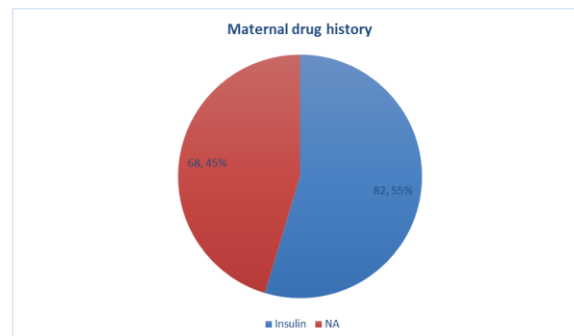


Fig.2: Maternal drug history for Diabetes (n= 150)

Table 1; Association of Serum Glucose level with maternal Insulin history

History of Insulin	Blood glucose after birth		P value
	Hypoglycemia	Normal	
Yes	44 (53.7%)	38 (46.3%)	0.012
No	50 (73.5%)	18 (26.5%)	

***The mean difference is significant at the level of 0.05**

The incidence of hypoglycemia was analyzed among insulin-treated mothers and non-insulin-treated mothers. The incidence of hypoglycemia in neonates of the insulin-treated mother was 44 (53.07%), which was lower than that of the non-insulin-treated mother 50 (73.5%) (P value 0.012). That implies insulin treatment for diabetic mothers lowers the risk of developing hypoglycemia in neonates.

Table 2; Association of Serum Calcium level with maternal Insulin history

History of Insulin	Blood calcium after birth		P value
	Hypocalcemia	Normal	
Yes	14 (17.1%)	68 (82.9%)	
No	20 (29.4%)	48 (70.6%)	0.07

***The mean difference is significant at the level of 0.05**

The incidence of hypocalcemia was also analyzed among insulin-treated mothers and non-insulin-treated mothers. The result did not show much strong association of hypocalcemia with insulin use, but that described a higher incidence of hypocalcemia 20 (29.4%) in neonates of the non-insulin treated diabetic mother than in neonates 14 (17.1%) of insulin-treated diabetic mothers.

General findings of neonates

The physical conditions of the neonates were evaluated in this study right after the birth of the neonate. The majority of the neonates, 141 (94%), were normal in general condition, 4 (2.7%) neonates were lethargic, and 5(3.3%) were irritable. Among all neonates, only 17 had Meconium stained. Only one neonate had an injury during birth. The temperature was raised among the neonates by only 15(10%). Whereas 7(4.7%) neonates had their forehead sweating. Among infants of diabetic mothers, 8 (5.3%) developed seizures.

Table 3: General findings of the neonates

General findings	Case (%)	Control (%)
General condition		
Normal	141 (94%)	143 (95.3%)
Lethargic	4 (2.7%)	4 (2.7%)
Irritable	5 (3.3%)	3 (2%)
Meconium stain	17 (11.3%)	0
Forehead sweating	7 (4.7%)	4 (2.7%)
Temperature raised	15 (10%)	4 (2.7%)
Jitteriness	39 (26%)	4 (2.7%)
Birth injury	1 (0.7%)	0
Seizure	8 (5.3%)	1 (0.7%)

n=150

Table 4: Clinical findings of neonates

Clinical findings	Case (%)	Control (%)
Cyanosis	8 (5.3%)	1 (0.7%)
Plethora	61 (40.7%)	8 (5.3%)
Jaundice	47 (31.3%)	8 (5.3%)
Muscle tone		
Normal	145 (96.7%)	146 (97.3%)
Hypotonic	5 (3.3%)	4 (2.7%)
Congenital malformation (Cleft palate)	1 (0.07%)	0

Blood glucose level

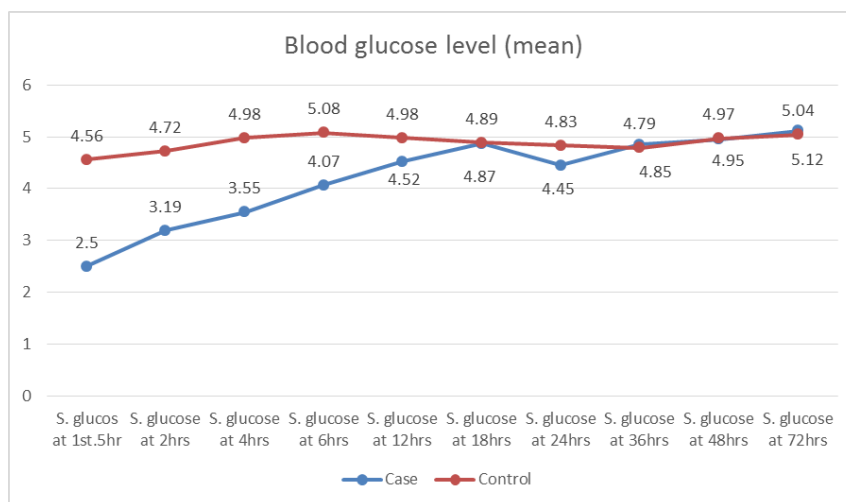
Blood glucose levels of the neonates were evaluated at different time points from the first ½ an hour of birth to 72 hours of age. The study revealed the incidence of hypoglycemia in neonates of diabetic and nondiabetic mothers. Right after birth, at their first ½ hour of age, 111 (37%) neonates developed hypoglycemia; after that, in the following hours' presence of hypoglycemia was as follows: at 6hrs were 27(9%), at 12hrs 16(5.3%), at 24 hrs 23(7.7%), at 48hrs 7(2.3%) and at 72 hrs 2 (0.7%).

Collectively the data showed initial low blood sugar levels and continuous rise to high blood sugar to improvement at a normal level (Fig: 4.10). The mean blood glucose levels among the cases were much lower than that of the control.

Table 5: Presence of hypoglycemia at different points in time

Hypoglycemia	At ½ hr.	At 6hrs	At 12hrs	At 24hrs	At 48hrs	At 72hrs
Infants of diabetic mother	94 (62.7%)	23 (15.3%)	13 (8.7%)	19 (12.7%)	7 (4.7%)	2 (1.3%)
Infants of nondiabetic mother	17 (11.3%)	4 (2.7%)	3 (2%)	4 (2.7%)	0 (0%)	0 (0%)
Total	111 (37%)	27 (9%)	16 (5.3%)	23 (7.7%)	7 (2.3%)	2(0.7%)

n= 300

Fig.3: Blood glucose level (mean) at different points in times

n= 300

Association of blood glucose level with maternal diabetes

Study variable analysis revealed that the mean of hypoglycemia in infants of a diabetic mother is 94 (62.3%) than in infants of nondiabetic mothers 17(11.4%). Where the p-value is < 0.001, which explains developing hypoglycemia in the infant of a diabetic mother is higher than nondiabetic mother.

Table 6: Association of blood glucose level with maternal diabetes

Presence of Diabetes	Blood glucose after birth		P value
	Hypoglycemia	Normal	
Cases	94 (62.7%)	56 (37.3%)	<0.001
Control	17(11.3%)	133 (88.7%)	

*The mean difference is significant at the level of 0.05

Association of blood calcium level with maternal diabetes:

Serum calcium levels of the selected infants were measured, and a discrepancy was found. The number of hypocalcemia in infants of diabetic mothers was 34 (22.7%), while hypocalcemia in infants of the nondiabetic mother was 8 (5.3%), which is significantly (p-value <0.001) lower. It implies that the risk of development of hypocalcemia is significantly higher in infants of diabetic mothers. The mean serum calcium level in the case was 7.85 (SD1.40) mg/dl, and that of the control was 8.52 (SD 1.11) mg/dl.

Table 7: Serum calcium level with maternal diabetes

Serum Calcium level	Frequency (mg/dl)		Mean (SD)
	Minimum	Maximum	
Infants of diabetic mother	4.10	11	7.85 (1.40)
Infants of nondiabetic mother	5.20	11.20	8.52 (1.11)

n= 300

Table 8: Association of Serum calcium level with maternal diabetes

Presence of Diabetes	Blood calcium after birth		P value
	Hypocalcemia	Normal	
Cases	34 (22.7%)	116 (77.3%)	<0.001
Control	8 (5.3%)	142 (94.7%)	

*The mean difference is significant at the level of 0.05

Clinical findings of neonates

Every selected neonate was clinically evaluated by clinical examinations. The majority of the neonates were well-oxygenated, but 8 (5.3%) neonates developed cyanosis after birth. 61 (40.7%) neonates had Plethora. Among 150 neonates, 47 (31.3%) neonates developed jaundice, the muscle tone of those neonates was evaluated, and it revealed only 5 (3.3%) neonates had Hypotonic muscle tone. Congenital malformations of the neonates were evaluated, and only one neonate was found to have a congenital anomaly.

Discussion

This Case-control study was carried out at the inpatient department of pediatrics, Rajshahi Medical College Hospital, Rajshahi, from January 2017 to June 2018, following a purposive non-probability type sampling technique. For the research total of 300 infants were selected. Their parents were interviewed by specific questionnaires, and infants underwent some clinical examinations and investigations to find out the association between infant hypoglycemia and hypocalcemia with maternal diabetes.

Respondents were taken from the neonate group irrespective of sex. The case and control were taken from the same population. Out of 300 neonates 209(70%) were male and 91(30%) were female. In the case group, 98 (65%) were male, and 521 (35%) were female, whereas in the control group, 111 (74%) were male, and 39 (26%) were female.

The mothers of selected neonates were taken from the reproductive age group (15 to 45 years). The case and control group of mothers were taken from the same population. The ages of those mothers were categorized into three groups. Among the case groups, 65 (21.67%) were between 18 to 25 years, 76 (25.33%) were in age 26 to 35 years, and 9(3.00%) were between 36 to 45 years, whereas in the control group 109 (36.33%) were in 18 to 25 years, 37 (12.33%) were in age 26 to 35 years and 4 (1.33%) were in 36 to 45 years of age. The mean age of mothers was 25.36 ± 5.50 years.

The 150 cases of this study were taken from the population whose mothers had Diabetes mellitus. The presence of diabetes in selected mothers of cases was classified into Gestational diabetes and Pre-gestational diabetes according to their detection. According to this study majority of the cases, the mother had Gestational Diabetes Mellitus (GDM). 114 (76 %) mothers had GDM, and the rest, 36 (24%) mothers, had Pre-gestational Diabetes (Pre-GDM).

The selected mothers were taken into account for having Diabetes during pregnancy; in this study, it was identified who took the medication for diabetes. In Fig. 1&2, it was shown that 82 (55%) of 150 mothers took insulin as the treatment, and

68 (45%) did not take insulin or any medicine as treatment. The analysis of insulin administration in diabetic mothers implies insulin treatment in diabetic mothers lowers the risk of developing hypoglycemia in neonates. The incidence of hypoglycemia in neonates of insulin-treated mothers was 44 (53.7%), and it was lower than that of non-insulin-treated mothers, which was 50 (73.5%) (p-value 0.012). There was a study by Dr. K. Umamaheswara Rao et al. where the hypoglycemic incidence in optimally controlled diabetic mothers was 7 (35%) less than in uncontrolled diabetic mothers 14 (46.66%).²³

The result did not show much strong association of hypocalcemia with insulin use, but that described a higher incidence of hypocalcemia that was 20 (29.4%) in neonates of non-insulin treated diabetic mothers in neonates of insulin-treated diabetic mothers were 14 (17.1%). A study by Dr. Umamaheswara Rao et al. revealed hypocalcemia is higher in neonates of sub-optimally controlled mothers 5 (16.66%) than in optimally controlled diabetic mother's neonates 1 (5%).²³

The physical conditions of the neonates were evaluated in this study right after birth (Table 3,4). The majority of the neonates, 141 (94%), were normal in general condition, 4 (2.7%) neonates were lethargic, and 5(3.3%) were irritable. Among all neonates, only 17 had meconium stains. Only one neonate had an injury during birth. The temperature was raised among the neonates only 15(10%), and seizures developed in 8 (5.3%). Compared to the case among neonates of nondiabetic mothers, 4 (2.7%) neonates were lethargic, 3 (2%) were irritable, 4 (2.7%) had forehead sweating, raised temperature, and Jitteriness.

Blood glucose levels of the neonates were evaluated at different times point (Table-5) from the first ½ hour of birth to 72 hours of age. The study revealed the incidence of hypoglycemia in neonates of diabetic and nondiabetic mothers. Right after birth, at their first ½ hour of age, 111 (37%) neonates developed hypoglycemia; after that, in the following hours' presence of hypoglycemia was as follows: at 6hrs were 27(9%), at 12hrs 16(5.3%), at 24 hrs 23(7.7%), at 48hrs 7(2.3%) and at 72 hrs 2(0.7%). In a research

Dr. K. Umamaheswara Rao showed that 21(42%) developed Hypoglycemia <6hrs, 4 (8%) in 6-24hrs and 3 (6%) in 24-48hrs.²³

Collectively the data showed initial low blood sugar level and continuous rise to high blood sugar to improvement at normal level (Fig: 3). The mean blood glucose level among the cases was much lower than that of the control. That directs that the blood glucose level of an infant of a diabetic mother is lower than the blood glucose level of infants of a nondiabetic mother.

Study variable analysis revealed that the mean of hypoglycemia in infants of a diabetic mother is 94 (62.7%) than in infants of nondiabetic mother 17(11.3%)(Table-6). Where the p-value is <0.001-which explains developing hypoglycemia in the infant of a diabetic mother is higher than nondiabetic mother. Wasim Rafiq et al. in 2015 showed hypoglycemia at 35.41%.²⁴ In a study, Mazumder et al. found that among the control group, 1 (3.1%) had hypoglycemia which may be due to delayed initiation and lack of proper feeding in normal-term babies and sometimes in sick babies with minor illnesses (n=32).

Serum calcium levels of the selected infants were measured in both groups, and the discrepancy was found (Tables 7 & 8). The exact percentage in the case and control number of hypocalcemic infants of the diabetic mother was 34 (22.7%), which is close to the result of M. Husain et al. in 2011 revealed hypocalcemia of 16.6%.²⁵ hypocalcemia (15%) was identified in the research of Alam M et al. 2006 26. In comparison, hypocalcemic infants of the nondiabetic mother were 8 (5.3%), which is significantly (p-value <0.001) lower. It implies that the risk of development of hypocalcemia is significantly higher in infants of diabetic mothers. The mean serum calcium level in the case was 7.85 (SD1.40), and that of the control was 8.52 (SD 1.11).

Conclusion

Our results demonstrated that low serum glucose and calcium levels were found in infants of diabetic mothers compared to well-matched controls and that the hypoglycemia and hypocalcemia in infants were directly associated with the presence of diabetes during pregnancy.

The onset of hypoglycemia was mostly seen within the first few hours of life in most of the items. Infants of diabetic mothers are at risk of developing many fetal, perinatal, and postnatal complications leading to both short and long-term morbidity. Diabetic pregnancies need not only control of maternal diabetes but also careful fetal monitoring and good perinatal and neonatal care so that overall outcomes in these babies can be improved and many future complications could be avoided that are likely to occur as consequences of severe metabolic derangements.

Limitation

There are some limitations in this study. The study sample was small, and the time was also short. The present study was a hospital-based study which may not reflect the situation of the whole population of infants of diabetic mothers in the community. A prospective study will be ideal for measuring and identifying complications in infants of the diabetic mother, which should take a long time to follow up with the patients, and it was not possible within this time frame of our study.

Recommendation

Successful management of infants of diabetic mothers is based on prevention or early recognition combined with treatment can prevent mortality and morbidity.

Conflict of interest: None declared

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