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# Influence of Maternal Glycemic Status ($HbA_{1c}$) at Delivery and Risk of Hypoglycemia in Infants of Diabetic Mothers

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## Abstract

***Objective: To examine the influence of maternal HbA1c level at delivery and risk of hypoglycemia in infants of diabetic mothers.***

***Method: This case-control study was done with sixty neonates born to diabetic mothers in BIRDEM hospital. Out of sixty neonates, 30 neonates who developed hypoglycemia during the first 24 hours of age were considered as cases and another 30 neonates who did not develop hypoglycemia during the first 24 hours were considered as controls. Maternal glycemic status was examined by measurement of Glycosylated hemoglobin (HbA1c) and level of <6 % considered good control. Babies were screened for hypoglycemia at birth, then 4, 6, 8, 12, 18 and 24 hours of life. Blood glucose value of less than 2.6 mmol/l was considered as hypoglycemia.***

***Results: Clinical characteristics of newborns and their mothers of cases and controls did not show any significant difference. In majority of cases (73.3%) hypoglycemia was detected by 6 hours of age. Most of babies were asymptomatic (93.3%). Majority of mothers (76.7%) in controls and 46.7% of were in good glycemic controls (HbA1c <6%). The mean HbA1c level of mothers of cases was significantly higher than that of control mothers (6.02 ± 0.98 vs 5.44 ± 0.78; P = 0.014) and significant negative correlation between maternal HbA1c and blood glucose level of neonates ( r=0.422 p= 0.001).***

***Conclusion: There is an association between maternal HbA1c level and neonatal hypoglycemia in infants of diabetic mothers.***

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## Introduction

In 2010, the International Diabetes Federation (IDF) estimated that 5.7 million (6.1%) and 6.7 million (7.1%) of people living in Bangladesh is suffering from diabetes and impaired glucose tolerance (IGT) respectively[1].

Diabetes is a fairly common medical complication of pregnancy associated with maternal, foetal and neonatal morbidities and mortalities. The gestational diabetes mellitus (GDM) is seen in almost 80%, whereas around 12-15% has pregestational diabetes[2].

Poor metabolic control of maternal diabetes during the first trimester is associated with foetal malformations, during the second and third trimester with metabolic derangement in the neonatal period [3].

Newborn IDMs are hyperinsulinemic due to pancreatic beta-cell hyperplasia induced by chronic maternal hyperglycemia and the neonatal hypoglycemia seems to result from this together with disorders of both catecholamine and glucagon response and have a diminished capability to mount compensatory response to hypoglycemia like glycogenolysis, gluconeogenesis and for utilizing alternative substrates[4]. Hypoglycemia in IDMs mostly asymptomatic. However, the absence of overt symptoms at low blood glucose levels does not rule out central nervous system injury[5].Moreover hyperinsulinemic hypoglycemia is a major risk factor for brain injury and subsequent neurodevelopmental handicap, the identification, rapid diagnosis and prompt management of patients with hyperinsulinemia is essential if brain damage is to be avoided[6].

It would be useful, therefore, if we could predict postnatal hypoglycaemia from the state of maternal glycemic control. Glycosylated hemoglobin reflects the glycemic control over preceeding 7-8 weeks [7]. Kline and Edwards reported that third trimester HbA1c >6.5% had a stronger association with

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neonatal hypoglycemia requiring aggressive intervention[8]. Indirectly, therefore, it may serve as a good surrogate marker for predicting hypoglycemia in early postnatal period in IDMs and stresses the importance of a target maternal third trimester HbA1c of <6.5%. International Diabetes Federation guidelines in pregnancy give emphasis the target HbA1c level in pregnancy <6%[9].

The present study was undertaken to examine the influence of maternal HbA1c and risk of hypoglycemia in babies born to diabetic mothers.

**Materials and methods**

This case-control study was carried out in the department of Obstetrics and Gynecology, and Special Care Baby Unit (SCABU) at BIRDEM. (Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders). Sixty neonates born to diabetic mothers between November 2004 and February 2005 were retrospectively analysed. Among them 30 neonates who developed hypoglycemia during the first 24 hours of age were included as cases and another 30 neonates who did not develop hypoglycemia during the first 24 hours were included as controls. Babies were screened for hypoglycemia at birth, then 4, 6, 8, 12, 18 and 24 hours of postnatal age life as per existing routine SCABU (Special care baby Unit) schedule irrespective of feeding status. Blood glucose value of less than 2.6 mmol/l was considered as neonatal hypoglycemia[10]. Exclusion criteria were IDMs with major congenital malformation at birth, severe perinatal asphyxia, and severe erythroblastosis foetalis.

Blood glucose level of IDMs was measured by Precision-plus (MediSense, USA) glucometer using glucose oxidase method at birth in cord blood, and thereafter at bed side blood sample obtained from heel-prick. Maternal glycemic status was measured by HbA1c at delivery by HPLC (High Performance Liquid Chromatography) method at BIRDEM using Bio-Rad Variant Analyzer (USA) and level of <6 % considered as good control[9]. Results were analyzed by employing Stastistical Package for Social Science (SPSS Version 11.0) software package.

**Results**

**Table-I**

*Characteristics of mothers and newborns*

| Characteristics of mothers | Cases (n=30) | Controls (n=30) |
|---|---|---|
| Age (year) mean (SD) | 29.47 ± 4.81 | 31.13 ± 5.51 |
| Weight(kg) mean (SD) | 61.17 ± 10.17 | 58.60 ± 8.88 |
| Type of Diabetes | | |
| GDM | 10 (33%) | 11 (36.7%) |
| Type 2 Diabetes | 18 (60%) | 19 (63.3%) |
| Type 1 Diabetes | 2 (6.7%) | 0 |
| Treatment of diabetes | | |
| Diet alone | 6 (20%) | 7 (23.3%) |
| Diet and Insulin | 24 (80%) | 23 (76.7%) |
| HbA1c (%) | | |
| < 6 | 14 (46.7% ) | 23 (76.7%) |
| =>6 | 16 (53.3%) | 7 (23.3%) |
| Mode of delivery | | |
| NVD | 3 (10%) | 0 |
| LUCS | 27 (90%) | 30 (100%) |
| Birth weight (gm) mean (SD) | 3065 ± 725 | 3252 ± 464 |
| Gestational age (week) mean (SD) | 37 ± 1.26 | 37.2 ± 0.71 |
| Male | 14 (46.6%) | 15 (50%) |
| Female | 16 (53.3%) | 15 (50%) |
| Term | 19 (63.3%) | 23 (76.7%) |
| Preterm | 11 (36.7%) | 7 (23.3%) |
| AGA | 27 (90%) | 28 (93.3%) |
| LGA | 3 (10%) | 2 (6.67%) |

AGA: appropriate for gestational age, LGA: large for gestational age.

**Table-II**

*Comparison of mean blood glucose levels between cases and controls at different times within 24 hours of postnatal age*

| Age (hour) | Cases (n=30) mean (SD) mmol/l | Controls(n=30) mean(SD) mmol/l | P value |
|---|---|---|---|
| "0" (cord blood) | 4.92 ± 2.19 | 4.37 ± 1.54 | 0.269 |
| 4 | 2.71 ± 0.92 | 3.38 ± 0.73 | 0.003 |
| 6 | 2.71 ± 0.71 | 3.45 ± 0.72 | 0.0004 |
| 8 | 2.87 ± 0.62 | 3.68 ± 0.84 | 0.0004 |
| 12 | 2.96 ± 0.54 | 3.47 ± 0.84 | 0.008 |
| 18 | 3.37 ± 0.73 | 3.90 ± 0.94 | 0.019 |
| 24 | 3.45 ± 0.65 | 4.0 ± 0.81 | 0.006 |

* Unpaired t- test

**Table-III**

*Comparison of mean maternal HbA1c level between of cases and controls*

| | Mothers of cases | Mothers of controls | P-value |
|---|---|---|---|
| $HbA_{1c}$ % mean( SD) | 6.02 ± 0.98 | 5.44 ± 0.78 | 0.014 |

**Table-IV**

*Correlation between neonatal blood glucose and maternal $HbA_{1c}$ level at 4 hours of age (n=60)*

| Antecedent variable | r value | P value |
|---|---|---|
| Maternal HbA1c (%) | 0.422 | 0.001 |

Pearson.s correlation (2-tailed)

**Results**

Table-I shows baseline characteristics of IDMs and their mothers in both groups. There is no significant difference in demographic features among cases and controls. Majority (76.7%) of mothers in control and 46.7% of cases were in good glycemic control ($HbA_{1c}$ <6%). Hypoglycemia was detected in 50% of cases at 4 hours of age and in 23.3% at 6 hours of age; so 73.3% by 6 hours of age. Trend of blood glucose status of babies during first 24 hours shown in table-II. At birth the glucose level of cases was higher than controls. In both groups, blood glucose level decreased rapidly after birth and subsequently increased steadily from 4 hours of age in both groups over next 24 hours, glucose level of cases were persistently remain in lower level than that of controls. There was also significant difference of mean blood glucose values between cases and controls at 4, 6, 8, 12 and 24 hrs of age. Table-III showed comparison of $HbA1_C$ level showed that the mean value of HbA1c was significantly higher among mothers of cases than that of controls (6.02 ± 0.98 vs 5.44 ± 0.78; p= 0.014). A significant negative correlation was observed between maternal $HbA_{1C}$ and blood glucose level of IDMs at 4 hours of age (r = -0.422, P = 0.001) shown in table-IV.

**Discussion**

No significant difference was observed between clinical characteristics of cases and controls and their mothers. Majority of mothers of both cases (66.7%) and controls (63.3%) had pre-gestational diabetes. Diabetes during pregnancy, 80% are caused by GDM as opposed to pre-gestational diabetes[2]. The predominance of pre-gestational diabetes over GDM in this study could be accounted for women being registered at BIRDEM at diagnosis of DM. Pregnancy itself is diabetogenic, the flow of fuels to the fetus is mediated by the sequential rise of hormones, which are diabetogenic[11]. Insulin requirement increases with each trimester of pregnancy in diabetic women [12]. In the present study majority of mothers in both cases (80%) and controls (76.7%) required treatment with insulin. So, modality of treatment is also an indicator of severity of glycemic status during pregnancy. Hypoglycemia was detected by 6 hours of age in 73.3% cases; 50% at 4 hours of age, 23.3% at 6 hours of age. At 8 hours and also at 12 hours of age hypoglycemia was detected only in 16.6% of cases.

The nadir in IDM's blood glucose usually occurs between 1 and 4 hours of life[4]. Kuhl et al[13] and Robert S et al[14] observed the lowest value at 2 hours of age, and mostly (83%) occurred within first 4 hours of age described by Lin and Ho[15]. Clinically, 2 hours levels of blood glucose are predictive of later hypoglycemia that may require repeat testing[16]. We did not examine the blood glucose at 2 hours and glucose level was done irrespective of feeding status, as we did follow the existing SCABU protocol. Hypoglycemia might be more frequent or severe if glucose estimation could have been done pre-feed and also at 2 hours of life.

Most IDMs have asymptomatic hypoglycemia[4]. The predominance (93.3%) of asymptomatic hypoglycemia in present study is consistent with previously reported studies[14, 15]. However, the absence of overt symptoms at low blood glucose levels does not rule out central nervous system injury[5]. This elevated prevalence of asymptomatic neonatal hypoglycemia in IDMs stress the importance of systematic glucose monitoring at risk babies to prevent severe and recurrent hypoglycemia.of these neonates.

Neonatal hypoglycemia is associated with poor psychoneurological development. Blood glucose should be maintained above 2.6 mmol/l to ensure normal neural function[10].

Measuring $HbA_{1C}$ % is considered as the gold standard for monitoring metabolic control in diabetes. A normal non-diabetic $HbA1_C$ is 3.5-5.5%. In diabetes about 6.5% is good[17]. International Diabetes Federation guidelines in pregnancy give emphasis the target HbA1c level in pregnancy <6%[9], considering this value 46.7% of mothers in cases were in good glycemic control compared to 76.7% of controls (HbA1c <6%). Nielsen et al[18] in a study demonstrated accepted upper level of HbA1c level as 5.6% in third trimester of pregnancy whereas Valaji and Seshiah in India recommended target value in pregnancy to be maintained 5.3%[12]. So morbidities considering good control at this level of HbA1c <6.5% or <6% may underscore the need to evaluate the different target value to overcome the effect of HbA1c lowering effect of pregnancy. Mean HbA1C level of mothers was in cases was significantly higher than mothers of controls (6.02 ± 0.98% vs 5.44 ± 0.78%; P= 0.014); signifies the association of maternal HbA1c with the development of hypoglycemia in IDMs. Recently Banerjee et al[19] observed the lower incidence of hypoglycemia in IDMs of mothers with tight glycemic control where $HbA_{1C}$ cut-off value was considered <6.5%.

Kline and Edwards[8] using multiple logistic regression methods found that a third trimester HbA1c of >6.5% had a stronger association with neonatal hypoglycemia requiring aggressive intervention. Ylien et al[20] found that neonatal hypoglycemia was seen in those mothers with higher mean HbA1c levels in the second and third trimester. Kulenthran and Nathira in their study reported HbA1c level of 6.8% in late pregnancy as optimal threshold value for predicting neonatal hypoglycemia by ROC (Receiver operator characteristic curve) curve with the area under curve 0.997 (95% CI 0.992 to 1)[21].

On the other hand, Taylor et al[22] showed that there was no correlation between neonatal hypoglycemia and HbA1c levels at any point in pregnancy or with mean pregnancy HbA1c levels. Stenninger et al[23] in his study of 59 mothers with insulin-treated diabetes, showed that neonatal hypoglycemia could still occur despite well controlled diabetes. We also examined the relationship by correlation analysis between maternal HbA1c and blood glucose level of IDMs at 4 hours of age , where a significant negative correlation was observed (r = –0.422, P= 0.001) which is in agreement with the studies done by Ylinen K et al[20] and Cooper et al[24] .

**Conclusion:**

Even in good glycemic control there is a risk of hypoglycemia in IDMs, needs blood glucose monitoring to prevent severe and recurrent hypoglycemia in these neonates, which is risk for brain injury.

**Limitation of the study**

Sample size was small. Blood glucose monitoring was not done in first 3 hours of age, which could demonstrate different frequency or values.

**Recommendation**: Studies with larger sample size, including blood glucose monitoring within first 3 hours, and to investigate if HbA1c could be a good predictor for neonatal hypoglycemia and to find the appropriate threshold value.

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