

Glycosylated Hemoglobin Level at 34 Weeks in Insulin Treated Diabetic Pregnancies: Relation to Fetal Outcome - A Prospective Cohort Study

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Abstract

Background: Diabetes control during pregnancy is essential in decreasing rate of neonatal adverse outcomes. Glycosylated hemoglobin (HbA1c) is one of the most important markers for diabetes control.

Objective: To evaluate the role of glycosylated hemoglobin at 34 weeks gestation in prediction of fetal outcome in insulin-treated diabetic pregnancies.

Patients and Methods: After approval of ethics committee, a prospective longitudinal cohort study was conducted among a total of 50 pregnant women recruited from the obstetric outpatient clinic and department at Suez Canal University Hospital from January 2014 to January 2015. Inclusion criteria included diabetic patients on insulin treatment, viable singleton fetus, gestational age about 34 weeks, no gross fetal anomalies and maternal age 18 - 35 years. Diabetic patients on diet control only, women with medical disorders not related to diabetes as SLE, thyroid disorders, hypertension, and preeclampsia were excluded from the study. Outcome parameters included mode of delivery, neonatal APGAR score at 1 and 5 minutes, neonatal weight, gestational age at delivery, neonatal respiratory distress syndrome, and neonatal hypoglycemia.

Results: Most of diabetic patients were uncontrolled with HbA1c > 7% (68%). There was a statistically significant difference between controlled diabetic and uncontrolled diabetic patients regarding amniotic fluid index and gestational age at delivery. There were statistically significant differences between controlled diabetic and uncontrolled diabetic patients concerning birth weight, Apgar score at 1 minute, Apgar score at 5 minutes, neonatal glucose level and neonatal macrosomia. Neonatal hypoglycemia was more prevalent among uncontrolled patients but without statistically significant difference. HbA1C level was statistically significant predictor of RDS, prematurity, CS delivery, neonatal hypoglycemia, and macrosomia with areas under the curve of 86%, 85%, 82%, 77%, and 73% respectively.

Conclusion: Poor glycemic control as evaluated by HbA1c is associated with and a significant risk factor for multiple adverse fetal and neonatal outcomes.

Keywords: Diabetes; Gestational Diabetes; Glycemic Control; Glycosylated Hemoglobin

Introduction

In 2019, an estimated 30.8 million persons in the United States had diagnosed diabetes mellitus, and another 84 million had pre-diabetes [1]. Strategies to prevent diabetes and its preventable risk factors are needed, especially for those at highest risk for diabetes, to

slow the rise in diabetes prevalence. Continued surveillance of diabetes prevalence and incidence, its risk factors and prevention efforts are essential to measure progress of preventive efforts. It is estimated that this incidence will increase another 16.5 percent by 2050 [2].

The increasing prevalence of type 2 diabetes in general and in younger people in particular, has led to an expanding number of pregnancies with this complication. Indeed, the incidence of diabetes complicating pregnancy has increased approximately 40 percent between 1989 and 2004 [3]. The annual prevalence rate of gestational diabetes in US ranged from 2 - 10% [4] while in Europe it ranged 2% - 6% [5].

In utero exposure to maternal hyperglycemia leads to fetal hyperinsulinemia, causing an increase in fetal fat cells, which leads to obesity and insulin resistance in childhood. This, in turn, leads to impaired glucose tolerance and diabetes in adulthood [6].

Hemoglobin A1c (HbA1c, or A1c) is currently the most prominent biomarker for assessing the glycemic status of people with diabetes and for making decisions on the appropriate therapy adjustments if needed. Over the years, many healthcare providers have come to view the HbA1c value as a “magic number” that comprises all of the information required for managing blood glucose concentrations to prevent complications in people with diabetes; the concept “the lower, the better” was considered a tempting approach [7].

The current study was conducted aiming to evaluate the role of glycosylated hemoglobin at 34 weeks gestation for prediction of fetal outcome in insulin-treated diabetic pregnancies.

Patients and Methods

After approval of the ethics committee of Faculty of Medicine, Suez Canal University; the present prospective longitudinal cohort study was conducted among 50 pregnant women recruited from the obstetric outpatient clinic and department at Suez Canal University Hospital from January 2014 to January 2015. Inclusion criteria included diabetic patients on insulin treatment, viable singleton fetus, gestational age about 34 weeks, no gross fetal anomalies and maternal age 18 - 35 years. Diabetic patients on diet control only, women with medical disorders not related to diabetes as SLE, thyroid disorders, hypertension, and preeclampsia were excluded from the study.

Methods of the study

All patients were evaluated via:

1. Detailed history: including personal history, past medical history, preconception menstrual history, and complete obstetric history.
2. Complete general medical examination and full obstetric examination including inspection of the abdominal contour, and palpation of fundal level and grip, umbilical and pelvic grips.
3. Routine obstetric ultrasound to:
 - a. Detect fetal viability
 - b. Exclude multiple pregnancies and major congenital anomalies
 - c. Estimate gestational age and fetal weight
 - d. Estimate placental maturation.
 - e. Estimate amniotic fluid index (AFI)
4. Laboratory investigations including:
 - a. Maternal glycosylated hemoglobin: HbA1c ≥ 7 was considered poor glycemic control. It was estimated once at time of presentation
 - b. Maternal fasting and 2 hours postprandial blood sugar.

Outcome parameters:

1. Mode of delivery (cesarean section versus normal vaginal delivery)
2. Apgar score at 1 and 5 minutes

3. Age of delivery. Less than 37w was considered prematurity
4. Estimated fetal weight and birth weight. Macrosomia was defined as birth weight greater than 4500g regardless of gestational age or as birth weight greater than the 90th percentile for gestational age.
5. Presence of signs of neonatal respiratory distress syndrome.
6. Neonatal hypoglycemia: If neonatal blood sugar after 1 hour of delivery is < 45 mg/dl.

Statistical analysis

The gathered information was processed using SPSS version 26 (SPSS Inc., Chicago, IL, USA.). Quantitative data were expressed as means ± SD while qualitative data were expressed as numbers and percentages (%). An unpaired t-test was used to test significance of difference for quantitative variables, and chi-square was used to test significance of difference for qualitative variables. Pearson correlation coefficient was used to test association between HbA1C and other quantitative parameters. Receiver Operating Characteristics (ROC) curve was used to estimate predictive value of HbA1c to detect adverse neonatal outcomes. A probability value (p-value) < 0.05 was considered statistically significant.

Results

The mean age of studied women was 27.76 years old, with a range from 19 to 36 years. Mean BMI was 30.96 kg/m² with range from 24.2 to 37.11 kg/m². Most of patients were gravida 2 or 3 (60%), and 20% were primigravida. Most of diabetic patients were uncontrolled with HbA1c > 7% (68%).

This study showed that there were statistically significant differences between controlled diabetic and uncontrolled diabetic patients regarding amniotic fluid index (14.5 versus 16.29 respectively, p-value = 0.02) and gestational age at delivery (38 weeks versus 37.35 respectively weeks, p-value = 0.03). Regarding neonatal outcome, it was found that there were statistically significant differences between controlled diabetic and uncontrolled diabetic patients concerning birth weight (3.225 kg versus 3.794 kg respectively), Apgar score at 1 minute (7 versus 6, respectively), Apgar score at 5 minutes (8.75 versus 7.82 respectively), neonatal glucose level (40.63 versus 33.29 respectively) and neonatal macrosomia (0% versus 29.41% respectively). Neonatal hypoglycemia was more prevalent among uncontrolled patients but without a statistically significant difference. Six cases of prematurity and respiratory distress syndrome (RDS) were reported among uncontrolled patients versus none of controlled diabetics without a statistically significant difference. Cesarean section (CS) rates were significantly more among uncontrolled diabetic patients (76.47%) versus 31.25% among controlled diabetic patients. The odds ratio for having CS delivery among uncontrolled diabetic patients was 7.15 times more than controlled diabetic patients.

Table 1 showed that there was a significant correlation between HbA1c level and estimated fetal weight, amniotic fluid index, birth weight (positive correlation), gestational age at delivery, Apgar score, and neonatal glucose level (negative correlation).

| Parameter | HbA1c | |
|-----------------------------|-------------------------------------|----------|
| | Pearson correlation coefficient (r) | p-value |
| Biparietal diameter | 0.07 | 0.6 (NS) |
| Estimated fetal weight | 0.4 | 0.009* |
| Amniotic fluid index | 0.4 | 0.008* |
| Gestational age at delivery | -0.5 | 0.004* |
| Birth weight | 0.4 | 0.002* |
| Apgar score at 1 min | -0.6 | 0.001* |
| Apgar score at 5 min | -0.6 | 0.001* |
| Neonatal glucose level | -0.6 | 0.001* |

Table 1: Correlation between HbA1c and outcome parameters.

*Statistically Significant; NS: No Statistically Significant.

Table 2 showed that HbA1C was a significant independent factor for various neonatal and fetal outcomes with statistical significance.

| Parameter | HbA1c | | | |
|-----------------------------|-------------|----------|---------------|-----------|
| | Coefficient | Constant | 95% CI | p-value |
| Biparietal diameter | 0.04 | 7.95 | -0.12 - 0.21 | 0.6 (NS) |
| Estimated fetal weight | 0.16 | 1.12 | 0.04 - 0.27 | 0.009* |
| Amniotic fluid index | 1.04 | 7.59 | 0.27 - 1.81 | 0.009* |
| Gestational age at delivery | -0.51 | 41.5 | -0.78 - -0.24 | 0.001* |
| Birth weight | 0.2 | 2.03 | 0.07 - 0.33 | 0.003* |
| Apgar score at 1 min | -0.65 | 11.38 | -0.91 - -0.39 | 0.001* |
| Apgar score at 5 min | -0.65 | 13.18 | -0.93 - -0.37 | 0.001* |
| Neonatal glucose level | -0.4 | 69.7 | -6.2 - -2.5 | 0.001* |
| Neonatal Hypoglycemia | 0.2 | -1.3 | 0.11 - 0.34 | 0.001* |
| Prematurity | 0.13 | -0.88 | 0.05 - 0.21 | 0.002* |
| Macrosomia | 0.103 | -0.61 | -0.001 - 0.21 | 0.05 (NS) |
| RDS | 0.12 | -0.79 | 0.04 - 0.19 | 0.006* |
| Death | 0.02 | -0.15 | -0.03 - 0.08 | 0.4 (NS) |
| Cesarean delivery | 0.24 | -0.25 | 0.13 - 0.35 | 0.001* |

Table 2: Simple linear regression analysis between HbA1c as an independent factor and outcome parameters and dependent factors.
*Statistically Significant; NS: No Statistically Significant; CI: Confidence Interval.

Table 3 showed that HbA1C level was a statistically significant predictor of RDS, prematurity, CS delivery, neonatal hypoglycemia, and macrosomia with areas under the curve of 86%, 85%, 82%, 77%, and 73% respectively.

| Parameter | HbA1c | | | | | | |
|-----------------------|-------|--------------|-------------|-------------|-------|-------|----------|
| | AUC# | Cutoff value | Sensitivity | Specificity | PPV | NPV | p-value |
| Neonatal Hypoglycemia | 77% | > 7.5% | 80% | 66.67% | 61.5% | 83.3% | 0.001* |
| Prematurity | 85% | > 7.56% | 100% | 59% | 25% | 100% | 0.006* |
| Macrosomia | 73% | > 7.4% | 100% | 50% | 33.3% | 100% | 0.02* |
| RDS | 86% | > 8.2% | 100% | 77.27% | 37.5% | 100% | 0.002* |
| Death | 75% | > 8.2% | 100% | 70.83% | 12.5% | 100% | 0.2 (NS) |
| Cesarean delivery | 82% | > 7.4% | 80.65% | 73.68% | 83.3% | 70% | 0.001* |

Table 3: Receiver operating characteristic curve analysis for HbA1c value to predict various outcome parameters.
PPV: Positive Predictive Value; NPV: Negative Predictive Value.
*Statistically significant; #: Area Under the Curve; NS: No Statistically Significant.

Discussion

Gestational Diabetes Mellitus (GDM) constitutes a significant health risk for mother and offspring during pregnancy, delivery and throughout the life course women affected by GDM, Their offspring are at increased risk for neonatal complications, in particular macrosomia, large for gestational age, respiratory distress, prematurity, hypoglycemia, polyhydramnios, and death. These offspring are also at high risk for obesity, insulin resistance and T2DM over their life course. Thus, the diagnosis and appropriate management of GDM has the potential to reduce significantly neonatal and maternal morbidity and the burden of T2DM [6].

The prevalence of polyhydramnios in this study population was 20%, and there is a significant positive relation between HbA1C and AFI ($P < 0.05$). This may be due to hyperglycemia lead to large placental volume or due presence of congenital anomalies. This agrees with result of Idris., *et al.* [7] the prevalence of polyhydramnios in their study population was 18.8%, this significantly higher than that in the general population, of around 1%.

The current study showed a significant positive relation between HbA1c with birth weight ($P < 0.05$) and fetal weight (FW) ($P < 0.05$) this agreed with Jodie., *et al.* [8] concluded that the association of HbA1C and birth weight was stronger when antepartum HbA1C was measured after GDM diagnosis (at 34w). Maternal hyperglycemia induces fetal hyperglycemia that augments fetal pancreatic maturation and hypertrophy, resulting in accelerated fetal growth. Modified Pederson hypothesis added amino acids and lipids to glucose that aggravate mixed fuel supplementation that contributes to fetal macrosomia.

Djelmis., *et al.* [9] reported significant relation ($P > 0.05$) between antepartum HbA1c measured after GDM diagnosis and birth weight. This study included women diagnosed with GDM and measured HbA1c 4 weeks before delivery. These findings were supported by the study of Gandhi., *et al.* [5] they measured HbA1C in the second and third trimester and found that when A1C was divided into more than (6.5%) and less than (6.5%) categories, mean 'birth weight centile' was highest among those with high HbA1C. Among women with T1DM, third trimester A1C is positively correlated with birth weight and macrosomia [10,11] but A1C in the first trimester is negatively correlated with birth weight, possibly due to limited placental development [12].

In this study the incidence of neonatal hypoglycemia was 40% and showed a highly negative significant correlation between HbA1c and neonatal glucose level ($P < 0.05$) and this agrees with Kulenthran., *et al* [4]. They had shown that HbA1c levels in late pregnancy are good predictors of hypoglycemia in the newborn, giving an area under the curve of 99%. In simple terms, what this means is that if there were two babies who were randomly selected, one with hypoglycemia and the other without, the probability that the hypoglycaemic neonate would have shown an abnormally high maternal HbA1c would be around 99% [13]. On the other hand, using mean HbA1c levels throughout pregnancy as a marker for neonatal hypoglycemia, Taylor., *et al.* [14] showed that there was no correlation between neonatal hypoglycemia and HbA1c levels at any point in pregnancy or with the mean pregnancy HbA1c levels. However, they found a significant negative correlation between neonatal blood glucose levels and maternal blood sugars during labor.

The current study showed that the percent of a preterm baby was about 30% and this agrees with the result of Yang and colleagues [15] who showed percentage of 28 in Pregnancy Outcomes of Births in Nova Scotia from 1988 to 2002 in Women with and without pre-gestational diabetes.

The current study showed a significant positive relation between HbA1c and prematurity rate ($p < 0.05$). This means that when HbA1c increases, the incidence of prematurity also increases this agree with result of Murphy., *et al* [16].

The rate of CS among the study population was 33 cases (66%), and there was a significant positive relation between HbA1c and CS rate ($p < 0.05$). This is because poor long term diabetic control results in more fetal complications that may need CS either elective or emergent and this doesn't agree with result of Murphy., *et al* [16]. They reported that Two-thirds of deliveries were by cesarean section with no difference between study and control groups.

Conclusion

In conclusion, the current study has ensured the importance of maternal glycemic control during pregnancy and that poor glycemic control as detected by maternal HbA1C at 34 weeks gestation \geq seven is significantly associated with many adverse neonatal outcomes as RDS, macrosomia, polyhydramnios, prematurity and low APGAR score.

Future Research Directions

Significant limitations of the current biomarkers for diagnosing gestational diabetes and predicting fetal outcomes are mainly imprecision [19]. The rapid progress made by multi-omics technologies, nanomedicine and molecular bioinformatics may provide definitive methods for accurate early diagnosis and hasten development in precision medicine of gestational diabetes. Several novel innovative

researches are ongoing such as using hair segment untargeted metabolomics, plasma, and urinary metabolites as promising future biomarkers of early gestational diabetes.

Conflicts of Interest

None of the researchers has any conflict of interests.

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