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The Role of Hemoglobin A1c Level in Prediction of Adverse Obstetric and Neonatal Outcomes in Pregestational Diabetic Pregnancies

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ABSTRACT

Background: An elevated HbA1c has been associated with a significantly increased risk of many adverse obstetric outcomes including congenital anomalies, spontaneous abortions, preeclampsia, and large for gestational age infants at birth. **Objective:** This study aimed to predict adverse obstetric and neonatal outcomes in pregestational diabetic pregnancies. **Patients and method:** The study included 72 pregnant diabetic women in the third trimester of pregnancy (28 weeks to 40 weeks) divided into two groups; Good glycemic control group (Hb A1c <6.5%) (n=30), and poor glycemic study group (HbA1c >6.5%) (n=42). Participants were followed up till delivery and maternal and perinatal outcomes were studied. All participants were subjected to careful history taking, through clinical and obstetric examination. The newborns were examined, and their conditions were assessed by pediatricians.

Result: There was a statistically non-significant association between glycemic control of the studied patients and mode of delivery; Poor glycemic study group had 35 (83.3%) cesarean sections (CS) versus 20 (66.7%) CS in good glycemic control group. There was a statistically significant association between glycemic control of the studied patients and body mass index. There was a statistically significant association between glycemic control of the studied patients and parity which was significantly higher in those with high parity. There was a statistically non-significant association between glycemic control of the studied patients and their age, gravidity, history of abortion, IUFD or macrosomia. **Conclusion:** Antenatal HbA1c values are useful to predict adverse obstetric and neonatal outcomes, especially preterm delivery and hyperbilruinemia in pregnancies complicated by pregestational diabetes. Also, antenatal HbA1c values are useful for objective risk stratification of patients with pregestational diabetes.

Keywords: Hemoglobin A1c, Pregnant diabetic, Women neonatal outcomes, Cesarean section.

INTRODUCTION

All women of childbearing age with diabetes should be counseled about the importance of tight glycemic control prior to conception. Observational studies show an increased risk of diabetic embryopathy, especially anencephaly, microcephaly, congenital heart disease, and caudal regression, directly proportional to elevations in HbA1c during the first 10 weeks of pregnancy [(1)].

There has been increasing interest in the use of the HbA1c during pregnancy for an objective assessment of glycemic control and risk stratification. An elevated HbA1c has been associated with a significantly increased risk of many adverse obstetric outcomes including congenital anomalies, spontaneous abortions, preeclampsia, and large for gestational age infants at birth [(2)].

There remains debate regarding the accuracy of HbA1c throughout gestation. As erythrocytes circulate, hemoglobin undergoes a gradual glycation that is significantly correlated with the degree and chronicity of hyperglycemia exposure. However, the accuracy of the HbA1c value can be affected by race/ethnicity, anemia, chronic renal failure, liver disease, HIV, as well as any condition that increases red blood cell turnover, including pregnancy [(3)]. Although there has been considerable debate on the ability of the HbA1c to predict obstetric outcomes, current published studies focus on single values in either the first or third trimester due to increased red blood cell turnover. Also, HbA1c is slightly lower in normal pregnancy than in normal non-pregnant women [(4)].

The aim of this work was to predict the adverse obstetric and neonatal outcomes in pregestational diabetic pregnancies by single 3rd trimester HbA1c level.

PATIENT AND METHODS

This study was a prospective cohort study was carried out in the Department of Obstetrics and Gynecology at Zagazig University Hospitals, Sharkia, Egypt in the period from December 2021 till June 2022. The study included 72 pregnant diabetic women in the third trimester of pregnancy (28 weeks to 40 weeks) attending at Zagazig University Hospitals Antenatal Care Clinic. They were divided into; ***Group I:*** Poor glycemic study group (Hb A1c >6.5%), and ***Group II:*** Good glycemic control group (Hb A1c <6.5%).

Inclusion criteria; Pregnant women with pregestational diabetes mellitus (type 1 or type 2 diabetes). Maternal age >18 years and gestational age 28 weeks to 40 weeks. Singleton pregnancy.

Exclusion criteria:

Multiple pregnancy. Placenta previa. Known fetal anomaly. Uncertain gestational age. Chronic medical disorder as thyroid, renal and cardiac disease. Pregnant women diagnosed with gestational diabetes mellitus (GDM). Pregnant diabetic women with vascular

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changes as retinopathy, nephropathy and neuropathy. Gestational age less than 28 weeks.

All women in this study were subjected to full history through clinical and obstetric examination and investigations.

Pregestational diabetic pregnancy was confirmed by prior diagnosis before pregnancy or either a 1-hour, 50-gram glucose challenge test >200 mg/dL or with 2 elevated values on a 3-hour, 100-gram glucose tolerance test at less than 20 weeks' gestation. Also, all participants were subjected to complete blood count, blood group, Rhesus factor, coagulation profile, fasting plasma glucose level and 2-hour post-prandial plasma glucose, liver and kidney functions test [(5)]**.** Finally, fundus examination was done for all diabetic women to exclude diabetic Retinopathy [(6)].

Fetal investigations:

Trans-abdominal ultrasound examination were done for fetal viability, gestational age confirmation, measurement of fetal abdominal circumference (AC), amniotic fluid index, and calculation of expected fetal birth weight (EFBW) before delivery. Trans-abdominal ultrasound was used for exclusion of fetal anomaly and for fetal biophysical profile [(7)]**.** Thereafter, Doppler US assessed placental vascularization and calculated flow indices (done to preeclamptic patients) and Doppler study of umbilical artery and middle cerebral artery if indicated [(7)].

Assay of hemoglobin A1c:

Blood samples were collected in heparinized disposable plastic tubes, EDTA containing plastic tubes and empty tubes. The heparinized tubes were centrifuged at 3000 rpm for 15 minutes and obtained plasma was aliquoted in Eppendorf tubes and was stored in deep freezer at–20c.

Turbidimetric method [(8)]:

This method utilizes the interaction of antigen and antibody to determine the HbA1c in whole EDTA blood. HbA1c in test samples is adsorbed onto the surface of latex particles, which react with anti-HbA1c (antigen-antibody reaction) and gives agglutination. The amount of agglutination is measured as absorbance which is proportional to HbA1c value.

Reagents:

(R1) Latex: Sodium azide (0.95 gm/L).
(R2) Anti-human hemoglobin A1c mouse monoclonal antibody and stabilizers.
(C) Calibrator: Nominal value stated on the vial label.
(LR) Lysing reagent.

Specimen collection and preparation [(8)]:

Collect venous blood with EDTA containing tube. To determine HbA1c, a hemolysate must be prepared for each sample.

1. Dispense 1 ml of lysing reagent into patient tubes.
2. Place 10 µl of well mixed whole blood into the appropriately labeled lysing reagent tube. Mix thoroughly.
3. Allow to stand for 5 minutes.

- **Procedure [(8)]: Wavelength:** 630 nm (620 optional). **Method:** Fixed rate, and **Temperature:** 37°C.
- **Range:** The HbA1c assay range is 3% to 16%. Results in this range can be reported and used directly.
- **Follow up** of our patients in antenatal outpatient clinic done every 2 weeks till 36 weeks, then every week till delivery for uncomplicated patients. All neonates were examined by pediatrician after delivery.

Obstetric management:

Decisions of delivery:

- Decisions of delivery were depended on fetal and maternal conditions.
- In uncomplicated cases, patients were admitted 2 weeks before EDD.
- Early hospitalization was required for; Diabetic stabilization for uncontrolled blood sugar. Complications e.g.: gestational hypertension, preeclampsia, polyhydramnios, and for termination of pregnancy for urgent causes.
- Antenatal steroids were given for fetal lung maturity and insulin must be simultaneously increased to maintain euglycemia.

Timing of delivery:

Under strict metabolic control and antenatal surveillance delay delivery until 38w or onset of spontaneous labor. In well controlled diabetic pregnancies, no good evidence for routine delivery before 38 weeks. Some patients were delivered preterm between (34 weeks and 36 weeks) due to; ROM, fetal distress, uncontrolled DM, polyhydramnios, poor metabolic control or other obstetric indication.

Mode of delivery:

A- Vaginal delivery either by:

1- Spontaneous onset of labor.

2- Induction of labor: Induction of labor either by amniotomy, oxytocin or prostaglandins tablets (PGE1 and PGE2) was done when the fetus not macrosomic and the cervix was considered favorable. If labor fails or doesn't progress satisfactorily, then patient to be taken up for LSCS. Continuous fetal monitoring and partogram were mandatory.

B- Lower segment cesarean section:

Indication for LSCS: Fetal distress. Previous history of IUFD and refuse of induction of labor. Elderly primigravida. Breech or unstable presentation. Macrosomic baby (EFW≥4.5 KG). Polyhydramnios, preeclampsia not favorable for induction, and diabetes which is difficult to control.

Neonatal care: The neonates of mothers with pre-gestational DM are at risk of developing complications, at the time of delivery all neonates were examined by pediatrician.

Ethical consent:

An approval of the study was obtained from Zagazig University Institutional Research Board with IRB number #9132. Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis:

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Data were tested for normal distribution using the Shapiro Walk test. Qualitative data were represented as frequencies and relative percentages. Chi-square test ($\chi 2$) was used to calculate difference between two or more groups of qualitative variables. Quantitative data were expressed as mean ± SD (Standard deviation). Independent samples t-test was used to compare between two independent groups of normally distributed variables (parametric data). P-value <0.05 was considered significant.

RESULT

Table 1 showed that there was a statistically significant association between glycemic control of the studied patients and BMI (Group I associated with high BMI). There was a statistically significant association between glycemic control of the studied patients and parity which was significantly poor in those with high parity. There was a statistically non-significant association between glycemic control of the studied patients and their age, gravidity, history of abortion, IUFD or macrosomia.

Table (1): Demographic data between study group and control group:

Variable	Glycemic control		Test	
	Poor control (Group I) N=42 (%)	Good control (Group II) N=30 (%)	t/U/χ^2	P-value
Age (year): Mean ± SD	30.12 ± 5.58	28.93 ± 4.17	1.031	0.306
Body mass index (BMI) (kg/m^2): Mean ± SD	35.39 ± 4.12	32.27 ± 4.6	3.02	0.004*
Gravidity: Median Range	3.5 2 – 8	3 0 – 9	-1.326	0.185
Parity: Median Range	2 0 – 6	1 1 – 4	-2.397	0.017*
Previous Abortion: No Yes	27 (64.3%) 15 (35.7%)	14 (46.7%) 16 (53.3%)	2.126	0.137
Previous IUFD No Yes	37 (92.5%) 5 (7.5%)	24 (80%) 6 (20%)	2.391	0.122
Previous Macrosomia No Yes	35 (83.3%) 7 (16.7%)	24 (80%) 6 (20%)	0.131	0.717

χ^2: Chi-square test, t: independent sample t test, U: Mann Whitney test *P<0.05 is statistically significant. IUFD**:** intrauterine fetal death, BMI: Body mass index.

Table 1 showed that there was a statistically significant association between glycemic control of the studied patients and type of diabetes. Type 2 diabetes increase the risk of poor glycemic control (***Group I***) by 3.7 folds that was detected by crude odds ratio (COR) with 95% confidence interval (95% CI) [1.11 – 12.33].

Table (2): Correlation between glycemic control and type of diabetes of the studied patients:

Type of Diabetes	Glycemic control		Test	
	Poor control (Group I)	Good control (Group II)	χ^2	P-value
Type 1(IDDM)	5 (11.9%)	10 (33.3%)	4.872	0.027*
Type 2 (NIDDM)	37 (88.1%)	20 (66.7%)		
Total	42	30		

χ^2: Chi-square test, *P <0.05 is statistically significant.

Table 3 showed that there was a statistically non-significant association between glycemic control of the studied patients and APGAR score at one minute. There was a statistically significant association between glycemic control of the studied patients and APGAR score at five minutes (significantly poor in those with *Group I*). In both groups, there is significant increase in APGAR score over time. There was a statistically non-significant association between glycemic control of the studied patients and either gestational age at delivery or birth weight. There was a statistically non-significant association between glycemic control of the studied patients and mode of delivery. In group I, there was a non-significantly increased risk of CS by 2.5 folds that was detected by COR about 2.5 (95% CI: 0.82 – 7.6).

Table (3): Difference between two groups according to fetal outcomes:

Variable	Glycemic control		Test	
	Poor control (Group I) N=42 (%)	Good control (Group II) N=30 (%)	t/χ^2	P
APGAR at 1 minute Mean ± SD	7.14 ± 1.24	7.57 ± 1.19	-1.475	0.149
APGAR at 5 minutes Mean ± SD	8.17 ± 1.23	8.77 ± 0.9	-2.475	0.019*
Birth Weight (g) Mean ± SD	3276.33 ± 762.75	3025.33 ± 634.41	1.474	0.145
Gestational age at delivery: Mean ± SD	36.46 ± 1.76	36.66 ± 1.58	-0.492	0.765
Mode of delivery: CS	35 (83.3%)	20 (66.7%)	2.695	0.101
VD	7 (16.7%)	10 (33.3%)		

t/χ^2: independent sample t test *P<0.05 is statistically significant **P≤0.001 is statistically highly significant.

Table 4 showed that there was a statistically non-significant association between glycemic control of the studied patients and preclampsia. Postpartum hemorrhage occurred in *Group II* as a result of atony due to anemia in about 3.4%, while in *Group I* due to over-sized uterus 7% and atony about 2.3%. Traumatic delivery (perineal 4.8% in *Group I* and 6.7% in *Group II* or cervical tear 2.4% in group I) but rates of traumatic delivery were higher in poor glycemic study group (group I).

Table (4): Maternal outcomes in the studied groups:

Variable	Glycemic control		Test	
	Poor control (Group I) N=42 (%)	Good control (Group II) N=30 (%)	χ^2	P-value
PET: No	32 (76.2%)	17 (56.7%)	3.068	0.08
Yes	10 (23.8%)	13 (43.3%)		
Traumatic delivery: Absent	39 (92.8%)	28 (93.3%)	2.66	>0.999
Present	3 (7.1%)	2 (6.7%)		
Postpartum hemorrhage: Absent	38 (90.4%)	29 (96.6%)	0.24	0.782
Present	4 (9.6%)	2 (3.4%)		

χ^2: Chi-square test. PET: Preclampsia.

Table 5 showed that there was a statistically significant relation between glycemic control of the studied patients and RDS. Group I significantly increase risk of RDS by 4.87 folds. There was statistically significant relation between glycemic control of the studied patients and hypoglycemia.

Group I significantly increase risk of hypoglycemia by 20.59 folds. There is statistically significant relation between glycemic control of the studied patients and preterm delivery. Group I significantly increase risk of preterm delivery by 4.5 folds. There was statistically non-significant relation between glycemic control of the studied patients and NICU admission. Group I non-significantly increases risk of NICU admission by 3.19 folds. There was statistically significant relation between glycemic control of the studied patients and hyperbilirubinemia. Group I significantly increase risk of hyperbilirubinemia. There was statistically non-significant relation between glycemic control of the studied patients and congenital anomalies. Group I non-significantly increases risk of congenital anomalies by 2.7 folds.

Table (5): Neonatal outcome of the studied groups:

Variable	Glycemic control		Test		COR (95% CI)
	Poor control (Group I) N=42 (%)	Good control (Group II) N=30 (%)	χ^2	P-value	
RDS:					
No	11 (26.2%)	19 (63.3%)	9.993	0.002*	4.87 (1.77 – 13.39)
Yes	31 (73.8%)	11 (36.7%)			
Hypoglycemia:					
No	17 (40.5%)	28 (93.3%)	20.861	<0.001**	20.59 (4.32 – 98.1)
Yes	25 (59.5%)	2 (6.7%)			
Preterm delivery:					
No	28 (66.7%)	27 (90%)	5.283	0.022*	4.5 (1.16 – 17.44)
Yes	14 (33.3%)	3 (10%)			
NICU:					
No	31 (73.8%)	27 (90%)	2.929	0.087	3.19 (0.81 – 12.66)
Yes	11 (26.2%)	3 (10%)			
Hyperbilirubinemia:					
No	33 (78.6%)	30 (100%)	Fisher	0.008*	Undefined
Yes	9 (21.4%)	0 (0%)			
Congenital anomalies:					
No	35 (83.3%)	27 (93.3%)	2.929	0.087	2.7 (0.52 – 14.06)
Yes	7 (16.7%)	2 (6.7%)			

*P <0.05 is statistically significant ** P ≤0.001 is statistically highly significant. χ^2:chi-square test. COR: crude odds ratio, CI: Confidence interval. RDS: respiratory distress syndrome, NICU: neonatal intensive care unit.

DISCUSSION

In the present study, there was statistically significant relation between glycemic control of the studied patients and body mass index (poor glycemic study group associated with high BMI), this is in agreement with the study performed by **Xodo *et al.* [9]**, that retrospective analysis had been performed at the University Hospital of Udine to determine glycemic control and adverse obstetric outcome in women affected by pre-gestational diabetes. That Ninety-four women satisfied the inclusion criteria was subdivided into two groups depending on the median HbA1c level into about 49 patients had HbA1c <7% and 45 patients >7%. They noted BMI were lower in the group with HbA1c <7% than in the group with higher HbA1c.

In the present study, there was a statistically non-significant relation between glycemic control of the studied patients and mode of delivery was 35 (83.3%) CS in poor glycemic study group versus 20 (66.7%) CS in good control group, this is in agreement with the study performed by **Heo *et al.* [10].** They reviewed the pregnancy outcome of diabetic patients. A total of 5212 women who delivered live singleton infants at Korea University Medical Center were included; 129 overt diabetes women and 322 gestational diabetes women were categorized as diabetic women, and the others were categorized as non-diabetic women. They noted a significant increase in the risk of CS in diabetic mothers**.**

The current study found no statistically significant differences between the studied groups regarding the maternal complications during vaginal delivery, including cervical lacerations, perinatal tears and postpartum hemorrhage. Postpartum hemorrhage occurred in good glycemic control group due to atony in patients suffering from anemia but in poor glycemic study group due to over-sized uterus and atony. This is in line with study of **Kong *et al.* [11]**, which revealed that there is no statistically significant relation between diabetes and the presence of perineal laceration or tears and subsequent postpartum hemorrhage

In the current study, there was statistically non-significant relation between glycemic control of the studied patients and birth weight, 3276.33 (SD 762.75) in poor glycemic study group versus 3025.33 (SD 634.41) good control group, this is not in harmony with results of **Mitrović *et al.* [12],** who analyzed the course and outcome of pregnancy in the patients with diabetes regarding preterm delivery, perinatal morbidity and mortality. There was a higher incidence of fetal macrosomia in the women with poor diabetic control compared to good controlled mothers, which could be explained by different sample size.

In the present study, there was a statistically significant association between glycemic control of the studied patients and preterm delivery. Poor glycemic study group significantly increases risk of preterm delivery by 4.5 folds. This is in harmony with the study

of **Xodo *et al.* [9]**, who performed a retrospective analysis at the University Hospital of Udine to determine glycemic control and adverse obstetric outcomes in women affected by pre-gestational diabetes. Women with HbA1c >7% tended to deliver significantly earlier (35.57–38) than women with HbA1c ≤7% (38–38.43). Several factors could explain the higher rate of preterm birth in women with increase HbA1c, including the high trend of iatrogenic birth at 35–36 weeks in the presence of both an altered glycemic diary and ultrasound signs of metabolic failure, or the increased rate of hypertensive disorders and preeclampsia.

In the present study, there was a statistically significant association between glycemic control of the studied patients and adverse perinatal outcome, poor glycemic study group significantly increases risk of hypoglycemia, admission to the NICU, hyperbilirubinemia, RDS, and congenital anomalies. This is in agreement with the study of **Knight *et al.*[13],** who investigated the outcomes in type 2 diabetic patient. Diabetic patients had higher rates of preeclampsia, polyhydramnios, LGA infant, shoulder dystocia, CS, fetal anomaly, neonatal hypoglycemia and hyperbilirubinemia, RDS and admission to the NICU.

The present study showed the ability of HbA1c in prediction of fetal outcome; There was a statistically non-significant association between glycemic control of the studied patients and APGAR at one minute, and there was a statistically significant association between glycemic control of the studied patients and APGAR at five minutes (significantly lower in those with poor glycemic study group). This is in agreement with **Al-Bakri *et al.* [14]** the study included a total of 102 neonates, 34 neonates of mothers with gestational diabetes (GDM), 34 neonates of mothers with pregestational diabetes (DM) and 34 neonates of mothers with normal pregnancy as control group. They conclusion that; neonate of pregnancies complicated by diabetic mellitus had lower may be explained by maternal hyperglycemia and fetal hyperinsulinism.

In a retrospective study conducted by **Ye *et al.*[15]** that an HbA1c cutoff value <6.5% (29 mmol/mol) showed adequate sensitivity to exclude diabetic related pregnancy complications (85.0%) but low specificity (31.8%), increase in the HbA1c level was significantly associated with the risk of preterm delivery, neonatal hyperbilirubinemia, and neonatal asphyxia. That in line with present study, there was statistically significant relation between glycemic control of the studied patients and adverse perinatal outcome, where poor glycemic study group significantly increases risk of hypoglycemia, hyperbilirubinemia and preterm delivery.

In our findings, there was a statistically non-significant association between glycemic control of the studied patients and mode of delivery that in poor glycemic study group there was non-significantly increased risk of CS by 2.5 folds that was detected by COR about 2.5 (95%CI: 0.82 – 7.6) and there was a statistically non-significant association between glycemic control of the studied patients and PET which were higher in poor glycemic study group. This is in agreement with those of **Owens *et al.* [16]** who demonstrated in a cohort of 323 diabetic women, including 215 with T1DM, an association between HbA1c and maternal and fetal complications, including LGA, preterm delivery, CS, and pre-eclampsia **[16].** However, they reported a cut-off of HbA1c >6.8% (51 mmol/mol) that could predict this comorbidity.

CONCLUSION

In conclusion, antenatal HbA1c values are useful to predict adverse obstetric and neonatal outcomes, especially preterm delivery and hyperbilruinemia in pregnancies complicated by pregestational diabetes. Also, antenatal HbA1c values are useful for objective risk stratification of patients with pregestational diabetes. Strict glycemic control throughout pregnancy with A1c target of <6.5% leads to reduced rates of obstetric and neonatal adverse outcomes independent of early pregnancy glucose control.

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