Correlation of HbA1c levels in late pregnancy with maternal and perinatal outcome in patients with gestational diabetes mellitus

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ABSTRACT

Background: Estimation of HbA1c in gestational diabetes mellitus patients is not being recommended by any societies/guidelines as studies regarding the role of HbA1c for monitoring of euglycemic control and predicting the maternal and perinatal outcomes in GDM patients (unlike overt diabetes) are conflicting and sparse.

Methods: This was a prospective study with an aim to evaluate the role of HbA1c estimation in late pregnancy (early and late third trimester) for prediction of pregnancy outcomes in GDM patients. 53 patients with GDM (diagnosed before third trimester) were recruited for the study. HbA1c levels were estimated in late pregnancy (at 28-32 weeks and again repeated at 37-39 weeks or at the time of delivery). Correlation of HbA1c levels in third trimester with maternal and perinatal outcome was studied in patients with gestational diabetes mellitus and cut off taken was 5.8%.

Results: Of the total 53 patients 54.7% had HbA1c levels <5.8% and 45.3% had HbA1c ≥5.8% done at 28-32 weeks. Also when HbA1c levels done at 37-39 weeks POG/ at the time of delivery, 52.8% patients had <5.8% and 47.2% had HbA1c ≥5.8%. Approximately one-fourth of the patients had HbA1c ≥5.8% even with normal blood sugar levels (euglycemic) control. There was statistically significant increased incidence of polyhydramnios, LGA (large for gestational age babies) and increased mean birth weight in patients with HbA1c ≥5.8%, done in late pregnancy. However there was no statistically significant difference in the incidence of preterm labour, gestational hypertension or preeclampsia, urinary tract infections, vulvovaginal infections, caesarean deliveries and postpartum haemorrhage in patients with HbA1c ≥5.8% compared to patients with HbA1c <5.8%.

Conclusions: The study revealed that in patients of GDM with HbA1c levels ≥5.8% done in third trimester was statistically significantly associated with increased incidence of polyhydramnios, large for gestational age babies and increased mean birth weight when compared to patients with HbA1c <5.8%.

Keywords: Gestational diabetes mellitus, HbA1c, Late trimester, LGA babies, Polyhydramnios

INTRODUCTION

The prevalence of gestational diabetes mellitus (GDM) is rising globally and there is wide variation in the prevalence due to ethnic heterogeneity among different population and also because of the different screening and diagnostic criteria being used.1

In 2017 International Diabetes Federation estimated that 21.3 million women had some form of hyperglycemia in pregnancy; of these 86.4% was due to GDM.2 GDM is associated with maternal complications like higher incidence of caesarean section, hypertensive disorders of pregnancy, birth trauma, increases the risk of Type 2 diabetes in later life etc.
Similarly perinatal and neonatal morbidities are also increased in GDM patients; these include macrosomia, shoulder dystocia, respiratory distress syndrome (RDS), birth injuries, polycythaemia, hypoglycaemia, hyperbilirubinemia etc. long term sequelae in offspring with in utero exposure to maternal hyperglycemia include higher risks of obesity, impaired glucose metabolism and diabetes in later life.\textsuperscript{2,6}

As there is high prevalence of diabetes in Indian ethnicity, universal screening for diabetes in pregnancy is recommended. There is no well-defined role of HbA1c in the diagnosis of GDM as yet. Attempts were made to determine whether HbA1c can be used as screening or diagnostic test for gestational diabetes.\textsuperscript{7,8} Although for making the diagnosis of overt diabetes during pregnancy the IADPSG (The International Association of the Diabetes and Pregnancy Study Groups) recommends that glycosylated hemoglobin (HbA1c) should be measured at the first prenatal visit. Values > 6.5% (for HbA1c) establish the diagnosis of overt diabetes.\textsuperscript{9}

Recent studies have indicated that HbA1c level during pregnancy may predict GDM in women at high risk for diabetes.\textsuperscript{10,11} The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study provided data that both HbA1c level and 75 g 2 hour (h) Oral glucose tolerance test (OGTT) done for screening, if abnormal are associated with adverse pregnancy outcomes. However, the association was more significant for the OGTT than the HbA1c levels.\textsuperscript{12}

HbA1c is a special fragment formed by the binding of glucose to the C or D chain of haemoglobin A (HbA) and as a result of non-enzymatic catalysis of mature haemoglobin (Hb) and glucose. HbA1c can reflect the mean blood glucose level within past 8 to 10 weeks and is not affected by daily fluctuations in the blood glucose concentration.\textsuperscript{13} It is lower in all three trimesters of normal pregnancy, although no consensus on the reference range of HbA1c in pregnant women at different period of gestation have been reached till now. To improve the adverse pregnancy outcomes in pregnant women with GDM, strict euglycemic control of the blood glucose with treatment is necessary. Daily self-monitoring of blood glucose is recommended in all patients of DIP (Diabetes in pregnancy) and GDM for euglycemic control. Measurement of blood glucose (fasting and post prandial) may not actually reflect the mean blood glucose levels. Thus, glycated hemoglobin (HbA1c) may serve as an adjunctive parameter reflecting the mean blood glucose in pregnancy over last 3 months.\textsuperscript{14}

The role of HbA1c in pregnancy with pre-gestational diabetes is well documented. 2015 NICE (National Institute for Health and Care Excellence) guidelines recommend to measure HbA1c levels in all pregnant women with pre-existing diabetes at first visit and also to consider measuring it in the second and third trimesters to assess the level of risk for the pregnancy.\textsuperscript{15}

The role of HbA1c in monitoring of euglycemia in GDM pregnancies and prediction of outcome has not been well defined till now. HbA1c levels not recommended to be done in pregnancy with GDM as published studies have found conflicting correlation between HbA1c levels with euglycemic control, maternal and perinatal outcomes. Most of the studies have focussed on HbA1c level at the time of screening for GDM in second trimester and the literature regarding HbA1c levels in third trimester with outcomes is very sparse.\textsuperscript{5,10}

As the role of HbA1c in GDM patients for prediction of maternal and foetal outcome has not been proven due to scarcity of data. So the study was planned to evaluate the usefulness of estimating HbA1c in late pregnancy, if any to predict the adverse maternal and perinatal outcomes in GDM patients.

**METHODS**

This was a prospective study in which 53 pregnant women with Gestational diabetes mellitus were recruited in the study. Approval from the Institutional Ethics Committee was taken. On the basis of 15% abnormal perinatal or pregnancy outcomes among GDM patients, 95% confidence level and 10% permissible error the calculated optimum sample size came out to be 49.

Patients with overt diabetes, multiple pregnancy, chronic hypertension, heart disease, liver disease, kidney disease, moderate and severe iron deficiency anemia, fetal congenital anomalies, Thalassemia and GDM diagnosed after 28 weeks of gestation were excluded from the study.

HbA1c was measured at 28 - 32 weeks and again at 37 - 39 weeks/at the time of delivery. From each patient 5c.c blood was collected in EDTA vials and HbA1c levels were measured with the help of latex agglutination inhibition assay method. Samples were taken at any time of the day irrespective of fasting status of the patients. Upper reference range of HbA1c that was taken in our study was 5.8%. Pregnancy outcomes were compared in patients with GDM in relation to HbA1c values. Study duration was 18 months.

**RESULTS**

Of the total patients recruited for the study (53), the mean age was 28 years. 94.3% women belonged to the middle socioeconomic strata and 5.66% belonged to lower strata. 92.5% of our patients were residing in urban areas as compared to 7.5% of the patients who came from rural areas. There was no statistically significant difference in demographic details and also in mean age and BMI in groups with patients with HbA1c levels more than or less than 5.8% (Table 1).
Table 1: Demographic distribution in patients with HbA1c < and ≥ 5.8% at 28-32 weeks and at 37-39 weeks at the time of delivery.

| Variables          | 28 - 32 weeks |            |            | 37 - 39 weeks/at the time of delivery |            |
|--------------------|---------------|------------|------------|---------------------------------------|------------|
|                    | HbA1c < 5.8%  | HbA1c ≥ 5.8% | P-value    | HbA1c < 5.8%                         | HbA1c ≥ 5.8% | P-value |
| Age (years)        |               |            |            |                                       |            |
| 20-25              | 6             | 8          | 0.475      | 6                                     | 8          | 0.474   |
| 26-30              | 12            | 11         |            | 13                                    | 10         |         |
| >30                | 8             | 8          |            | 6                                     | 10         |         |
| BMI (kg/m²)        | 18-25         | 10         | 0.888      | 9                                     | 12         | 0.808   |
| 26-30              | 13            | 10         |            | 14                                    | 9          |         |
| >30                | 6             | 3          |            | 4                                     | 5          |         |
| Background         | Rural         | 2          | 2          | 0.606                                 | 1          | 3       | 0.544   |
|                    | Urban         | 27         | 22         |                                       | 27         | 22      |         |
| Socioeconomic strata | Upper class  | 0          | 0          | 0.685                                 | 0          | 0       | 0.646   |
|                    | Middle        | 26         | 24         |                                       | 23         | 27      |         |
|                    | lower         | 2          | 1          |                                       | 2          | 1       |         |
| Educational status | Illiterate    | 1          | 1          |                                       | 1          | 1       |         |
|                    | Primary education | 7      | 9          | 0.455                                 | 8          | 8       | 0.404   |
|                    | Upto 10th standard | 12     | 13         |                                       | 10         | 15      |         |
|                    | Graduates and post graduates | 5 | 5 |                                       | 4          | 6       |         |

Table 2: Obstetric history.

| Primigravidae | At 28-32 weeks | At 37-39 weeks/at the time of delivery |
|---------------|----------------|---------------------------------------|
|               |                |                                       |
| Multi         | 23             | 16                                    | 22                                    | 17         |
| Para 1        | 16             | 15                                    | 17                                    | 14         |
| Para 2        | 3              | 5                                     | 4                                     | 4          |
| Para>2        | 0              | 0                                     | 0                                     | 0          |
| Abortion1     | 3              | 7                                     | 6                                     | 4          |
| Abortion2     | 1              | 2                                     | 1                                     | 2          |
| Abortion3     | 0              | 1                                     | 0                                     | 1          |
| Abortions>3   | 0              | 1                                     | 0                                     | 1          |
| Live1         | 4              | 12                                    | 4                                     | 12         |
| Live2         | 3              | 3                                     | 3                                     | 3          |
| Live>2        | 0              | 0                                     | 0                                     | 0          |

Previous obstetric history was also comparable in patients with HbA1c value < 5.8% and ≥ 5.8% done at late pregnancy Table 2. 39.5% of patients with controlled blood sugars (based on fasting and post-prandial sugars) had HbA1c levels ≥5.8% at 28-32 weeks. 27% of the patients who had controlled blood sugars had HbA1c levels ≥5.8% at 37-39 weeks/time of delivery. 100% of the patients with uncontrolled blood sugars had HbA1c ≥5.8% when done at 28-32 weeks as well as at 37-39 weeks/time of delivery (Table 3).

The incidence of polyhydramnios was significantly higher in the patients with HbA1c ≥ 5.8% at 28 - 32 weeks (p = 0.015) and at 37-39 weeks/at the time of delivery (p = 0.02). However there was no statistical difference in the incidence of preterm labor, gestational hypertension or preeclampsia, urinary tract infections, vulvovaginal infections, cesarean deliveries and postpartum hemorrhage in patients with HbA1c ≥ 5.8% compared to patients with HbA1c < 5.8% (Table 4).

Mean birth weight of neonate was 2.85 kg (±0.54) in patients having HbA1c < 5.8% (done at 28 - 32 weeks) as compared to 3.22 kg (±0.57) in patients having HbA1c ≥ 5.8% and this difference was statistically significant (p value = 0.02). Similarly mean birth weight of neonates was 2.82 kg (±0.53) in patients having HbA1c < 5.8%...
Table 3: Association of glycemic control with HbA1c levels in early (28 - 32 weeks) and late third trimester (37-39 weeks/ at the time of delivery).

| Blood sugar control | No. of patients (n = 53) | At 28 - 32 weeks | At 37 - 39 weeks/ time of delivery |
|---------------------|--------------------------|------------------|-----------------------------------|
|                     | HbA1c <5.8% | HbA1c ≥5.8% | HbA1c <5.8% | HbA1c ≥5.8% |
| Controlled blood sugar levels | 48 | 29 | 19 (39.5%) | 28 | 13 (27.0%) |
| Uncontrolled blood sugar levels | 5 | 0 | 5 (100%) | 0 | 12 (100%) |
| Total patients | 53 | 29 | 24 (45.3%) | 28 | 25 (47.2%) |

Table 4: Association of maternal outcomes with HbA1c in the early third trimester and late third trimester.

| Variable | HbA1c<5.8% (% | HbA1c≥5.8% (N = 24) | P-value | HbA1c<5.8% | HbA1c≥5.8% | P-value |
|----------|----------------|---------------------|---------|------------|------------|---------|
| Pre-eclampsia | 3 (10.3%) | 6 (25.0%) | 0.271 | 4 (14.3%) | 5 (20.0%) | 0.719 |
| UTI | 3 (10.3%) | 5 (20.8%) | 0.293 | 3 (10.7%) | 5 (20.0%) | 0.453 |
| Vulvo vaginal infections | 1 (3.4%) | 2 (8.3%) | 0.584 | 2 (7.1%) | 1 (4.0%) | 1.000 |
| Polyhydramnios | 1 (3.4%) | 7 (29.2%) | 0.02 | 1 (3.6%) | 7 (28%) | 0.02 |
| Preterm labour | 4 (16%) | 4 (16.6%) | 0.590 | 4 (14.2%) | 4 (16.2%) | 1.000 |
| Postpartum haemorrhage | 1 (3.4%) | 2 (8.3%) | 0.584 | 0% | 3 (12.0%) | 0.098 |
| Caesarean deliveries | 9 (31%) | 10 (41.7%) | 0.422 | 9 (32.1%) | 10 (40.0%) | 0.55 |

Table 5: Association of perinatal outcomes with HbA1c in the early third trimester and in late third trimester.

| Variable | HbA1c<5.8% | HbA1c≥5.8% | P-value | HbA1c<5.8% | HbA1c≥5.8% | P-value |
|----------|------------|------------|---------|------------|------------|---------|
| Gestational age at delivery | 37.18 (±1.61) | 37.44 (±1.19) | 0.51 | 37.18 (±1.61) | 37.44 (±1.19) | 0.51 |
| Birth Weight | 02.85 (±0.54) | 03.23 (±0.57) | 0.022 | 2.82 (±0.53) | 3.23 (±0.56) | 0.01 |
| Large for gestational age baby | 0 (0%) | 05 (20.8%) | 0.015 | 0 (0%) | 05 (20.0%) | 0.02 |
| CMF baby | 0 (0%) | 0 (%) | ---- | 0 (0%) | 0 (%) | ---- |
| Shoulder dystocia | 0 (0%) | 01 (4.2%) | 0.453 | 0 (0%) | 01 (4%) | 0.472 |
| Neonatal hypoglycemia | 03 (10.3%) | 06 (25%) | 0.271 | 04 (14.5%) | 05 (20%) | 0.719 |
| Still birth | 0 (0%) | 1 (4.2%) | 0.453 | 0 (0%) | 1 (4%) | 0.472 |
| RDS | 03(10.3%) | 2(8.3%) | 0.557 | 2(7.1%) | 3 (12.0%) | 0.65 |
| Cardiomyopathy | 0 (0%) | 0 (%) | ---- | 0 (0%) | 0 (%) | ---- |
| Polycythemia | 0 (0%) | 0 (0%) | ---- | 0 (0%) | 0 (%) | ---- |
| Hyperbilirubinemia | 8 (27.65%) | 9 (37.5%) | 0.557 | 7 (25%) | 10 (40%) | 0.377 |
| Needs NICU care | 0 (0%) | 0 (%) | ---- | 0 (0%) | 0 (0%) | ---- |
| Hypocalcemia | 0 (0%) | 0 (0%) | ---- | 0 (0%) | 0 (%) | ---- |
| Erb’s palsy | 0 (0%) | 0 (0%) | ---- | 0 (0%) | 0 (%) | ---- |

There was statistically significant increased incidence of LGA babies in patients with HbA1c > 5.8% (done both at 28 - 32 weeks and 37 - 39 weeks/time of delivery). There was no statistically significant difference in other perinatal complications in patients with HbA1c levels < 5.8% versus ≥5.8% - shoulder dystocia, neonatal
hypothenar, stillbirth, respiratory distress syndrome and neonatal hyperbilirubinemia (Table 5).

**DISCUSSION**

Diabetes complicating pregnancy is on the rise especially in the South Asian countries like India. The incidence is reported to be as high as 41% in one of the Indian study using the criteria of IADPSG for diagnosis. Screening, diagnosing and managing GDM optimally is of utmost importance to decrease the short term and long term maternal and fetal complications. The hallmark of managing GDM and decreasing the maternal and fetal complications is to have euglycaemic control which is monitored by doing fasting and post prandial blood sugar levels. The usefulness of glycated hemoglobin (HbA1c) as a tool to assess glycaemic status in pregnant women remains controversial. HbA1c levels are affected by red blood cell turnover in addition to plasma glucose and its level during pregnancy has not been standardized. NICE guidelines recommend measuring HbA1c levels in all pregnant women with pre-existing diabetes at the booking appointment to determine the level of risk for the pregnancy and preconceptionally also. It also recommends considering measurement of HbA1c levels in the second and third trimesters of pregnancy for women with pre-existing diabetes to assess maternal and fetal complications. The role of HbA1c in second and third trimester in GDM patients to predict the maternal and fetal outcomes is not clear. Currently it is not recommended by any of the societies/guidelines and also the literature regarding this is very sparse.

There is no consensus on the cut off levels of normal HbA1c values that should be used during pregnancy for studying the correlation of HbA1c with maternal and fetal outcomes. Although HbA1c levels can be used for diagnosing overt diabetes taking the cut off as 6.5% according to IADPSG.

Different studies have used different cut offs of HbA1c in second and third trimester to predict the pregnancy outcomes. Versantvoort et al studied HbA1c levels in healthy pregnant women and concluded that the cut off levels of HbA1c in first, second and third trimester were 5.4%, 5.5% and 5.8% respectively. Cut off levels taken for HbA1c in our study was 5.8% in third trimester. Other studies done to predict the outcomes in correlation to the HbA1c levels in GDM patients have taken cut off values for third trimester as 5.0% by Baquerel et al, 6.0% by Sen Gupta et al and 5.9% by Rador et al study.

In the study 45.3% of the patients had HbA1c levels ≥5.8% at 28 - 32 weeks and 47.2% had HbA1c ≥5.8% at 37 - 39 weeks/ at the time of delivery. 39.5% of patients with controlled blood sugars had HbA1c levels ≥ 5.8% at 28 - 32 weeks. 27% of the patients with controlled blood sugars had HbA1c levels ≥ 5.8% at 37 - 39 weeks/ at the time of delivery.

There was no statistically difference in the maternal complications (preterm labor, gestational hypertension or preeclampsia, urinary tract infections, vulvovaginal infections, caesarean deliveries and postpartum haemorrhage) when the HbA1c level was ≥ 5.8% or <5.8% at 28 - 32 weeks as well as at 37 - 39 weeks/ at the time delivery. The incidence of polyhydramnios was significantly higher in patients with HbA1c ≥ 5.8% at 28 - 32 weeks (p = 0.010) as well as at 37 - 39 weeks/at the time of delivery (p = 0.02). The study done by Yi-Ran Ho et al in Taiwanese women correlating the level of HbA1c (cut off taken was 5.7% in third trimester) with maternal complication in GDM patients, showed that there was significant increase in the incidence of preterm labour and pre-eclampsia when the HbA1c was > 5.7%.

In another study done on 100 patients by Sen Gupta et al, there was significant increase in the incidence of vulvovaginitis, preterm delivery, polyhydramnios and post partum haemorrhage when the HbA1c level was > 6% in 2nd and 3rd trimester in patients with GDM or pregestational diabetes.

Mean gestational age at the time of delivery of all patients in our study was 37 weeks. Mean birth weight of neonate was found out to be statistically more in patients with HbA1c value ≥ 5.8% as compared to patients with HbA1c < 5.8%.

There was statistically significant increased incidence of Large for gestational age (LGA) babies when the HbA1c levels were ≥ 5.8% done at early and late third trimester (p = 0.015 and 0.02 respectively). Similar to our results, study done by Barquiel et al and Subash et al also showed that increased level of HbA1c in third trimester were significantly associated with large for gestational age babies in GDM patients. Hassan Khairy et al also showed similar results in their study that high HbA1c levels in third trimester are good predictor of macrosomia in pregnancy with GDM.

In the study, of the total Large for gestational baby, 39.5% of the babies were born to mother who had euglycemic control (as per their fasting and blood sugar levels) but with HbA1c level ≥ 5.8%, indicating HbA1c level is a better marker for predicting large for gestational age babies in third trimester.

Other perinatal complications seen in our study population (N = 53) were neonatal hypoglycemia (17%), respiratory distress syndrome (7.5%), shoulder dystocia (1.9%), still birth (1.9%) and neonatal hyperbilirubinemia (32.1%) but there was no statistically significant difference in the incidence of these complications between the patients who had HbA1c ≥5.8% (done at early and late third trimester) as compared to patients with HbA1c<5.8%. Contrary to the study, Hassan Khairy et al in their study in GDM patients showed that the incidence of neonatal hypoglycemia and RDS were significantly higher when the HbA1c level were raised with the cut offs of HbA1c levels taken as > 7.9%. Similarly study done by Sen Gupta et al in patients with
pregestational diabetes/GDM showed statistically significant higher incidence of hypoglycemia, hyperbilirubinemia and respiratory distress syndrome when the HbA1c levels were >6% in 2nd and 3rd trimester.

CONCLUSION

The study revealed that when the levels of HbA1c was ≥5.8% done at late pregnancy in GDM patients, there was statistically significant increased incidence of polyhydramnios, large for gestational age babies and had increased mean birth weight; however no statistically difference in other maternal and perinatal complications were seen. The study also revealed that 39.5% of patients in early and 27% of the patients in late third trimester with euglycemic controls (based on fasting and postprandial blood sugars) had HbA1c value ≥5.8%. These correlations between HbA1c and maternal and fetal outcomes and with blood sugar levels are depicting significance of HbA1c even at late pregnancy of GDM patients, which is routinely not being done. Short comings of the study was that as there are no standardised HbA1c values available for third trimester for prediction of maternal and perinatal outcomes, the cut-off of raised HbA1c value was took as ≥ 5.8%. Also number of patients (53) recruited in the study was less and more long term maternal and neonatal follow up should have been done. More large scale and long term studies are required to ascertain whether HbA1c should be routinely advised in third trimester for prediction of maternal and fetal outcomes in GDM patients.

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