

A Prospective Research on HbA1c Levels in Individuals without GDM and its Association with Pregnancy Outcome

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Abstract

Aim: The study on HbA1c levels in patients without GDM and its correlation with pregnancy outcome. **Methods:** The prospective analytical study was conducted in the Department of Obstetrics and Gynaecology, Darbhanga Medical College and Hospital, Laheriasarai, Darbhanga, Bihar, India, from February 2020 to February 2021. 50 Healthy antenatal women who are neither previously overt diabetic nor having gestational diabetes in the previous pregnancies were selected. A total of 50 antenatal mothers between the age group of 18 and 35 years and with gestational period more than or equal to 24 weeks, who were willing to participate were included in the study after getting proper informed and written consent. **Results:** A total of 50 nondiabetic pregnant were taken in the study. The mean age of the population was 25.09 years. All of them were belonging more or less to same socioeconomic status. The majority of participants presented in their 2nd trimester and few in third trimester. Congenital anomalies were ruled out by anomaly scan. At the time of sample collection for HbA1c all the foetuses of the participating mothers were in cephalic presentation and the liquor was adequate on clinical examination. The mean HbA1c was found to be 5.19%. Among the study population 36 (72%) had normal vaginal delivery, 1(2%) had forceps assisted vaginal delivery and the remaining 13 (26%) had caesarean section for various reasons. 48(96%) of the study subjects came with labour pains, 1 (2%) among them had foetal distress and meconium stained liquor each respectively for which they were taken up for emergency caesarean section. Remaining 1 (2%) antenatal mother had oligohyramnios during her last trimester. About 90% participants had normal birth weight babies and the mean glycaemic status of the neonate was 55.75 mg/dL. Among the subjects 2 new-borns (4%) had NICU admission, one for 1 day for phototherapy and the other was born with congenital ichthyosis for which the baby was admitted and was on continuous monitoring. **Conclusion:** Our study showed no significant association between the maternal HbA1c levels in non-diabetic mothers and the adverse pregnancy outcome.

Keywords: GDM, HbA1c, pregnancy

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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, hypoglycemia, 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.[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.[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.[9]

Recent studies have indicated that HbA1c level during pregnancy may predict GDM in women at high risk for diabetes.[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.[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.[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.[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.[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.[16]

Material and methods

The prospective analytical study was conducted in the Department of Obstetrics and Gynaecology, Darbhanga Medical College and Hospital, Laheriasarai, Darbhanga, Bihar, India, from February 2020 to February 2021, after taking the approval of the protocol review committee and institutional ethics committee.

50 Healthy antenatal women who are neither previously overt diabetic nor having gestational diabetes in the previous pregnancies were selected. A total of 50 antenatal mothers between the age group of 18 and 35 years and with gestational period more than or equal to 24 weeks, who were willing to participate were included in the study after getting proper informed and written consent.

Methodology

All the pregnant women who are obese (with BMI 30), who had history of previous delivery by cesarean section or delivered an anomalous baby were excluded. Those patients with multiple pregnancy or those with anomalous baby (confirmed by anomaly scan), those who have other medical and pregnancy related complications like anemia, hypertension, pre-eclampsia, previous bad obstetric history and associated surgical complications or if the patient has conceived by ART/IVF techniques in the index pregnancy were also not included in

the study. Those who were immune - compromised e.g. infection with HIV or Hepatitis B or C were also not taken in the study.

Routine blood investigations along with an obstetric ultrasonography were done for these patients. About five milliliter of blood sample is collected and was given for HbA1c assessment by high performance liquid chromatography which was done on the same day of OGTT. Then the antenatal mothers were followed up till their delivery and the details of the delivery and newborn were collected at the time of delivery as follows: 1) type of delivery, 2) gestational age at the time of delivery, 3) newborn plasma glucose levels estimated as soon as possible after delivery and 4) Neonatal Intensive Care Unit (NICU) admission of the newborn with number of days (if any) and the reason for admission are recorded. The above mentioned parameters were studied separately and correlated with the HbA1c values.

Results

A total of 50 non diabetic pregnant were taken in the study. The mean age of the population was 25.09 years. All of them were belonging more or less to same socioeconomic status. The majority of participants presented in their 2nd trimester and few in third trimester. Congenital anomalies were ruled out by anomaly scan. At the time of sample collection for HbA1c all the foetuses of the participating mothers were in cephalic presentation and the liquor was adequate on clinical examination. The mean Hba1c was found to be 5.19%.

The gross period of gestation at the time of delivery is shown in the Table 2.

Among the study population 36(72%) had normal vaginal delivery, 1(2%) had forceps assisted vaginal delivery and the remaining 13(26%) had caesarean section for various reasons. 48(96%) of the study subjects came with labour pains, 1(2%) among them had foetal distress and meconium stained liquor each respectively for which they

were taken up for emergency caesarean section. Remaining 1(2%) antenatal mother had oligohyramnios during her last trimester. She was closely followed up with medical and supportive treatment but was finally taken up for elective caesarean section at term in view of unresponsive severe oligohydramnios.

The birth weight and glycaemic status of the newborn were recorded and are found to be as Table 3

As seen from the Table 4 about 90% participants had normal birth weight babies and the mean glycaemic status of the neonate was 55.75 mg/dL. Among the subjects 2 new-borns (4%) had NICU admission, one for 1 day for phototherapy and the other was born with congenital ichthyosis for which the baby was admitted and was on continuous monitoring. Later the mother refused further management and was discharged at request and so lost for follow-up.

Table 1: Distribution of HbA1c among the study subjects

	Mean	Median	Mode	Standard deviation	Minimum	Maximum
HbA1c	5.19	5.18	5.20	0.36	4.11	6.14

Table 2: Distribution of period of gestation in the participants

Variable	Frequency	%
Term	42	84
Preterm	8	16

Table 3: Birth weight category distribution

Variable	Frequency	%
≤2.5 Kg	5	10
>2.5 kg	45	90

Table 4: Distribution of glycaemic status of the new-born immediately after delivery

	Mean	Median	Mode	Standard deviation	Minimum	Maximum
Glycaemic status (in mg/dL)	55.75	56.00	48	6.55	41	70

Table 5: The comparison of HbA1c values from various related studies

Studies with non-diabetic pregnant women as participants	Mean of HbA1c (in %)
Present study	5.19
Shobha et al ¹⁷	5.29
Nielsen et al ¹⁸	5.0
Yu et al ¹⁹	5.0
Bhavadharani et al ²⁰	4.9
Versantvoort et al ²¹	4.9

Table 6: Trimester specific reference ranges of HbA1c

Studies	Second trimester mean HbA1c	Third trimester mean HbA1c
Present study	5.13%	5.33%
O'Conner et al ²²	4.4%-5.4%	4.7%-5.4%
O'Kane et al ²³	4.9%	5%
Versantvoort et al ²¹	4.6%	4.9%
Gunter HH et al ²⁴	4.38%	4.33%

Discussion

Estimation of HbA1c value in healthy pregnant women after 24 weeks of pregnancy and its correlation with the delivery and foetal outcomes at the time of delivery was the main objective of the study.

In our study we found that the mean HbA1c was 5.19% among all the study subjects. The minimum and the maximum values of HbA1c estimated from our patients were found to be 4.11% and 6.14% respectively. In our study 11 (22%) of women were in their second trimester and estimated mean HbA1c was 5.13%, whereas the mean HbA1c of the remaining 39 (78%) women belong to third trimester was 5.33%.

The mean HbA1c value in our study was found to be 5.19%. This value when compared with the values of mean HbA1c from other similar studies is shown in Table 5.

Mean HbA1c value determined by our study was more or less comparable with all the above mentioned studies. The difference noticed may be due to difference in time of assessment, haemoglobin statuses or mild unnoticed haemoglobinopathies.

In our study trimester specific mean HbA1c values for second trimester was 5.13% whereas it was 5.33% for third trimester.

Trimester specific reference ranges of HbA1c observed in various studies are tabulated as given in Table 6.

In our present study the HbA1c value and parameters like birth weight of the baby, glycemic status of the newborn and NICU admission showed no significant association.

In our study, complications during delivery and foetal complications showed no association with the HbA1c value. We found no association between body mass index(BMI) and HbA1c and foetal birth weight in different groups of women which is

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similar to study conducted by Radder et al.[17] Versantvoort et al.[18] found no correlation between trimester specific HbA1c value and birth weight percentile. In a study conducted by Bhavadharani et al.,[19] it is observed in groups with HbA1c >5% and < 5%, except for macrosomia there were no differences in maternal and neonatal complications. But in a study conducted by Shobha et al.[20] they found that there was a possible association between the birth weight of the baby with that of maternal HbA1c value. In a study conducted by Mane et al.[21] the incidence of macrosomia in the newborns was found to be raised (16.7% from 5.9%) in the participants with HbA1c of 5.9% also they found that they had an elevated risk of pre-eclampsia (9.32% vs. 3.9%).

In a study conducted by Ribero et al.[22] in 2018 to calculate the increased maternal HbA1c levels and evaluate its relation with that of the infant's low birth weight, they found that there was no significant association between glycosylated haemoglobin and low birth weight in any of the groups even after adjusting the possible confounding factors.

In the study conducted by Bhavadharani et al.[19] there was considerably higher rate of normal vaginal delivery among the pregnant women who has <5% HbA1c value. According to a study conducted by Zheng et al.[23] the prevalence of primary caesarean section was higher in GDM mothers when compared to non-diabetic pregnant women, whereas HAPO, [24] a multicenter study, showed there were less number of primary caesarean deliveries with increasing maternal sugar levels. Mane et al.[21] also showed that the specificity and sensitivity for predicting the type of delivery especially primary caesarean section were 59% and 63% respectively. But in our study there is no significant association between type of delivery and maternal HbA1c value.

In a study conducted by Yi Ran Ho et al.[25] to assess the relationship between

mid-pregnancy HbA1c and the risk of unfavorable pregnancy outcome in non-diabetic pregnant women they found that there was significant association of elevated mid pregnancy HbA1c levels when compared to lower levels of <5%, with elevated risk of obstetric complications like pre-eclampsia, gestational hypertension, pre-term delivery and neonatal complications like macrosomia, sometimes low birth weight and elevated chances of intensive care unit admissions for the newborn.

Conclusion

Our study showed no significant association between the maternal HbA1c levels in non-diabetic mothers and the adverse pregnancy outcome. This shows that all the confounding factors and possible variables should be taken into consideration while estimating the HbA1c level and correlating its effect on maternal and foetal outcomes.

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