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Original Research Article

A prospective study on HbA1c levels in patients without GDM and its correlation with pregnancy outcome

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ABSTRACT

Introduction: Pregnancy is a diabetogenic state which places the mother as well as the foetus at high risk for certain complications even though the woman is neither GDM nor overt diabetic. This study aims at estimation of HbA1c value after 24 weeks of pregnancy and its correlation with the pregnancy outcome.
Materials and Methods: The study was done among 60 healthy pregnant women who are between 18-35 years. HbA1c was estimated and they were followed up for assessing pregnancy outcome. Birth weight >90th percentile, primary C-section, neonatal hypoglycaemia, any NICU admissions and neonate's condition at discharge were assessed.
Results: The mean of haemoglobin, OGTT (fasting, 1-hour and 2-hours) and HbA1c were 11.25mg/dL, 81.73mg/dL, 120.75mg/dL, 104.13mg/dL and 5.24% respectively. The trimester specific HbA1c levels in the second and third trimesters in the present study were found to be 5.11% and 5.27% respectively. Among the study subjects 51 (85%) women had term delivery whereas 9 (15%) women had preterm delivery. 42 women (70%) had normal delivery, 1(1.7%) patient had operative vaginal and the remaining 17(28.3%) patients had emergency caesarean section. It was observed that 5(8.3%) subjects had LBW and 55(91.7%) had normal birth weight neonates. Two neonates among the study subjects had NICU admission for other reasons.
Conclusion: The results obtained by this study showed low or no significant relationship between HbA1c levels estimation during pregnancy and pregnancy as well as foetal outcome, also adverse pregnancy outcomes have multifactorial influences rather than maternal glycaemic status alone.

1. Introduction

Pregnancy is a period where there will be considerable modifications in the maternal metabolism to adapt for the physical, structural, hormonal and psychological adjustments in the process of welcoming a new guest. As there is a continuous rise in post-prandial blood sugars during the whole pregnancy and in late pregnancy there will be increased insulin response, normal pregnancy is observed as a diabetogenic state.[1]

There will be energy stored in the early gestation which can be seen in the form of elevated maternal fat stores and reduction in concentration of free fatty acids. Maternal fasting glucose will be progressively decreased as there will be increase in fetoplacental utilization of glucose in later weeks of gestation.[1] Also there is significantly lower insulin sensitivity during pregnancy when compared to that after delivery.[2]

There are two forms of diabetes mellitus during pregnancy: pre-gestational or overt diabetes mellitus and gestational diabetes mellitus (GDM).[3] Because of this poor glycaemic control preconceptionally in woman with overt diabetes and who is more prone for diabetes during her pregnancy, particularly during first trimester, the foetus is placed at a high risk of congenital anomalies especially cardiac and neural tube defects.[4]

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GDM usually appears in the second half of pregnancy and it will generally be resolved after delivery. GDM has greater impact on the foetal development and it has got higher risk of the foetus acquiring disorders like diabetes or obesity in the adult life. Likewise it may lead to adverse outcome in the mother like increased risk of development of gestational hypertension which may lead to pre-eclampsia. GDM itself, along with other associated conditions, is one of the most common causes of operative interventions. In India the rate of prevalence of GDM is reported to be ranging between 3.8% and 41%.[5]

There are studies showing that women who previously had GDM have increased insulin resistance, reduced capacity of insulin secretion or in some cases a combination of these both findings and these pregnant women are more prone to diabetes and other medical co-morbidities in the long term.[6–8] Hence prompt diagnosis and appropriate control of the disease may help in reduction of adverse pregnancy and foetal outcomes.

Diabetes mellitus in general population or GDM is conventionally diagnosed by oral glucose tolerance test (OGTT) which is considered as the test of choice. Other screening strategies can be used preceding OGTT like fasting glucose levels in the plasma (FPG) or a glucose load test.[9] OGTT has been standardized for GDM diagnosis for several years. This test detects diabetes more effectively than fasting plasma glucose (FPG).[10]

But for OGTT or FPG testing the patient requires overnight fasting and she is subjected to glucose intake in bolus which may be unpleasant for most of the women. It also requires intense labour, the test is time consuming and the test has low reproducibility. The American Diabetes Association, in the year 2010, integrated estimation of glycated haemoglobin (HbA1c) as a diagnostic standard for diabetes mellitus in the general population with a cut-off value of 6.5% which was later validated by WHO in the year 2011.[11,12] This cut off was found to have high specificity for the diagnosis of diabetes mellitus.[13–15]

Glycated haemoglobin (HbA1c) is a formed by non-enzymatic linkage of haemoglobin with any sugar. When the blood sugar levels are increased, which is observed in case of diabetes, it is depicted by elevated levels of glycated haemoglobin in the plasma. Therefore this feature can be used as a criterion for the diagnosis of diabetes mellitus. HbA1c is a measure which ascertains the average plasma glycemic level for the preceding three months. Hence it can also be used as a test for monitoring and surveillance of glycemic control in the diabetics.[16]

Hence in this study we are determining the estimation of HbA1c and correlating its value with the maternal and foetal outcome.

2. Materials and Methods

This prospective cohort study was conducted in a multispecialty tertiary care hospital catering to both rural and semi-urban population during September 2018 to June 2020. Healthy antenatal women who are neither previously overt diabetic nor having gestational diabetes in the previous pregnancies were selected. A total of 60 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.

All the pregnant women who are obese (with BMI $\geq$ 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.

The institutional ethical committee approval was taken before starting the study. General, physical and antenatal examinations were done for all the study subjects. 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.

3. Results

Different parameters were recorded for all the 60 patients and analyzed by studying them under various headings and the following variables:

1. HbA1c
2. Period of gestation at the time of delivery
3. Type of delivery
4. Birth weight of the newborn
5. Glycemic status of the newborn
6. NICU admission of the newborn and number of days of admission (if any)

Table 1: Distribution of HbA1c among the study subjects

	Mean	Median	Mode	Standard deviation	Minimum	Maximum
HbA1c	5.24	5.20	5.00	0.38	4.32	6.20

A total of 60 non diabetic pregnant were taken in the study. The mean age of the population was 24.17 years. All of them were belonging more or less to same socioeconomic status. The majority of participants presented in their 2^{nd} 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 5.24%.

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

Table 2: Distribution of period of gestation in the participants

Variable	Frequency	%
Term	51	85.0
Preterm	9	15.0

Among the study population 42(70%) had normal vaginal delivery, 1(1.7%) had forceps assisted vaginal delivery and the remaining 17(28.3%) had caesarean section for various reasons. 59(98.3%) of the study subjects came with labour pains, 2(3.3%) among them had foetal distress and meconium stained liquor each respectively for which they were taken up for emergency caesarean section. Remaining 1(1.7%) 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.

Table 3: Birth weight category distribution

Variable	Frequency	%
≤ 2.5 kg	5	8.3
>2.5 kg	55	91.7

As seen from the Table 4 about 91.7% participants had normal birth weight babies and the mean glycaemic status of the neonate was 56.75 mg/dL.

Among the subjects 2 new-borns (3.3%) had NICU admission, one for 1 day for phototherapy and the other was born with congenital icthyosis 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.

4. 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 5.24% among all the study subjects. The minimum and the maximum values of HbA1c estimated from our patients were found to be 4.32% and 6.20% respectively. In our study 12 (20%) of women were in their second trimester and estimated mean HbA1c was 5.11%, whereas the mean HbA1c of the remaining 48 (80%) women belong to third trimester was 5.27%.

The mean HbA1c value in our study was found to be 5.24%. 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 5.11% whereas it was 5.27% 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 similar to study conducted by Radder et al.[25] Versantvoort et al.[21] found no correlation between trimester specific HbA1c value and birth weight percentile.

In a study conducted by Bhavadharani et al.,[20] 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.[17] 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.[26] 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 our present study we did not include variables like macrosomia or preeclampsia but,

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)	56.75	57.00	49	6.78	42	72

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	5.24
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:

	Second trimester mean HbA1c	Third trimester mean HbA1c
Present study	5.11%	5.27%
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%

HbA1c value ≥5.15% has sensitivity for predicting type of delivery (caesarean section), gestational age (preterm) and birth weight of baby (low birth weight) as 63%, 67% and 58% respectively whereas specificity of the same variables were found to be 59%, 47% and 60% respectively

In a study conducted by Ribero et al.[27] 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 glycated 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.[20] 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.[28] the prevalence of primary caesarean section was higher in GDM mothers when compared to non-diabetic pregnant women, whereas HAPO,[29] a multicenter study, showed there were less number of primary caesarean deliveries with increasing maternal sugar levels. Mane et al.[26] 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.[30] 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.

5. 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.

6. Source of Funding

None.

7. Conflict of Interest

The authors declare that there is no conflict of interest.

References

1. Catalano P. The Diabetogenic State of Maternal Metabolism in Pregnancy. *NeoReviews*. 2002;3(9):165e–72. doi:10.1542/neo.3-9-e165.
2. Bowes SB, Hennessy TR, Umpleby AM, Benn JJ, Jackson NC, Boroujerdi MA. Measurement of glucose metabolism and insulin secretion during normal pregnancy and pregnancy complicated by gestational diabetes. *Diabetologia*. 1996;39(8):976–83.
3. Gestational Diabetes in Primary Care ; 2020. Available from: https://www.medscape.com/viewarticle/408910_2.
4. Reece EA, Homko CJ, Hagay Z. Prenatal diagnosis and prevention of diabetic embryopathy. *Obstet Gynecol Clin North Am*. 1996;23(1):11–

28. doi:10.1016/s0889-8545(05)70242-4.
5. Mithal A, Bansal B, Kalra S. Gestational diabetes in India: Science and society. *Indian J Endocrinol Metab*. 2015;19(6):701–4. doi:10.4103/2230-8210.164031.
6. Ward KW, Johnston CLW, Beard JC, Benedetti TJ, Porte D. Abnormalities of islet B-cell function, insulin action and fat distribution in women with histories of gestational diabetes: relationship to obesity. *J Clin Endocrinol Metab*. 1985;61(6):1039–45. doi:10.1210/jcem-61-6-1039.
7. Dornhorst A, Bailey PC, Anyaoku V, Elkeles RS, Johnston DG, Beard RW. Abnormalities of Glucose Tolerance Following Gestational Diabetes. *Quart J Med*. 1990;77(3):1219–28. doi:10.1093/qjmed/77.3.1219.
8. Ryan EA, Imes S, Liu D. Defects in insulin secretion and action in women with a history of gestational diabetes. *Diabetes*. 1995;44:506–12.
9. Renz PB, Cavagnolli G, Weinert LS, Silveiro SP, Camargo JL. HbA1c Test as a Tool in the Diagnosis of Gestational Diabetes Mellitus. *PLOS ONE*. 2015;10(8). doi:10.1371/journal.pone.0135989.
10. Aekplakorn W, Tantayotai V, Numsangkul S, Sripho W, Tatsato N, Burapasiriwat T, et al. Detecting Prediabetes and Diabetes: Agreement between Fasting Plasma Glucose and Oral Glucose Tolerance Test in Thai Adults. *J Diabetes Res*. 2015;2015:1–7. doi:10.1155/2015/396505.
11. American Diabetes Association. Classification and diagnosis of Diabetes. *Diabetes Care*. 2015;38:s8–s16.
12. WHO Guidelines Approved by the Guidelines Review Committee. Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus: abbreviated report of a WHO Consultation. Geneva: World Health Organization; 2011.
13. Cavagnolli G, Comerlato J, Comerlato C, Renz PB, Gross JL, Camargo JL. HbA1cmeasurement for the diagnosis of diabetes: is it enough? *Diabetic Med*. 2011;28(1):31–5. doi:10.1111/j.1464-5491.2010.03159.x.
14. Kramer CK, Araneta MR, Barrett-Connor E. HbA1c and diabetes diagnosis: The Rancho Bernardo Study. *Diabetes Care*. 2010;33:101–3.
15. Carson AP, Reynolds K, Fonseca VA, Muntner P. Comparison of A1C and Fasting Glucose Criteria to Diagnose Diabetes Among U.S. Adults. *Diabetes Care*. 2010;33(1):95–7. doi:10.2337/dc09-1227.
16. Use of Glycated Haemoglobin (HbA1C) in the Diagnosis of Diabetes Mellitus: Abbreviated Report of a WHO Consultation. Geneva: World Health Organization; 2011.
17. Shobha P, Mathen S, Abraham J. Glycosylated hemoglobin values in nondiabetic pregnant women in the third trimester and adverse fetal outcomes: An observational study. *J Fam Med Prim Care*. 2016;5(3):646. doi:10.4103/2249-4863.197313.
18. Nielsen LR, Ekbom P, Damm P, Glumer C, Frandsen MM, Jensen DM, et al. HbA1c Levels Are Significantly Lower in Early and Late Pregnancy. *Diabetes Care*. 2004;27:1200–1. doi:10.2337/diacare.27.5.1200.
19. Luzolo GM, Beya DT, Numbi DK, Nyota PK, Ngandu PC, Manzambi BSM, et al. The Profile of Glycated Hemoglobin in Non-Diabetic Pregnant Women with Preeclampsia: A Case-Control Study in Kinshasa, the Democratic Republic of Congo. *Open J Obstet Gynecol*. 2020;10(03):365–89. doi:10.4236/ojog.2020.1030034.
20. Mohan V, Bhavadharini B, Mahalakshmi MM, Deepa M, Harish R, Ranjit U, et al. Elevated glycated hemoglobin predicts macrosomia among Asian Indian pregnant women (WINGS-9). *Indian J Endocrinol Metab*. 2017;21(1):184. doi:10.4103/2230-8210.196003.
21. Versantvoort ARE, Roosmalen J, Radder JK. Course of HbA1c in non-diabetic pregnancy related to birth weight. *Neth J Med*. 2013;71(1):22–5.
22. O'Connor C, O'Shea PM, Owens LA, Carmody L, Avalos G, Nestor L, et al. Trimester-specific reference intervals for haemoglobin A1c (HbA1c) in pregnancy. *Clin Chem Lab Med*. 2012;50(5):905–14. doi:10.1515/cclm.2011.397.
23. O'Kane MJ, Lynch PLM, Moles KW, Magee SE. Determination of a diabetes control and complications trial-aligned HbA1c reference range in pregnancy. *Clin Chim Acta*. 2001;311(2):157–9. doi:10.1016/s0009-8981(01)00579-4.
24. Gunter HH, Ritter C, Reinhardt W, Strahl B, Niesert S, Mitzkat HJ. Influence of non diabetic pregnancy on fructosamine and HbA1c concentration. *Z Geburtshilfe Neonatol*. 1995;4:199.
25. Radder JK, Roosmalen J. HbA1c in healthy, pregnant women . *Neth J Med*. 2005;63(7):256–9.
26. Mañé L, Roux JFL, Benaiges D, Rodríguez M, Marcelo I, Chillarón JJ, et al. Role of first trimester HbA1c as a predictor of adverse obstetric outcomes in a multi-ethnic cohort. *J Clin Endocrinol Metab*. 2016;102(2):390–7. doi:10.1210/jc.2016-2581.
27. Ribeiro L, Cruz S, Alves J, Filho IG, Soares JP, Figueiredo A, et al. High Level of Maternal Glycated Hemoglobin and Low Birth Weight. *Epidemiol Open Access*. 2018;8(1):1–7.
28. Zheng Y, Shen Y, Jiang S. Maternal glycemic parameters and adverse pregnancy outcomes among high risk pregnant women. *BMJ Open Diab Res Care*. 2019;7:e000774.
29. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. *Intl J Gynaecol Obstet*. 2002;78:69–77.
30. Ho YR, Wang P, Lu MC, Tseng ST, Yang CP, Yan YH. Associations of mid-pregnancy HbA1c with gestational diabetes and risk of adverse pregnancy outcomes in high-risk Taiwanese women. *PLoS One*. 2017;12(5):e0177563.

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