

# Association of HbA1c Value in Early Pregnancy in Nondiabetic Pregnant Woman with Obstetric Outcome: A Prospective Observational Study

Gayathri Kaveriappan<sup>1</sup>, Pushpa Kotur<sup>2</sup>, Thumjaa A<sup>3</sup>, Sasmita Mishra<sup>4</sup>

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## ABSTRACT

**Introduction:** Normal pregnancy is a diabetogenic state since during pregnancy there is an increase in insulin resistance. Gestational diabetes mellitus (GDM) is now emerging as the most common medical complication during pregnancy which leads to serious consequences. It is observed that women with GDM had a 7 times higher chance of manifestation of developing impaired glucose tolerance (IGT) or type 2 diabetes mellitus (T2DM) during the later part of life. The present study was planned to find out the association between HbA1c level before 14 weeks of gestation and cut-off values for better pregnancy outcomes.

**Materials and methods:** This hospital-based prospective observational study was conducted with 112 patients at the Department of Obstetrics and Gynaecology, Aarupadai Veedu Medical College & Hospital, Vinayaka Mission's Research Foundation (Deemed to be University), Puducherry, India, during the period of January 2021 to June 2022. Healthy 112 patients fulfilling the inclusion criteria were included in this study. The patient was asked to undergo screening for GDM at 24–26 weeks of gestation [International Association of Diabetes and Pregnancy Study Groups (IADPSG)]. Patients were followed up closely throughout pregnancy till delivery and 5 days postnatal period. Chi-square test and multivariate analysis were adapted to analyze the data by using the statistical package for the social sciences (SPSS), version 25.0, software.

**Results:** A total of 112 participants fulfilling the criteria for inclusion were evaluated for HbA1c levels during pregnancy. The oral glucose tolerance test (OGTT) was used for the detection of gestational diabetes between 24 and 28 weeks. The occurrence of GDM in the study population is 23.5%. The participants who had HbA1c  $\geq$  5.7% developed maternal, fetal, and neonatal complications. In the present study, it was observed that HbA1c  $\geq$  5.7% has a sensitivity of 89% and specificity of 80%.

**Conclusion:** The HbA1c value estimated during early pregnancy (<14 weeks) is useful in the prediction of GDM and it correlates well with adverse pregnancy outcomes. The cut-off value of 5.7% can be used for the prediction of GDM with good sensitivity and specificity. It can be an additional screening tool for GDM in addition to OGTT.

**Keywords:** Gestational diabetes mellitus, Hemoglobin A1c, Pregnancy outcome.

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## INTRODUCTION

Gestational diabetes mellitus (GDM) is characterized by irregular high blood glucose levels of changing rigorousness with onset or first recognition during pregnancy. Also, GDM is the most common metabolic disorder with a worldwide prevalence rate ranging from 5 to 25.5%. The prevalence varies with race, ethnicity, age, and body composition, as well as screening and diagnostic criteria. In India, in the past two decades, the burden of GDM has increased, with the prevalence ranging from 5 to 18%.<sup>1</sup> Malnutrition is another additional factor that also plays a major role in raising the prevalence rate. It has been shown that women with gestational diabetes and their offspring have an increased risk of developing type 2 diabetes mellitus (T2DM). During the past two decades, progressive changes are happening in the identification of risk factors of GDM, especially, the genetic risk factors and their relationship with T2DM.<sup>2</sup>

Hence, the routine screening of HbA1c is essential. Although HbA1c levels in early pregnancy are recommended as a screening test by some of the researchers in nondiabetic women, there is little clue regarding the threshold level to identify nondiabetic women who have an increased risk of adverse pregnancy outcomes and may need intervention.

<sup>1,2</sup>Department of Obstetrics and Gynaecology, Aarupadai Veedu Medical College & Hospital, Vinayaka Mission's Research Foundation (Deemed to be University), Puducherry, India

<sup>3</sup>Department of Pediatrics, Aarupadai Veedu Medical College & Hospital, Vinayaka Mission's Research Foundation (Deemed to be University), Puducherry, India

<sup>4</sup>Department of Biochemistry, Aarupadai Veedu Medical College & Hospital, Vinayaka Mission's Research Foundation (Deemed to be University), Puducherry, India

**Corresponding Author:** Gayathri Kaveriappan, Department of Obstetrics and Gynaecology, Aarupadai Veedu Medical College & Hospital, Vinayaka Mission's Research Foundation (Deemed to be University), Puducherry, India, Phone: +91 9597827058, e-mail: drgayathri9999@gmail.com

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Very few studies are available on the correlation of its value in the first trimester (<14 weeks) and pregnancy outcomes. Moreover, these studies have focused on only one or two adverse pregnancy outcomes like macrosomia/or maternal complications such as preeclampsia and the risk of developing T2DM.

The present study is planned to find out the association between HbA1c level before 14 weeks of gestation and cut-off values for better pregnancy outcomes.

## MATERIALS AND METHODS

This hospital-based prospective observational study was conducted at the antenatal outpatient department (OPD) of the Department of Obstetrics and Gynaecology, Aarupadai Veedu Medical College & Hospital, Vinayaka Mission's Research Foundation (Deemed to be University), Puducherry, India in a 700-bedded multispecialty tertiary hospital catering both rural and urban population, Puducherry, India, from January 2021 to June 2022. The study participants were all nondiabetic singleton pregnant women, between the age-group of 18–35 years with HbA1c  $\leq$ 5.9% before 14 weeks of gestation were selected for the study. Patients with HbA1c  $\geq$ 6%, period of gestation above 14 weeks, who were known cases of diabetes, history of GDM/preeclampsia in a previous pregnancy, eclampsia complicating pregnancy, chronic hypertension, renal disease, severe anemia with Hb below 7 g/dL (WHO) were excluded from the study.

All pregnant women fulfilling the criteria were counseled and requested to participate in the study after obtaining informed written consent. Demographic data and detailed history followed by general, physical examination, and antenatal examination were carried out. Routine investigations and ultrasound were carried out to determine the gestational age and to rule out complications of pregnancy. Furthermore, 5 mL of venous blood samples were collected and HbA1c estimation was done by the direct method. Routine investigations and ultrasonography were also carried out in subsequent trimesters.

The patient was asked to undergo screening for GDM at 24–28 weeks of gestation. Patients were followed up closely throughout pregnancy till delivery and 5 days postnatal period. The oral glucose tolerance test (OGTT) = 24–26 weeks, according to the International Association of Diabetes and Pregnancy Study Groups (IADPSG), FBS – 92 mg%; 1 hour – 180 mg%; and 2 hours – 153 mg%. If any one of these values was equal to or more than the cut-off value, it was treated accordingly. The participants were followed up till the delivery and various findings are noted.

## Statistical Analysis

Data were analyzed using a statistical package for the social sciences (SPSS), version 25.0, software, and results expressed as percentages, bar diagrams, the sample size was calculated with absolute precision of 4% and based on Bhavadharani et al.<sup>3</sup> considering the prevalence of macrosomia to be 4.7% with Chi-square test and multivariate analysis.

## RESULTS

The present study included 112 participants fulfilling the inclusion criteria and who were subjected to the estimation of HbA1c during pregnancy below 14 weeks and later subjected to screening at 24–28 weeks of pregnancy with OGTT for detection of GDM and pregnancy outcomes. These participants were followed up till 5 days postnatal.

**Table 1:** Relation of GDM with HbA1c level

HbA1c (%)	GDM			p-value
	Total (%)	No (%)	Yes (%)	
5.4	47 (42)	47 (52)	0	<0.001*
5.5	17 (15)	17 (19)	0	
5.6	19 (17)	18 (20)	1 (4.7)	
5.7	<b>6 (5)</b>	2 (2)	4 (19)	
5.8	<b>11 (9)</b>	3 (3)	8 (38)	
5.9	<b>13 (12)</b>	1 (1)	9 (42.8)	
Total	112 (100)	91 (100)	21 (100)	

\*Statistically significant difference

In the present study, out of 112 participants, 21 developed GDM and out of these 21 (23.5%) women, 20 (95.2%) had HbA1c  $\geq$ 5.7%, based on this observation HbA1c value of 5.7% can be taken as the cutoff value for the prediction of GDM. Hence, HbA1c  $>$ 5.7% has a significant *p*-value of 0.035 (Table 1).

In the present study, the mean age of the participants was  $\geq$ 26 years; 38.4% of the study population was in the age-group 21–25 years; 48.2% of the study population was in the age-group 26–30 years. The incidence of GDM was found to be 20% in the age-group of  $\geq$ 26 years with HbA1c cut-off  $\geq$ 5.7%. Overall, 97 (86.6%) women were between 21 and 30 years out of which 23 (23.7%) women had HbA1c  $>$ 5.7 out of which 17 (73.9%) women developed GDM whereas none of the women who had HbA1c  $<$ 5.7 developed GDM.

Out of 53 primigravida 13 (24.5%) and 17 (28.8%) were having HbA1c  $>$ 5.7%. Out of these, primigravida of 9 (42.9%) and multigravida of 12 (57.1%) developed GDM during their latter part of pregnancy. There is no significant correlation between parity and the development of GDM.

Twenty-one participants developed GDM in whom HbA1c was found to be  $>$ 5.7%, they underwent estimation of HbA1c only after 9 weeks of gestational age, whereas the women who got HbA1c estimated prior to 9 weeks did not develop GDM. Hence, 9–14 weeks would be optimal period of gestation for utilizing HbA1c for diagnosing GDM.

Pregnancy outcome is adverse in cases where HbA1c is elevated  $>$ 5.7%, whereas none of the patients developed GDM or any other adverse pregnancy outcome in women who had HbA1c  $<$ 5.7%. Therefore, HbA1c  $>$ 5.7% has a significant *p*-value of below 0.001 (Table 2).

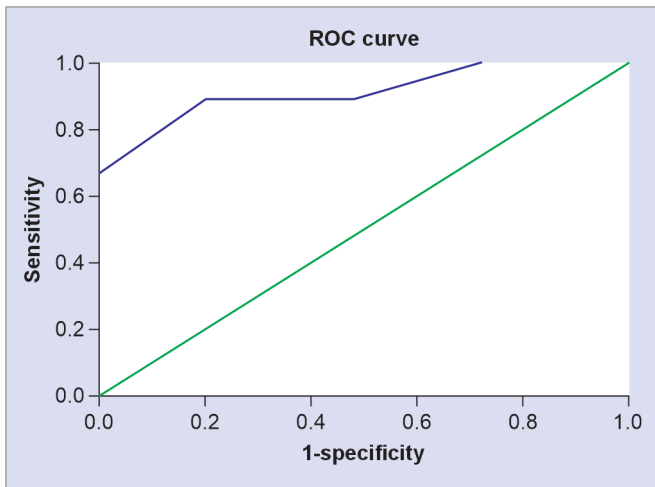
These babies of women who have HbA1c  $\geq$ 5.7% irrespective of whether they develop GDM or not have adverse fetal outcomes. However, a study with a larger sample size may explain this and will clarify whether this HbA1c cut-off value of 5.7 should be considered or not with regard to fetal outcome. However, there is significant *p*-value of below 0.001 in correlation with HbA1c  $>$ 5.7% (Table 2).

In the present study, out of 112 participants 58 (51.8%) women had had normal vaginal delivery out of which 49 (84.4%) women were having HbA1c  $>$ 5.7%. Total of 28 (25%) women underwent primary lower segment cesarean section out of which 11 (39.3%) participants had HbA1c  $>$ 5.7%; of those, 7 (33.3%) were found to have GDM and 4 (44.4%) did not have GDM. The participants who had instrumental delivery were 9 (8.1%) out of which 6 (7.3%) had HbA1c below 5.7% and 3 (27%) had HbA1c  $\geq$ 5.7%. Among whom only one woman (8%) had GDM and 2 (22%) were non-GDM. Hence, HbA1c  $\geq$ 5.7% has significance in the mode of delivery irrespective of the GDM status (Fig. 1).

**Table 2:** Distribution of maternal and fetal and neonatal complications in correlation with HbA1c level

Maternal complications	HbA1c <5.7%		HbA1c ≥5.7%		p-value
	GDM (%)		GDM (%)		
	No	Yes	No	Yes	
No complication	82 (100)	0	1 (11.1)	6 (28.6)	0.136
Oligohydramnios	0	0	0	2 (9.5)	<0.001*
Polyhydramnios	0	0	5 (55.6)	12 (57.1)	
Infections	0	0	3 (9)	1 (4.8)	
Total	82 (100)	0	9 (100)	21 (100)	
Fetal complications					
No complication	82 (100)	0	4 (44.4)	17 (81)	0.119
Macrosomia	0	0	3 (33.4)	3 (14.2)	0.1
Prematurity	0	0	2 (22.2)	1 (4.8)	
Total	82 (100)	0	9 (100)	21 (100)	
Neonatal complications					
No complication	82 (100)	0	7 (77.8)	15 (71.4)	0.473
Respiratory distress syndrome	0	0	2 (22.2)	2 (9.5)	<0.001*
Hypoglycemia	0	0	0	1 (4.8)	
Hyperbilirubinemia	0	0	0	3 (14.3)	
Total	82 (100)	0	9 (100)	21 (100)	

\*Statistically significant difference



**Fig. 1:** Hemoglobin A1c as a predictor for GDM. [Area under the curve, 0.911; Coordinates of the curve: Test result variable(s): HbA1c]

**DISCUSSION**

The prediction of GDM is important for providing adequate measures, especially through antepartum surveillance, thereby preventing maternal and fetal complications.

The present study was conducted by estimating HbA1c values in the first trimester with the assumption that women with elevated HbA1c values in the first trimester have the risk of developing GDM in the later part of pregnancy or have increased chances of adverse maternal and fetal outcomes. Several studies conducted with a similar objective reported that women with elevated HbA1c during early pregnancy have a higher risk of developing GDM. A total of seven similar studies (five prospective and two retrospective studies), conducted during the last decade, were reviewed and compared with the present study.

In the present study, it was observed that the pregnant women with elevated HbA1c ≥5.7% when subjected to OGTT had higher glucose levels and thus had chances of developing GDM. Although the accuracy of the test was moderate-to-fair level, HbA1c cut-off value of ≥5.7% is fairly good for predicting GDM and thus helpful for the prevention of complications and early management of GDM.

In the aforementioned studies, the percentage of women who developed GDM ranges from 11.2 to 23%, whereas in the study conducted by Trigona Rupala et al.,<sup>4</sup> and Arbib et al.,<sup>5</sup> the prevalence of GDM was 91 and 5.6%, respectively. The study conducted by Trigona Rupala et al.,<sup>4</sup> had a higher percentage of women who developed GDM because the participants included were in a high-risk group, those with obesity and previous history of GDM. In the retrospective study conducted by Arbib et al.,<sup>5</sup> the number of women who developed GDM was less because the selection criteria/inclusion criteria were stringent and only participants who underwent OGTT at 24 weeks were included. Probably their number would have been more if the women who underwent OGTT at 26 or 28 weeks of gestation. This study suggests that adverse pregnancy outcomes can be predicted with an HbA1c concentration of ≥5.45% and this was taken as the cut-off value. Further, it is also mentioned that with this cut-off value prediction of GDM and adverse pregnancy outcome with 83.3% sensitivity and 69% specificity.

A recent retrospective study revealed an interesting observation that measurement of HbA1c at least 1 year before pregnancy is a very good predictor of developing GDM. This study also states that increased maternal HbA1c above 5.7% was associated with the risk of delivering LGA (low for gestational age) infants despite taking measures to treat GDM. Most probably periodic monitoring of HbA1c and maintaining it below the cut-off value of 5.7% may help to bring down the risk of macrosomia. Hence, it is not only enough to measure HbA1c in the first trimester of pregnancy but also to monitor it and maintain it below cut-off value during each trimester is essential for the prevention of GDM and macrosomia.

Whereas in a prospective study conducted by Balaji Bhavadharani et al.,<sup>3</sup> where 11.6% of women developed GDM with the cut-off of 5.0% with sensitivity and specificity from 5.0 to 5.5% (37 mmol/mol) and 5.7% (39 mmol/mol), the specificity improved to 92 and 96.8%, respectively, but the sensitivity drastically came down to 24.6 and 14.9%, respectively. Conversely, when the HbA1c cut-off was lowered to 4.7% (28 mmol/mol), the sensitivity increased to 88.2%, but specificity decreased to 27.8%. Hence, HbA1c cut-off was taken as 5.0%. In the present study, it was observed that increased HbA1c ≥5.7% may be having an impact on β-cell function predisposing to GDM. Hence, comparing to other literature and their outcome, we can conclude that HbA1c 5.5 ± 3 can be used as cut-off for the prediction of GDM.

It is well-known fact that GDM in pregnancy predisposes to adverse maternal, fetal, and neonatal pregnancy outcomes.

In the present study, three non-GDM mothers delivered macrosomia babies. The study conducted by Walsh and McAuliffe,<sup>6</sup> mentioned that the majority of babies with macrosomia are born to nondiabetic mothers, and women delivering babies with macrosomia in the past are at higher risk of developing babies with macrosomia.

In concurrence with aforementioned study, the study conducted by Balaji Bhavadharani et al.,<sup>3</sup> found that pregnant women who had HbA1c >5% had a higher risk of developing macrosomia although they were not detected as having GDM. It is also mentioned that HbA1c can be taken as the marker for macrosomia independent of

diagnosis of GDM, the association of pregnancy outcomes including macrosomia, preterm, preeclampsia, and shoulder dystocia was also observed. Our results support the proposed HbA1c threshold of  $\geq 5.7\%$  in early pregnancy, although the association found with adverse outcomes differed in several ways.

However, the study conducted by Hughes et al.,<sup>7</sup> and Mañé Laure et al.,<sup>8</sup> found that women who had HbA1c  $< 5.9\%$  had an increased risk of preeclampsia of 2.3–3.9%, respectively. In the present study, none of the patients developed preeclampsia. If the present study is continued with a larger sample size a definite conclusion about preeclampsia can be drawn.

Incidence of polyhydramnios (14.7%) and fetal anomalies in 3% cases was quite high in the study conducted by Trigona Rupla et al.,<sup>4</sup> due to, as discussed earlier, the inclusion of women with a previous history of GDM and obese women. In the present study, the incidence of polyhydramnios is 57.1% (12) despite continuous monitoring and proper management.

The present study shows 25% of women underwent cesarean section which is comparable to that reported by Hughes et al.<sup>7</sup> which is 30%. The study was conducted in a relatively low-risk, and predominantly white population, whereas the population in the current study, although of low-risk group, was characterized by a majority of women belonging to ethnic minorities such as southcentral Asians.

From the observations of the present study, it can be stated that there is a definite correlation between a higher level of HbA1c during the first trimester ( $< 14$  weeks gestation) and the development of GDM which may lead to adverse pregnancy outcomes.

Finally concluding that HbA1c  $> 5.7\%$  has a strong prediction for detecting GDM and thus maternal and fetal complications can be reduced. The HbA1c test is a simple tool that can be used in prenatal and antenatal women to easily screen for GDM. The advantage of this test is that it does not require fasting and gives an idea about glycemic control in the preconception period as well as the period of organogenesis. Hence, it would be wiser to use this test to know the basal level of HbA1c and can be re-estimated in both the second and third trimesters to identify the threshold level of variations in HbA1c level. First-trimester HbA1c of  $> 5.7\%$  may be a useful screening tool to exclude from further testing of GDM in later pregnancy.

## CONCLUSION

The HbA1c value estimated during early pregnancy ( $< 14$  weeks) is useful in the prediction of GDM and it correlates well with adverse pregnancy outcomes. The cut-off value of 5.7% can be used for the prediction of GDM with good sensitivity and specificity. It can be an additional screening tool for GDM in addition to OGTT.<sup>9</sup> The strengths of the present study are as follows: All participants are of uniformly low-risk group. The variables studied were not limited to the development of GDM at latter part of pregnancy

or just a few complications of GDM but also various pregnancy outcomes. During the COVID-19 pandemic although following up on women was difficult, all efforts to follow the participants with the help of advanced technologies were continued and none of the participants were allowed to drop out and also appropriately managed throughout the pregnancy. The sensitivity (89%) and specificity (80%) with 5.7% as the cut-off value of HbA1c was reasonably good.<sup>10</sup>

## Limitation

The sample size was limited to 112, because of the COVID-19 pandemic duration, and the sample size could not be extended. The larger sample size would have given more weight to the study.

## ORCID

Gayathri Kaveriappan  <https://orcid.org/0000-0003-3589-1424>

## REFERENCES

1. Cunningham FG, Leveno KJ, Bloom SL, et al. Williams Obstetrics, 25th edition. New York: McGraw Hill Professional; 2022.
2. Clausen TD, Jensen DM, Mathiesen ER, et al. High prevalence of type II diabetes and prediabetes in adult offspring of women with gestational diabetes mellitus or type I diabetes: The role of intrauterine hyperglycaemia. *Diabetes Care* 2008;31(2):340–346. DOI: 10.2337/dc07-1596.
3. Bhavadharni B, Mahalakshmi MM, Deepa M, et al. Elevated glycated haemoglobin predicts macrosomia among Asian Indian pregnant women (WINGS). *Indian J Endocrinol Metab* 2017;21(1):184–189. DOI: 10.4013/2230-8210.196003.
4. Kulshreshtha, Shabdika, Patel TPK, et al. HbA1c as a predictor in early diagnosis of gestational diabetes mellitus. *Eur J Mol Clin Med* 2022;9(3):1731–1740.
5. Arbib N, Shmueli A, Salman L, et al. First trimester glycosylated hemoglobin as a predictor of gestational diabetes mellitus. *Int J Gynecol Obstet* 2019;145(2):158–163. DOI: 10.1002/ijgo.12794.
6. Walsh JM, McAuliffe FM. Prediction and prevention of the macrosomic fetus. *Eur J Obstet Gynecol Reprod Biol* 2012;162(2):125–130. DOI: 10.1016/j.ejogrb.2012.03.005.
7. Hughes RC, Moore MP, Gullam JE, et al. An early pregnancy HbA1c  $\geq 5.9\%$  (41 mmol/mol) is optimal for detecting diabetes and identifies women at increased risk of adverse pregnancy outcomes. *Diabetes Care* 2014;37(11):2953–2959. DOI: 10.2337/dc14-1312.
8. Mañé L, Flores-Le Roux JA, Gómez N, et al. Association of first-trimester HbA1c levels with adverse pregnancy outcomes in different ethnic groups. *Diabetes Res Clin Pract* 2019;150:202–210. DOI: 10.1016/j.diabres.2019.03.017.
9. Garg R, Roy P, Agrawal P, et al. Gestational diabetes mellitus: Challenges in diagnosis and management. *J South Asian Feder Obst Gynae* 2018;10(1):54–60. DOI: 10.5005/jp-journals-10006-1558.
10. Punnose J, Malhotra RK, Sukhija K, et al. HbA1c in the first trimester associated with adverse outcomes among pregnant Asian Indian women without gestational diabetes. *J Diabetes Complications* 2022;36(5):108187. DOI: 10.1016/j.jdiacomp.2022.108187.