

## To Study the Association between Early Pregnancy HbA1C and Pre-Eclampsia

D. Sujithra<sup>1</sup>, Narmadha R<sup>2</sup>, S. Cyril Prabha<sup>3</sup>

<sup>1</sup>Assistant Professor, Department of OBG-Srinivasan Medical College, Tiruchirapalli, India

<sup>2</sup>Assistant Professor, Department of OBG, Dhanalakshmi Srinivasan Medical College, Tiruchirapalli, India

<sup>3</sup>Assistant Professor, Department of OBG-Srinivasan Medical College, Tiruchirapalli, India

---

Received: 08-01-2023 / Revised: 10-01-2023 / Accepted: 04-03-2023

Corresponding author: Dr D. Sujithra

Conflict of interest: Nil

---

### Abstract

**Background:** Pre-eclampsia is a potentially serious condition that may lead to adverse effects in both mothers and neonates. Early detection and intervention may decrease morbidity. It is found that pre-eclampsia is associated with high HbA1c especially when GDM is detected early 1, 2.

**Aims:** To study the association between early pregnancy HbA1C and pregnancy outcomes (pre-eclampsia) and perinatal outcomes (Birth weight).

**Objectives:** To use early pregnancy HbA1c as a marker for pre-eclampsia.

### Materials and Methods:

#### Inclusion criteria:

- All antenatal women attending OPD in a tertiary care centre before 12 weeks of gestation.

#### Exclusion criteria:

- Overt diabetics
- HbA1c  $\geq 6.5$
- Hemoglobinopathies
- Anemia(hb<10)
- Chronic renal disease
- Multiple pregnancies

Patients were selected based on the above criteria. In this study, 100 patients were enrolled, and Blood was drawn for HbA1c levels at their first antenatal visit or before 12 weeks of gestational age along with other routine antenatal investigations. All of them were subjected to a 75gram GTT at 22-26 weeks of gestation, and values were interpreted using (IADPSG 2010/WHO 2013) criteria HbA1c was measured using HPLC (high-performance liquid chromatography) method. The objective of the study was to detect pre-eclampsia in patients with HbA1c ( $\geq 5.7$  &  $\leq 6.5$ ) which is taken as a standard cut-off. Variables studied were abortions anomalies, mode of delivery, maternal weight gain, baby's birth weight, Parity, previous history of GDM, family history of diabetes, maternal age.

**Statistical Analysis:** Statistical analysis was performed using IBM SPSS version 20.0. The categorical variables were expressed using frequency and percentage. The numerical variables were presented using mean and standard deviation. To find the statistical significance of agreement

of early pregnancy HbA1C cut off value with GDM, McNemars test was applied. To find the association of categorical factors with HbA1C chi-square test were used.

**Results: Pre-eclampsia** is associated with GDM<sup>14</sup> as seen in previous studies and higher HbA1c level detected in early pregnancy. Its early detection can prevent both the diseases reducing morbidity in both mother and the fetus.

**Keywords:** Preeclampsia, GDM, HbA1C and Pregnancy Outcomes.

This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>) and the Budapest Open Access Initiative (<http://www.budapestopenaccessinitiative.org/read>), which permit unrestricted use, distribution, and reproduction in any medium, provided original work is properly credited.

## Introduction

Pre-eclampsia is a potentially serious condition that may lead to adverse effects in both mothers and neonates. Early detection and intervention may decrease the morbidity. It is found that pre-eclampsia is associated with high HbA1c especially when GDM is detected early [1,2]. GDM is associated with a higher rate of hypertensive complications than normal pregnancy. Risk of pre-eclampsia is increased in GDM (15- 20% vs 5-7 % in non GDM).

This is due to a combination of factors like insulin resistance, genetic factors, age and BMI [3-5]. Macrosomia is defined as babies whose birth weight is above 90<sup>th</sup> percentile for gestational age. American College of Obstetrics and Gynaecology defines 4.5kg as cut off to define macrosomia but there is some increased risk of morbidity if birth weight is >4kg [6].

Infants of mothers with GDM have asymmetrical macrosomia with abnormal thoracic and abdominal circumference. Organomegaly will be present. In untreated GDM the risk of macrosomia is as high as 40% (person hanson).

On the other hand severe maternal diabetes (particularly type 1) with vasculopathy and impaired renal function may be associated with intra uterine growth restriction and SGA [7,8].

## Materials and Methods

### Inclusion criteria:

- All antenatal women attending AIMS OPD before 12 weeks of gestation.

### Exclusion criteria:

- Overt diabetics
- HbA1c  $\geq 6.5$
- Hemoglobinopathies
- Anemia(hb<10)
- Chronic renal disease
- Multiple pregnancies

Patients were selected based on the above criteria. In this study, 100 patients were enrolled, Blood was drawn for HbA1c levels at their first antenatal visit or before 12 weeks of gestational age along with other routine antenatal investigations. All of them were subjected to a 75 gram GTT at 22-26 weeks of gestation, and values were interpreted using ( IADPSG 2010/WHO 2013 ) criteria HbA1c was measured using HPLC (high-performance liquid chromatography) method.

Objective of the study was to detect pre-eclampsia in patients with HbA1c ( $\geq 5.7$  &  $\leq 6.5$ ) which is taken as a standard cut off. Variables studied were abortions anomalies, mode of delivery, maternal weight gain, baby's birth weight, Parity, previous history of GDM, family history of diabetes, maternal age.

**Study design:** This is a prospective observational study done in a tertiary care hospital

Statistical analysis was performed using IBM SPSS version 20.0. The sample size was taken as 100.

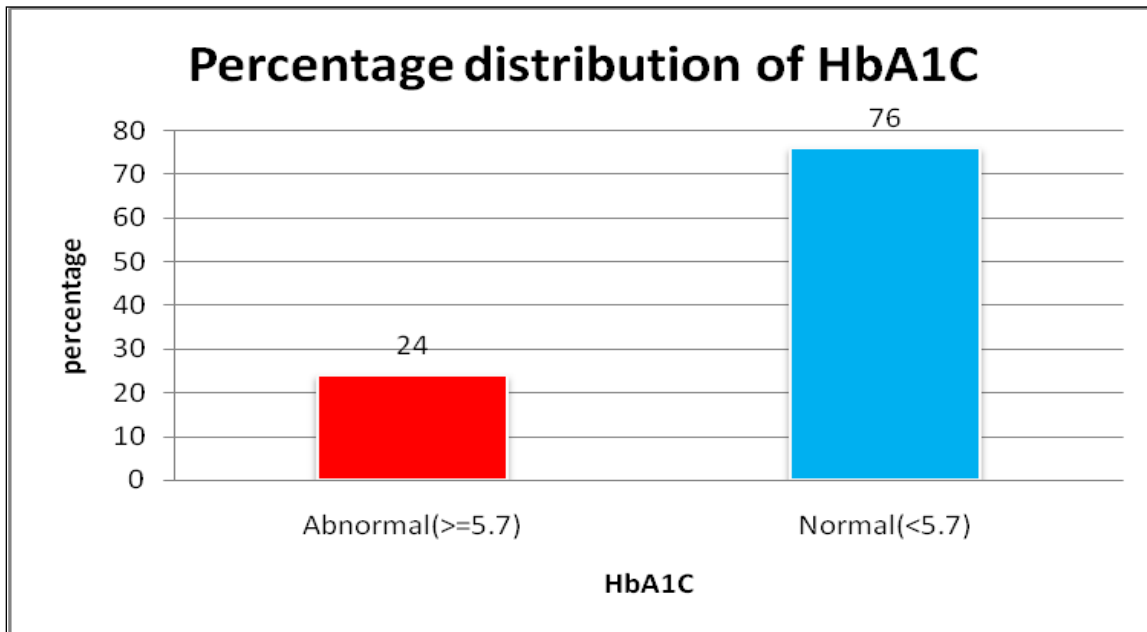
**Results and Observations**

The average gestational age in my study is 7 ± 0.85 weeks.

Mean age of patients was 27.6±4.67, mean weight gain was 14.12±2.99. Out of 100 patients 27 were detected with GDM (abnormal GTT) and 73 patients had no GDM (normal GTT). Of the 27 patients with abnormal GTT 24 had abnormal HbA1c ≥5.7 and 19 developed GDM. Results were tabulated accordingly

**Table 1: Frequency Distribution of Hba1c**

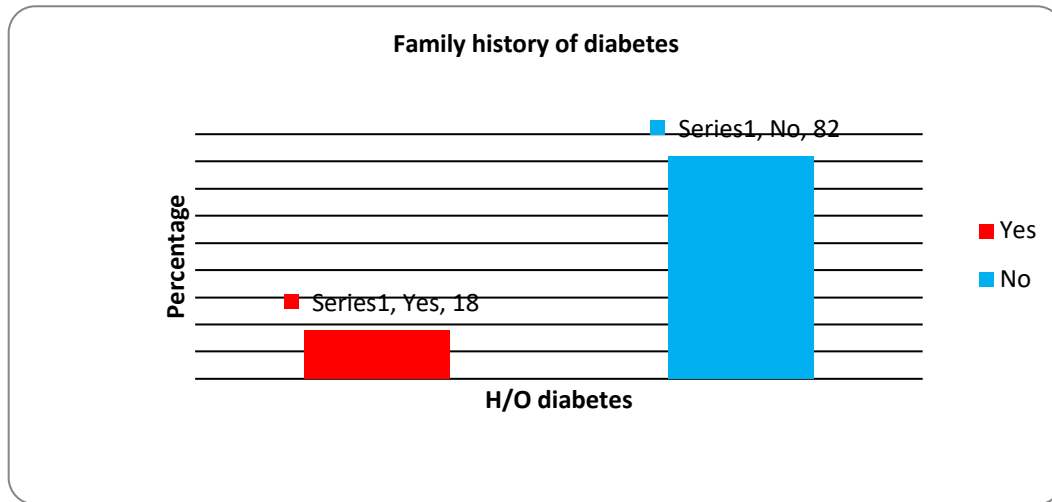
HbA1C	Frequency	Percent
Abnormal(>=5.7)	24	24.0
Normal(<5.7)	76	76.0



**Graph 1**

**Table 2: Percentage Distribution of Family History of Diabetes**

	Frequency	percent
Yes	18	18
No	82	82
Total	100	100

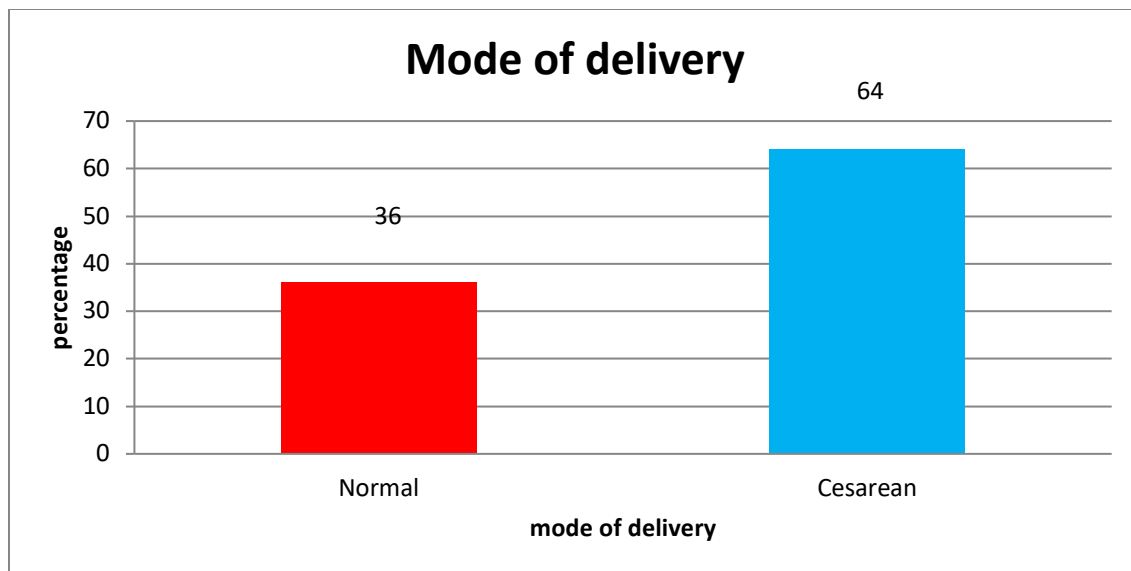


**Graph 2**

Out of 100 patients 18 had a positive family history of diabetes and was a significant risk factor for developing GDM.

**Table 3: Frequency Distribution Of Mode Of Delivery**

	Frequency	Percent
Normal	36	36
Cesarean	64	64
Total	100	100

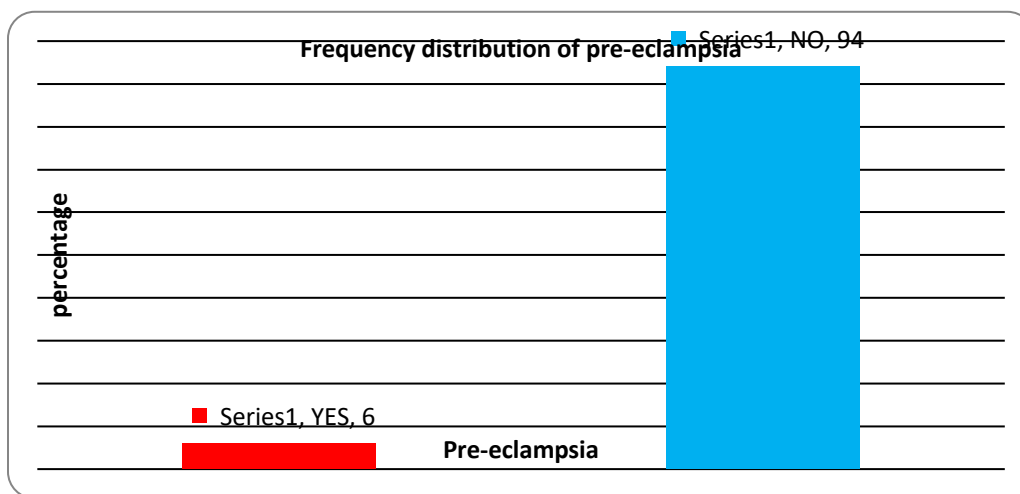


**Graph 3**

Increased in rate of caesarean seen but it was not specific to GDM / HbA1c, many other causes was also found.

**Table 4: Frequency distribution of Preeclampsia**

	Frequency	Percent
YES	6	6%
NO	94	94%
TOTAL	100	100



**Graph 4**

Out of 100 patients in my study 6 patients developed pre- eclampsia

**Table 5: Association of Pre-Eclampsia with Hba1c Abnormal and Normal Group**

Factors	Category	HbA1c		p value
		Abnormal $\geq 5.7$ n=24(%)	Normal <5.7 n=76(%)	
Pre-eclampsia	Yes	5(83.3)	1(16.7)	0.003*
	No	19(20.2)	75(79.8)	

Out of 100 patients in my study 6 patients had pre-eclampsia, 5 patients had an abnormal Hba1c  $\geq 5.7$ , 1 patient had HbA1c <5.7.

Hence showed both clinical and statistical significance (p=0.003).

**Table 6: Comparison Of Factors Based On Maternal Weight Gain, Mode Of Delivery & Birth Weight Between Hba1c Abnormal And Normal Group**

Factors	Category	HbA1c		p value
		Abnormal $\geq 5.7$ n=24(%)	Normal <5.7 n=76(%)	
Maternal weight gain	< 14 (59)	13 (22.1)	46(77.9)	0.581
	> 14 (41)	11(26.8)	30(73.2)	
Delivery	Normal (36)	6(16.7)	30(83.3)	0.198
	Caesarean (64)	18(28.1)	46(71.9)	
Birth weight	<4(98)	22(22.4)	76(77.6)	0.08
	$\geq 4$ (2)	2(100)	0(0)	

Out of 24 patients who had a caesarean section, 18 patients had abnormal Hba1c  $\geq 5.7$ , 6 had normal vaginal delivery which has clinical significance but showed no statistical significance.

There is a no statistically significant association between birth weight >4kg and HbA1c (p value=0.08)., but clinically showed significance as both babies  $\geq 4$  kg had HbA1c  $\geq 5.7$ .

## Discussion

During normal pregnancy, a decrease in fasting blood glucose occurs early in pregnancy, mainly between weeks 6 and 10, and is sustained during the remaining part of pregnancy [9]. New erythrocytes formed will therefore be exposed to a lower time-averaged glucose concentration than those of nonpregnant women, and the degree of glycosylation might therefore be less [10]. Hba1c levels are lower in first and third trimester compared to non-pregnant women [11].

Hba1c  $\geq 6.5$  is considered as diabetes in non-pregnant population (WHO) [13]. The objective of my study was to find out whether Early pregnancy HbA1C (between  $\geq 5.7$  &  $\leq 6.4$ ) can be used as a predictor for GDM. Hba1c  $\geq 5.7$  was taken as a standard cut off in reference to earlier studies. HbA1c was taken in all 100 antenatal patients before 12 weeks of gestation and GDM was diagnosed using GTT(modified IADPSG 2010) at 22-26 weeks. The Sensitivity and specificity of Hba1c  $\geq 5.7$  in my study is found to be 70.4%

& 93.2% respectively. Early pregnancy HbA1c has been found to be a predictor of preeclampsia and GDM [14].

There is a no statistically significant association between birth weight (LGA babies) and HbA1c  $\geq 5.7$  (p value=0.08). But clinically shows significance as both babies whose birth weight was  $\geq 4$ kg had HbA1c ( $\geq 5.7$ ). Macrosomia is defined as a birthweight greater than 4000 g, and large for gestational age (LGA) is defined as a birthweight greater than the 90<sup>th</sup> percentile for gestational age, based on national growth curves [12]. A study by Hughes *et al.* (64) in 2014 showed that HbA1c  $>5.9$  was associated with LGA babies( $>4$ kg) but that study was based on ethnicity, maternal weight and gestational age at delivery. A study by ostaeder *et al* in 2015 aimed to correlate 1<sup>st</sup> trimester HbA1c with birth weight and pre-eclampsia in pco's patients and results showed that most of them were SGA babies as most of them with HbA1c  $\geq 5.7$  developed pre-eclampsia thereby having SGA babies.

**Table 7: Comparison of BIRTH WEIGHT  $\geq 4$ kg with other studies**

	HbA1c cut off	n (%)	P value
Hughes <i>et al</i> (64)	5.9	21(10.1%)	0.93
Our study	5.7	2(100)	0.08

**Table 8: Comparison of Incidence of preeclampsia with other studies in abnormal Hba1c group**

	HbA1c cut off	n (%)	P value
Hughes <i>et al</i> (64)	5.9	11 (5.5)	
Odsaeter <i>et al</i> (67)	5.7	14 (6.1 %)	0.01
Our study	5.7	5(20.8)	0.003

Study by Hughes *et al* showed a relative risk of 2.5 for development of pre-eclampsia when hba1c  $>5.9$ . Odsaeter *et al* proved that hba1c  $\geq 5.7$  was significantly associated with pre-eclampsia (p = 0.01) but this study was

done in PCO patients. In my study out of 6 patients with pre-eclampsia 5 patients had HbA1c ( $\geq 5.7$ ) (p= 0.003), hence HbA1c ( $\geq 5.7$ ) is a significant marker for pre-eclampsia

In a study by Hughes *et al* HbA1c  $\geq 5.9$  &  $\leq 6.4$  was associated with major congenital anomalies, but in my study no congenital anomaly was observed in all 100 patients.

Parity index was almost equal in distribution between primi and multi gravidas and showed no statistical significance.

### Summary

It is seen that HbA1c can be used as a predictor for GDM [14] and pre-eclampsia, especially when done in early trimester (< 9 weeks). The study also shows there is a strong association with high HbA1c and macrosomia, which shows an indirect evidence to development of GDM.

### Conclusion

- Early pregnancy HbA1c can be used as a tool for predicting GDM [14] and preeclampsia.
- Family history of diabetes especially in 1<sup>st</sup> degree relatives is a significant risk factor for higher HbA1c in early trimester.
- Previous history of GDM is a borderline risk factor for higher HbA1c and developing GDM.
- Increasing maternal age are associated with HbA1c  $\geq 5.7$  and development of GDM.
- Birth weight  $\geq 4$ kg is statistically not associated with HbA1c  $\geq 5.7$  but clinically shows association.
- Pre-eclampsia is associated with higher HbA1c in early pregnancy.

In all 100 patients there was no abortions or anomalies observed. Other factors like mode of delivery, parity, and maternal weight gain showed no comparable association which could be due to smaller sample size. HbA1c can be done routinely in early pregnancy (1<sup>st</sup> trimester). Patients with higher levels of (HbA1c  $\geq 5.7$ ) can benefit from early interventions like appropriate diet and

lifestyle modification early in pregnancy thereby preventing GDM and pre-eclampsia. This will help in reducing the adverse perinatal and pregnancy outcomes.

Limitations: As the study excludes a few participants we do not know the interpretation in them.

### References

1. Bartha JL, Martinez-Del-Fresno P, Comino-Delgado R. Gestational diabetes mellitus diagnosed during early pregnancy. American journal of obstetrics and gynecology. 2000 Feb 29; 182(2): 346-350.
2. Hawkins JS, Lo JY, Casey BM, McIntire DD, Leveno KJ. Diet-treated gestational diabetes mellitus: comparison of early vs routine diagnosis. American journal of obstetrics and gynecology. 2008 Mar 31; 198(3):287-e1.
3. Yogeve Y, Xenakis EM, Langer O. The association between preeclampsia and the severity of gestational diabetes: the impact of glycemic control. American journal of obstetrics and gynecology. 2004 Nov 30;191(5):1655-1660.
4. McIntyre HD. Hyperglycemia and adverse pregnancy outcome (HAPO) study: preeclampsia. In American journal of obstetrics and gynecology 2010; 202(3): 255-e1. Mosby.
5. Innes KE, Wimsatt JH, McDuffie R. Relative glucose tolerance and subsequent development of hypertension in pregnancy. Obstetrics & Gynecology. 2001 Jun 1;97(6):905-910.
6. Esakoff TF, Cheng YW, Sparks TN, Caughey AB. The association between birthweight 4000 g or greater and perinatal outcomes in patients with and without gestational diabetes mellitus. American journal of obstetrics and gynecology. 2009 Jun 30;200(6):672-e1.
7. Howarth C, Gazis A, James D. Associations of Type 1 diabetes mellitus,

- maternal vascular disease and complications of pregnancy. *Diabetic Medicine*. 2007 Nov 1;24(11):1229-1234.
8. Haeri S, Khoury J, Kovilam O, Miodovnik M. The association of intrauterine growth abnormalities in women with type 1 diabetes mellitus complicated by women with gestational diabetes mellitus or type 1 diabetes the role of intrauterine hyperglycemia. *Diabetes care*. 2008 Feb 1;31(2):340-346.
  9. Mills JL, Jovanovic L, Knopp R, Aarons J, Conley M, Park E, Lee YJ, Holmes L, Simpson JL, Metzger B. Physiological reduction in fasting plasma glucose concentration in the first trimester of normal pregnancy: the diabetes in early pregnancy study. *Metabolism*. 1998 Sep 30;47(9):1140-4
  10. Lind T, Cheyne GA. Effect of normal pregnancy upon the glycosylated haemoglobins. *BJOG: An International Journal of Obstetrics & Gynaecology*. 1979 Mar 1;86(3):210-3.
  11. Nielsen LR, Ekbom P, Damm P, Glümer C, Frandsen MM, Jensen DM, Mathiesen ER. HbA1c levels are significantly lower in early and late pregnancy. *Diabetes care*. 2004 May 1;27(5):1200-1.
  12. Kramer MS, Platt RW, Wen SW *et al*. Infant Health Study Group of the Canadian Perinatal Surveillance System: a new and improved population-based Canadian reference for birth weight for gestational age. *Pediatrics*. 2001;108: E35.
  13. Pettitt DJ, Knowler WC, Baird HR, Bennett PH. Gestational diabetes: infant and maternal complications of pregnancy in relation to third-trimester glucose tolerance in the Pima Indians. *Diabetes care*. 1980 May 1;3(3):458-464.
  14. Sujithra D., Mukherjee S, Sudha S. Glycated hemoglobin in early pregnancy as a predictor of gestational diabetes mellitus. *Ind J Obstet Gynecol Res*. 2018;5(3):327-330.