A Study on Glycosylated Haemoglobin Values at 6 - 12 Weeks of Pregnancy as an Early Predictor of Gestational Diabetes Mellitus

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ABSTRACT

BACKGROUND

Gestational diabetes mellitus (GDM) is a major health problem arising due to insulin resistance in pregnant women. It is associated with multiple maternal complications which may cause end organ failure, complicated labour and delivery and thereby increasing the maternal morbidity and mortality. The foetus is also at risk for problems beginning from in utero and extending into the neonatal period and adult life. We wanted to correlate first trimester HbA1c values with the subsequent development of gestational diabetes mellitus and identify if glycosylated haemoglobin can be used as an adjunct with other screening methods.

METHODS

It is a prospective cohort study. This study was conducted from August 2015 to August 2017. All women of gestational age 6 to 12 weeks who came to Sri Ramachandra University outpatient department were taken for this study. Informed consent was obtained and a detailed history taking was done as per proforma. Along with routine antenatal investigations, Glycosylated haemoglobin (HbA1c) was also done. Oral Glucose Tolerance Test was to be performed at 24 - 28 weeks as per the World Health Organisation -with 75gm criteria and the results were tabulated and analysed to know the significance of Glycosylated haemoglobin (HbA1c) in the outcome of gestational diabetes mellitus. Further a fasting and postprandial blood sugar was done in the 3rd trimester for all patients as a secondary screening tool for gestational diabetes mellitus. Secondary outcomes of obstetric and neonatal complications were also studied.

RESULTS

In the present study a total of 323 patients were screened for HbA1c during the first trimester and followed till delivery. Only 21.9 % developed gestational diabetes mellitus. Elevated Glycosylated haemoglobin (HbA1c) value of 5.7 - 6.4 % was seen in 5.9 %.

CONCLUSIONS

Most of the patients with elevated Glycosylated Haemoglobin in the first trimester had high chance of developing gestational diabetes mellitus. Glycosylated haemoglobin is indeed a simple way of screening, but its solitary use remains controversial and hence could possibly be tried as an adjunct with other screening methods.

KEY WORDS

Glycosylated Haemoglobin, Gestational Diabetes Mellitus, Glycaemic Control, Maternal and Foetal Morbidity and Mortality

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BACKGROUND

Gestational diabetes mellitus (GDM) is a major health problem arising due to insulin resistance in pregnant women. There is an increase in its incidence over the past decade owing to the sedentary lifestyle practices. It is associated with multiple maternal complications which may cause end organ failure, complicated labour and delivery and thereby increasing the maternal morbidity and mortality. The foetus is also at risk for problems beginning from in utero and extending into the neonatal period and adult life. This is the reason for obstetricians and endocrinologists to have an extra eye on patients who are prone to develop gestational diabetes mellitus. Hence, screening for gestational diabetes mellitus is more important than diagnosing it later in the course of antenatal period. Initially screening was opted only for women with risk factors but currently it is done for all as a large proportion of women develop gestational diabetes mellitus despite having no risk factors. Screening techniques vary from obstetrician and the most accepted methods are the non challenge glucose test or the glucose challenge tests like the American Diabetic Association (ADA)¹ which approved 3 hours 100gm oral glucose tolerance test (OGTT) for the diagnosis of GDM, it has recently included in its recommendations the use of 2 hours 75 gms oral glucose tolerance test. WHO panel although in general maintaining previous diagnosis recommendations, now characterizes gestational diabetes mellitus as the joint category of diabetes and impaired glucose tolerances and they have adopted in pregnancy the same diagnostic criteria applied to a 2 hr 75gms. Oral Glucose tolerance test in non pregnant women. (IGT – 2 hr PPG 140 – 200 mg / dl). The pregnant women who meet the WHO criteria for impaired glucose test (IGT) are classified as having gestational diabetes mellitus. Using 2 hours' plasma glucose > 140 mg / dl as a one step procedure is simple and economical particularly for the countries ethnically more prone to high prevalence of diabetes. There is a tendency all over the world to accept the 75gms oral glucose tolerance test as a universal test for screening. Glycosylated haemoglobin (HbA1c) is an evolving tool in the world of diabetes but its significance in screening for gestational diabetes mellitus is still a mystery. Studies have been made to assess if glycosylated haemoglobin values of 5.7 - 6.4 % which has been considered as impaired glucose tolerance in non obstetric population can be used as a cut off for the obstetric population. When blood glucose levels are high, the glucose molecules attach itself to the haemoglobin in red blood cells. The longer the hyperglycaemia persists in blood, the more the glucose binding to haemoglobin in the red blood cells and higher the glycosylated haemoglobin. The average level of glycosylated haemoglobin is seen in red blood cells life cycle and changes accordingly. Haemoglobin molecule undergoes glycosylation and cannot be changed. Glycosylated Haemoglobin is used to assess the long term effectiveness of serum glucose regulation. HbA1c is the average blood glucose level of red blood cells during its lifetime. The life time of RBC is 117 days for men and 106 days for women. The glucose levels which are done on days next to the test have more levels than those done on days far away from the test. Glycosylated haemoglobin test is done to check the glycaemic control in women who might be having risk factors and in those who may be pre-diabetic. Monitoring and achieving the target glycaemic control in diabetic

patients. Prenatal counselling of women with diabetes. The NICE guidelines for diabetes in pregnancy state that women with diabetes should aim to achieve HbA1c result of 6.1% or lower. If the target is achieved it will help to minimise the congenital malformations. If the woman has HbA1c above 10%, it is strongly advised to avoid pregnancy until good diabetic control is achieved and sustained. Glycosylated haemoglobin as a screening tool for gestational diabetes mellitus and also as a target scale in monitoring of glycaemic control is still a matter of debate with several ambiguous studies. Long term vascular complications like coronary artery diseases, stroke, peripheral neuropathy especially loss of sensation in the feet, heart attack, blindness, kidney failure, heart failure, gastroparesis which is slow emptying of the stomach, and gangrene are seen in those with persistent elevations in blood sugar levels. Wound healing is also delayed because of poor glycaemic control which is a short-term complication. Glucose-6-phosphate dehydrogenase deficiency, any condition causing premature red blood cell death and sickle cell disease have shortened lifespan of red blood cells and therefore low levels of HbA1c. Further more if a woman has undergone blood transfusion there will be rapid replacement of the lost red blood cells with the newly formed red blood cells and these newly formed cells will lead to low levels of glycosylated haemoglobin and hence the newly formed red blood cells will lead to underestimation of actual average levels. People with Vitamin B12 deficiency and folate deficiency have longer lifespan of red blood cells than others and hence have higher than the expected values of glycosylated haemoglobin. If there was a blood transfusion previously about two months prior, there will be a distortion in the value of glycosylated haemoglobin resulting in overestimation of actual average blood glucose levels due to abnormal synchronisation of the age of the red blood cells, which further results in older than normal average blood cell life.

METHODS

It is a prospective observational study. This study was conducted from August 2015 to August 2017. All women of gestational age 6 to 12 weeks who came to tertiary care institute were taken for this study. Informed consent was obtained and a detailed history taking was done as per proforma. Along with routine antenatal investigations, glycosylated haemoglobin (HbA1C) was also done. Oral Glucose Tolerance Test (OGTT) was to be performed at 24 - 28 weeks as per the World Health Organisation - 75gm criteria and the results were tabulated and analysed to know the significance of glycosylated haemoglobin (HbA1C) in the outcome of gestational diabetes mellitus. Further fasting and postprandial blood sugar tests were done in the 3rd trimester for all patients as a secondary screening tool for gestational diabetes mellitus. Secondary outcomes of obstetric and neonatal complications were also studied.

Inclusion Criteria

- Antenatal women of gestational age 6 to 12 weeks. All the pregnant women gave informed consent for the study.

Exclusion Criteria

- Overt diabetic
- HbA1c value > 6.4 %

Statistical Analysis

The P value was calculated by chi-square Test. The Statistical software used was SPSS-16- Statistical Package for Software Solution.

RESULTS

Glycosylated Haemoglobin HbA1c (N=323)	2 ND Trimester (N=38)	3 RD Trimester (N=33)	Total Gestational Diabetes Mellitus (N=71)
4.0 - 4.5 (N=50)	-	2 (2.8 %)	2 (2.8 %)
4.6 - 5.0 (N=148)	7 (9.9 %)	9 (12.7 %)	16 (12.7 %)
5.1 - 5.6 (N=106)	23 (32.4 %)	16 (22.5 %)	39 (54.9 %)
5.7 - 6.4 (N=19)	8 (11.3 %)	6 (8.5 %)	14 (19.7 %)

Table 1. Total Number of Patients with Glycosylated Haemoglobin HbA1c in the 2nd and 3rd Trimester and Total Number of Patients with Gestational Diabetes Mellitus

71 patients (21.9 %) were diagnosed with gestational diabetes mellitus.

Treatment	HbA1c < 5.7 % (N=57)	HbA1c 5.7 - 6.4 % (N=14)	Total GDM (N=71)
Diet	31	3	34(47.8 %)
OHA	22	6	28(39.4 %)
Insulin	2	1	3(4.2 %)
OHA + Insulin	2	4	6(8.4 %)

Table 2. Gestational Diabetes Mellitus and Treatment

- Diet modification was required for majority of patients (47.8 %).
- Oral hypoglycaemic drugs were required by 28 patients (39.4 %).
- Insulin was necessary for glycaemic control in 3 patients (4.2 %).
- Oral hypoglycaemic drugs with insulin was required in 6 patients (8.4 %).
- 29 patients (40.8 %) had a spontaneous vaginal delivery.
- 4 patients (5.6 %) had assisted vaginal delivery.
- 38 patients (53.5 %) had lower segment caesarean section.

Mode of Delivery	Normal Glycosylated Haemoglobin HbA1c(N=57)	Increased Glycosylated Haemoglobin HbA1c(N=14)	Total Gestational Diabetes Mellitus(N=71)
Spontaneous vaginal delivery	21	8	29(40.8 %)
Assisted vaginal delivery	4	-	4(5.6 %)
Lower segment caesarean section	32	6	38(53.5 %)

Table 3. Mode of Delivery in Patients with Gestational Diabetes Mellitus

Maternal Complications	Total
Shoulder dystocia	1
Perineal tear	2
Perinatal Complication	
NICU admissions	16
Macrosomia	2
Congenital anomalies	-
Foetal hypoglycaemia	9
Stillbirth	-

Table 4. Maternal and Neonatal Complications in GDM

Most of the babies required Neonatal Intensive Care Unit.

Glycosylated Haemoglobin (HbA1c)	Sample (N=323)	Gestational Diabetes Mellitus(N=71)	% of Gestational Diabetes Mellitus
<5.7	304	57	18.7 %
5.7 - 6.4	19	14	73.6 %

Table 5. Correlation between Glycosylated Haemoglobin and Gestational Diabetes Mellitus

73.6 % of patients from the study population with elevated glycosylated haemoglobin of 5.7 - 6.4 % had gestational diabetes mellitus.

DISCUSSION

Glycosylated haemoglobin has been well accepted in the non-obstetric population as a tool for diagnosis of diabetes. In normal individuals glycosylated haemoglobin (HbA1c) value of 5.7 - 6.4 % indicates impaired glucose tolerance as well as a high risk of developing diabetes in the future. Our study is aimed to correlate early HbA1c levels with the subsequent development of gestational diabetes mellitus, with the hypothesis that patients with the value of 5.7 - 6.4 % are at greater risk of developing gestational diabetes mellitus than those with a level < 5.7 %. In our study, glycosylated haemoglobin was done in the first trimester and further diagnosed gestational diabetes mellitus based on the WHO criteria of 2 hr PPBS $\geq$ 140 mg / dl in second trimester and PPBS in third trimester. No correlation was seen in the trimester of diagnosis of gestational diabetes mellitus with glycosylated haemoglobin. Similarly, Alex Fong et al. (2014)² in his retrospective study of 526 women who underwent HbA1c in the first trimester followed by oral glucose tolerance test in the second trimester. The study showed that there was no correlation in the trimester of diagnosis with HbA1c values but a significance was noted in the fasting glucose tolerance value with glycosylated haemoglobin (P value < 0.001) Aldasouqi et al. (2008)³ in their retrospective study of 145 eligible patients found gestational diabetes mellitus in 124 patients with oral glucose tolerance test. The sensitivity percentage of patients with glycosylated haemoglobin (HbA1c) values equal to or above sequential cut-off values of 5.0 %, 5.5 %, 6.0 %, 6.5 %, and 7.0 % were 100 %, 98.4 %, 87.1 %, 62.9 %, and 39.5 %, respectively. The mean glycosylated haemoglobin (HbA1c) of the patients with gestational diabetes mellitus was 6.9 ± 0.8 % compared with 6.4 ± 0.6 % for those without gestational diabetes mellitus.

At an arbitrary glycosylated haemoglobin (HbA1c) cut-off value of 6.0 % nearly 87.1 % of patients could have been diagnosed with gestational diabetes mellitus. This study suggested that glycosylated haemoglobin (HbA1c) is a reasonably sensitive screening measure for gestational diabetes mellitus in this high-risk population. Balaji et al. (2007)⁴ established the normal mean glycosylated haemoglobin (HbA1c) values in Asian - Indian pregnant women as 5.36 ± 0.36 %. They also found that the mean glycosylated haemoglobin (HbA1c) level in women with gestational diabetes mellitus at diagnosis during different trimesters was 6 %.

Rajesh Rajput et al. (2012)⁵ conducted a study with 607 patients in 2012, the values of glycosylated haemoglobin (HbA1c) ranged from 4.0 - 6.1 %. Gestational diabetes

mellitus was diagnosed by International association of diabetes and pregnancy study groups (IADPSG). The mean standard deviation glycosylated haemoglobin (HbA1c) value in women with gestational diabetes mellitus was 5.73 ± 0.34 %, while it was 5.34 ± 0.35 % in women without gestational diabetes mellitus. The difference in the two HbA1c values was found to be statistically significant.

It was observed that a glycosylated haemoglobin (HbA1c) cut-off value of 5.95 % had a sensitivity of 28.6 % and a specificity of 97.2 % in diagnosing gestational diabetes mellitus whereas a glycosylated haemoglobin (HbA1c) cut-off value of 5.45 % had a sensitivity of 85.7 % and a specificity of 61.1 %. Using glycosylated haemoglobin (HbA1c) as the initial test, if the level of HbA1c is ≥ 5.95 %, then the woman can be labelled as having gestational diabetes mellitus. If the cut off glycosylated haemoglobin (HbA1c) value is 5.95 % then it has a specificity of > 97 % in identifying cases of gestational diabetes mellitus. Ingrid Hov Odsaeter et al.⁶ conducted a study on 855 women in whom World Health Organisation / International association of diabetes and pregnancy study groups (IADPSG)⁷ was used to diagnose gestational diabetes mellitus along with HbA1c values done at 18 - 22 and 32 - 36 weeks.

The study concluded that around 30 % of pregnant women could have potentially avoided an oral glucose tolerance test by using glycosylated haemoglobin (HbA1c) ≤ 4.8 % to exclude GDM - IADPSG with a sensitivity of 88 % at pregnancy weeks 18 - 22 and by using glycosylated haemoglobin (HbA1c) ≤ 5.0 % with a sensitivity of 97 % at pregnancy weeks 32 - 36. Further, 16 % could have potentially avoided an oral glucose tolerance test with a sensitivity of 96 % by using HbA1c ≤ 4.7 % at pregnancy weeks 18 - 22 to exclude GDM - IADPSG⁷ throughout pregnancy.

Adding other variables to predict gestational diabetes mellitus did not significantly increase the number of potentially avoidable oral glucose tolerance test. HbA1c was not accurate at diagnosing GDM - IADPSG⁷ since most of those diagnosed would have been false positives.

Glycosylated Haemoglobin (HbA1c) was inaccurate at screening for GDM - WHO at any time point. Neither HbA1c nor gestational diabetes mellitus was accurate in predicting preeclampsia or birth weight. Our study showed no significance between glycosylated haemoglobin and type of medical treatment or rate of caesarean delivery. Birth weight had significance with glycosylated haemoglobin in our study and the same was seen with Ingrid Hov Odsaeter et al. (2016).⁶ Alex Fong et al. (2014)² showed no statistical significance in the type of treatment, mode of delivery and birth weight. Although the overall diagnostic accuracy for HbA1c in diagnosing gestational diabetes mellitus by IADPSG / World Health Organisation criteria was similar for the present and previous studies, the diagnostic thresholds for glycosylated haemoglobin (HbA1c) and the sensitivity and specificity at the same levels of HbA1c differ between studies.⁷ These differences probably reflect diversities between populations, testing at different gestational lengths and the analytical methods used.

Summary

In the present study a total of 323 patients were screened with first trimester glycosylated haemoglobin (HbA1c) and followed till delivery. Only 21.9 % developed gestational diabetes mellitus. Elevated HbA1c value of 5.7 - 6.4 % was seen in 5.9 %. Among the patients with elevated glycosylated haemoglobin (HbA1c) of 5.7 - 6.4 %, 73.6 % of them developed gestational diabetes mellitus.

Gestational diabetes mellitus was diagnosed in 54 % of patients during the second trimester and 46 % of patients in the third trimester. Family history of diabetes was equivocal as 47.8 % of patients with gestational diabetes mellitus had either parents being diabetic whereas 52.1 % of patients had neither of the parents diabetic.

47.8 % patients had good glycaemic control with just diet. 89.1 % patients delivered at term and 16.8 % patients delivered preterm. 46.2 % patients delivered by Normal Vaginal delivery and 53.5 % delivered by Lower Segment Caesarean Section. 22.5 % of babies were admitted in the Neonatal Intensive Care Unit for preterm care, hypoglycaemia, macrosomia, and other reasons. Foetal hypoglycaemia (56.2 %) was the commonest reason for admission in patients with gestational diabetes mellitus.

CONCLUSIONS

Most of the patients with elevated glycosylated haemoglobin in the first trimester had high chance of developing gestational diabetes mellitus. With the increasing incidence of gestational diabetes mellitus, it is important to improvise on our screening methods and also consider screening the entire population and not restrict it to a certain group of high risk patients, as quite a number of patients are being undiagnosed leading to an increase in maternal and foetal morbidity and mortality. Glycosylated haemoglobin is indeed a simple way of screening, but its solitary use remains controversial and hence could possibly be tried as an adjunct with other screening methods.

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