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First trimester HbA1c as an early predictor of gestational diabetes mellitus

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Abstract
Objective: To analyze the predictive value of first trimester HbA1c test in early detection of gestational diabetes mellitus. And, to study the association of high-risk factors with raised HbA1c levels in patients with gestational diabetes mellitus.
Method: The study was a hospital based observational prospective study conducted in the department of Obstetrics and Gynecology of tertiary care hospital, GMERS Medical College and Hospital, Gotri, Vadodara, Gujarat, India over a 10 months period from October 2022 to August 2023.The study population comprised of 150 pregnant women with singleton gestation of less than 12 weeks. HbA1c test and 75gm OGTT (Oral Glucose Tolerance Test) / DIPSI test (Diabetes in Pregnancy Study group of India) were done in all the women in their first trimester excluding patients with HbA1c≥6.5% or DIPSI ≥140 mg/dL. Further, a second trimester (24-28 weeks) and third trimester OGTT (32-34 weeks) were done to detect GDM using WHO 2013 criteria.
Result: Using the cutoff value of 5.3% HbA1c was able to detect 16 (69.6%) out of 23 cases of GDM. The area under the ROC curve was 0.82 (95% CI 0.73-0.91; p<0.01). Patients with an HbA1c >5.3% had a 3.05-fold risk of developing GDM. For the optimal cut-off of the ROC analysis the sensitivity was 69.6% (95% CI- 47.1%-86.8%), the specificity was 77.2% (95% CI – 68.9%-84.1%), the positive predictive value was 35.6% (95% CI-26.6% -45.6%) and the negative predictive value was 93.3% (88.2%-96.3%). Overall diagnostic accuracy of HbA1c value >5.3% was 76.0% (95% CI-88.2%-96.2%).
Conclusion: The present study results suggested that HbA1c can be an appropriate biomarker for GDM prediction, probably not in isolation, but rather as a part of a multi-marker algorithm for high-and low-risk populations.

Keywords: HbA1c, gestational diabetes mellitus, predictor, first trimester, early diagnosis

Introduction
Gestational Diabetes Mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy [1]. Pregnancies affected by GDM are at risk of developing a number of serious maternal and fetal morbidities.
Worldwide, 1 in 10 pregnancies is associated with diabetes, 90% of which are GDM [2]. The prevalence of GDM varies from 7.7% to 17.8% in various parts of India based on geographic location and diagnostic methods used [3-5]. GDM is found to be more prevalent in urban areas than in rural areas [3-5]. For a given population and ethnicity, the prevalence of GDM corresponds to the prevalence of Impaired Glucose Tolerance [IGT, in non-pregnant adult] within that given population [6]. Indians are at eleven fold increased risk of developing glucose intolerance during pregnancy than European women [7].
Maternal complications such as polyhydramnios, preeclampsia, operative delivery and perineal injuries are well documented. Fetal complications include macrosomia, shoulder dystocia, intrauterine growth retardation, neonatal hypoglycemia and perinatal mortality, birth injury and prematurity, as well as long-term implications for the wellbeing of the mother and the infant [8]. The risk of adverse perinatal and maternal outcomes is directly proportional to the degree of hyperglycemia, with a linear relationship between maternal glucose and various neonatal outcomes [8].
The International Association of the Diabetes and Pregnancy Study Groups, [9] the American Diabetes Association,[10] and the World Health Organization [11] suggested screening for pre-existing diabetes as early as at the first antenatal visit; however, the most appropriate test and threshold are not yet defined. Recently, WHO adopted the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria, which has increased the detected incidence of GDM [12].

The guidelines recommend that at 24-28 weeks a 75 g oral glucose tolerance test should be done for all pregnant women [12]. OGTT is an inconvenient test as it consumes time, the pregnant women must fast and wait for 2 hours and should have at least 3 vene-punctures. They also get nausea and vomiting due to the 75 g glucose consumption and delayed gastric emptying. This, coupled with gestational edema compromising venous access, can lead to an invalid test result. Furthermore, the recommendation for universal screening has significantly increased the burden of testing [13].

With these methods, there was a possibility of missing patients with abnormal sugars in the first trimester. The instability of blood glucose ex vivo leads to a significant inter- laboratory variation of results. It is thought to vary by up to 14% in a third of cases [14]. Moreover, as it is a specialized test, many collection centres do not provide this service, particularly in rural and remote locations, potentially disadvantaging an already vulnerable cohort of women [15].

There is an apparent need for a universally acceptable, much simpler and accessible test for GDM screening in first trimester. Glycosylated HbA1c is currently a good measure to know sugar control [14].

HbA1c is the product of an irreversible non-enzymatic binding of glucose to plasma proteins, specifically hemoglobin (Hb). The mean plasma glucose over the erythrocyte life span is correlated with a degree of glycosylation. It is a single, non-fasting blood test and reflects glucose levels over the previous 4-8 weeks. As compared with glucose testing, it has been shown to have greater reliability with <6% inter-laboratory variation [14]. Thus, HbA1c test has improved analytical stability with greater standardization between assays and less pre-analytical variation. Further comparisons with fasting blood glucose and 2 hour postprandial glucose have shown HbA1c to have less intra-individual variation [16] as it does not appear to be affected by diurnal variation, meals, fasting, acute stress or by the large number of common drugs known to influence glucose metabolism [17].

The test is validated for a red cell survival time of approximately 3 months. Therefore, results need to be interpreted carefully in the clinical situation whereby erythrocyte half-life is significantly shortened by, for example, hemoglobinopathies, hemolysis, transfusion, anemia and chronic renal failure.

HbA1c has two technical advantages over plasma, blood or serum glucose measurements, which makes it particularly attractive as a candidate for diagnosing and monitoring GDM:

1. Measurement does not require the fasting or multiple timed measurements of the OGTT, and thus the burden on pregnant women (physical discomfort, fasting, and ingesting the concentrated glucose beverage) and staff (to administer the beverage and draw repeated blood samples) is minimized.
2. Unlike glucose, HbA1c remains relatively stable after collection and has less intra-individual variation compared with fasting plasma glucose.

An HbA1c level ≥6.5% (48 mmol/mol) is the recommended diagnostic cut-off point for diabetes in pregnancy [11]. However, this is based on data in non-pregnant subjects. The optimal HbA1c threshold in pregnancy is likely to be lower since the HbA1c level falls in the first trimester and is 0.5% (5.5 mmol/mol) lower by 14 weeks [18].

GDM cases go unidentified with inadequate screening methods which in turn increases the maternal and neonatal morbidity which may be preventable. Healthcare costs can be reduced by avoiding strategies which result in false positive cases [1]. Considering the overwhelming effects of GDM on maternal and neonatal health and the urgent need for early diagnosis and control of maternal glucose levels, we hypothesized that HbA1c may be important for screening and as a prognostic indicator of GDM.

Materials and Methods

The study was a hospital based observational prospective study conducted in the department of Obstetrics and Gynecology of tertiary care hospital, GMERS Medical College and Hospital, Gotri, Vadodara, Gujarat, India over a 10 months period from October 2022 to August 2023. First, the purpose of the study was explained to the study subjects attending Antenatal clinic in the local language with the help of the information sheet. After taking written/informed consent, their parameters were filled in a pre-designed proforma.

150 pregnant women of gestational age less than 12 weeks were selected. HbA1c test and 75 gm DIPSI test were done in all the women in their first trimester. Women with HbA1c ≥ 6.5%, DIPSI ≥ 140mg/dl were diagnosed as pre-gestational diabetes and treated and they were excluded from the study. In other women second trimester (24-28 weeks) and third trimester OGTT (32-34 weeks) were done to detect GDM. During the study period, all women received standard antenatal care from an obstetrician of their choice. These subjects were followed to the end of their pregnancy to see if and when they develop GDM and correlate with HbA1c level. Then they were followed up to find the mode of delivery and different maternal and perinatal outcome and high-risk factors were assessed.

Table 1: Diagnostic Test – Estimating the sensitivity of a new test

Sensitivity/Specificity of the new test (%)	85
Precision (%)	6
Desired confidence level (1- alpha) %	95
No. of subjects needed	136
No. of subjects needed with 10% Dropout	150

Estimating the Sensitivity of a new test

Assumption

- The variable must be a categorical.

Formula

$$n = \frac{z^2_{1-\frac{\alpha}{2}} p(1-p)}{d^2}$$

Where,

p : Sensitivity of the new test

d : precision

$Z_{1-\alpha/2}$: Desired Confidence level

A valid measure of disease should have two characteristics: it should be both sensitive and specific. Sensitivity refers to its

ability to detect a high proportion of the true cases, that is, to yield few false negative results. Specificity is the ability to correctly identifies the true negatives, and hence yields few false positive verdicts. The components of validity are calculated by setting up a '2 X 2' contingency table.

Table 2: '2 x 2' contingency table

Screening test	Reference test		
	Positive	Negative	Total
Positive	a	b	a+b
Negative	c	d	c+d
Total	a+c	b+d	**N**

The Sensitivity of the test or the proportion of true positives is = a/(a+c). The Specificity of the test or the proportion of true negatives is = d/(b+d). The Positive Predictive Value (PPV) of the test or the proportions of false positives is calculated as a/(a+b). The Negative Predictive Value (NPV) of the test or the proportions of false negatives is calculated as d/(c+d).

The collected data was transformed into variable, coded and entered in Microsoft Excel. Data was analyzed and statistically evaluated using SPSS-PC-19 version. Quantitative data was expressed in mean, standard deviation and difference between two comparable groups and tested by student's t-test (unpaired) or Mann Whitney 'U' test. Three or more groups' mean was analyzed using one-way ANOVA, while qualitative data was expressed in percentage. Statistical differences between the proportions were tested by chi square test or Fisher's exact test. 'P' value less than 0.05 was considered statistically significant. ROC curve was drawn to know the cut-off value of HbA1c value and sensitivity, specificity and positive and negative predictive values (all with exact 95% confidence intervals) were calculated from the analysis of patient values to determine the ability of the test to correctly identify diagnostic claim.

Results

Out of total 150 pregnant women included in the study, majority were in the age group of 26-30 years (41.3%) followed by 21-25 years (32.0%) and 31-35 years (18.0%). Only 13 (8.7%) women belonged to less than 20 years of age group. Mean age of study subjects was 26.59±4.06 years. 39 (26.0%) women were nullipara while 47 (31.3%) were primigravida. 19 (12.7%) women had parity ≥3. 80 (53.3%) women had normal BMI while 23 (15.3%) were overweight and 47 (31.3%) were obese.

Table 3: General characteristics of study subjects (n=150)

Age group	**No.**	**%**
Up-to 20 years	13	8.7
21-25 years	48	32.0
26-30 years	62	41.3
31-35 years	27	18.0
Parity	No.	%
0	39	26.0
1	47	31.3
2	45	30.0
≥3	19	12.7
BMI category	No.	%
Normal (18.5-24.99 kg/m^2)	80	53.3
Overweight (25-29.99 kg/m^2)	23	15.3
Obese class I (30-34.99 kg/m^2)	16	10.7
Obese class II (≥35 kg/m^2)	31	20.7

PCOD (Polycystic ovarian disease) was present in 24 (16.0%) subjects, history of GDM in previous pregnancy was reported in 30 (20.0%) subjects while family history of DM was present in 15 (10.0%) subjects. 30 (20.0%) women gave history of delivery of neonates >4 kgs in previous pregnancy.

Table 4: Risk Factors distribution in study subjects (n=150)

Risk Factors	**No.**	**%**
PCOD	24	16.0
h/o GDM in previous pregnancy	30	20.0
h/o IUD	2	1.3
h/o Delivery of neonates >4 kgs	30	20.0
Family History of DM	15	10.0

Out of 150 pregnant women GDM was developed in 23 pregnant women, so the prevalence of GDM was 15.3% in our study. Out of 150 pregnant women 123 (82.0%) were delivered vaginally while LSCS was required in 27 (18.0%) women.

Table 5: Prevalence of GDM in study subjects and type of delivery

Type of delivery	**No.**	**%**
Prevalence of GDM	23	15.3%
Vaginal	123	82.0
LSCS	27	18.0

Mean age in subjects with GDM (27.01±3.61 years) and without GDM (26.51±4.14 years) was comparable. Mean HbA1c value of women who developed GDM was significantly higher (5.47±0.31%) then those who did not develop (5.04±0.34). Similarly, BMI was also significantly higher in pregnant women with GDM (30.72±5.85 Kg/m^2) compare to without GDM (26.05±5.55 kg/m^2).

Table 6: Comparison of parameters between subjects with and without GDM

	With GDM (n=23)	**Without GDM(n=127)**	**P value**
Age in years	27.01±3.61	26.51±4.14	0.59
BMI (Kg/m^2)	30.72±5.85	26.05±5.55	<0.001
HbA1c (%)	5.47±0.31	5.04±0.34	<0.001
Mean RBS at 1st trimester	102.39±12.36	94.65±13.14	0.01

Table 7: Comparison of risk factors between subjects with and without GDM

Risk factors of GDM	**With GDM (n=23)**		**Without GDM (n=127)**		**P value**
	No.	**%**	**No.**	**%**	
PCOD	5	21.7	19	15.0	0.41
h/o GDM in previous pregnancy	12	52.1	18	14.2	<0.001
Family history of DM	11	47.8	19	15.0	<0.001
h/o IUD	2	8.7	0	0.0	0.02
h/o delivery of neonates >4 kg	6	26.1	9	7.1	<0.01

Table 7 shows comparison of different risk factors between pregnant women with and without GDM. History of gestational diabetes mellitus in previous pregnancy was seen in almost half of the women with GDM (52.1%) while it was seen in 14.2% women without GDM. Family history of diabetes mellitus was also seen more commonly in women with GDM (47.8%) compared to without GDM (15.0%) which was also significantly different. 6 out of 23 (26.1%) women who developed GDM informed history of delivery of neonates >4 kg in previous pregnancy while only 7.1% women without GDM reported >4

kg of neonates delivered in previous pregnancy. History of IUD was also present in 2 women with GDM while none in women without GDM. PCOD was also present in 5 (21.7%) women with GDM and 19 (15.0%) women without GDM.

Table 8: Prevalence of GDM in different category of obesity

BMI category	No.	Development of GDM	Prevalence of GDM
Normal (18.5-24.99 kg/m^2)	80	6	7.5%
Overweight (25-29.99 kg/m^2)	23	4	17.4%
Obese class I (30-34.99 kg/m^2)	16	4	25.0%
Obese class II (≥35 kg/m^2)	31	9	29.0%

Table 8 shows prevalence of GDM in different category of BMI. Prevalence of GDM in subjects with normal BMI was 7.5%, in subjects with BMI between 25-29.99 kg/m^2 was 17.4%, in subjects with BMI between 30-34.99 kg/m^2 prevalence of GDM was 25.0% while in Obese class II subjects, prevalence of GDM was 29.0%. This shows that chances of developing GDM in pregnancy increasing with increasing BMI.

Table 9: Maternal outcome in term of development of pre-eclampsia in subjects with and without GDM

Pre-eclampsia	With GDM (n=23)		Without GDM (n=127)		P value
	No.	%	No.	%	
Present	2	8.7	0	0.0	0.02
Absent	21	91.3	123	100.0	

Out of 23 women with GDM, pre-eclampsia was developed in 2 (8.7%) women while no women without GDM developed pre-eclampsia. This association was found statistically significant (p=0.02).

Table 10: Mode of delivery between subjects with and without GDM

Mode of delivery	With GDM (n=23)		Without GDM (n=127)		P value
	No.	%	No.	%	
NVD	15	65.2	108	85.0	0.03
LSCS	8	34.8	19	15.0	

Table 10 shows outcome of women with and without GDM in term of mode of delivery. Out of 27 women with GDM, LSCS was required in 8 (34.8%) women and 19 (15.0%) women without GDM.

Table 11: Neonatal outcome between subjects with and without GDM

Neonatal outcome	With GDM (n=23)		Without GDM (n=127)		P value
	No.	%	No.	%	
Preterm delivery	2	8.7	8	6.3	0.65
Shoulder dystocia	1	4.3	0	0.0	0.15
Macrosomia	1	4.3	0	0.0	0.15
Congenital anomaly	1	4.3	0	0.0	0.15
Neonatal hypoglycaemia	9	39.1	1	0.8	<0.001
Perinatal death	0	0.0	0	0.0	-
RDS	6	26.0	1	0.8	0.06
SGA	2	8.7	4	3.1	<0.01
AGA	18	78.3	122	96.1	<0.01
LGA	3	13.0	1	0.8	<0.01

Table 11 shows neonatal outcome in pregnant women with and without GDM. Congenital anomaly was seen in 1 (4.3%) neonate (patent ductus arteriosus) of women with GDM while in subjects without GDM congenital anomaly was not seen in any of the neonates. Neonatal hypoglycemia was developed in 9(39.1%) neonates of women with GDM which was significantly higher compare to neonates of women without GDM (0.8%). Other neonatal complications seen in women with GDM were respiratory distress syndrome (n=6; 26.0%), shoulder dystocia (n=1; 4.3%) and preterm delivery (n=2; 8.7%). In women without GDM preterm delivery (n=8; 6.3%) and RDS (n=1; 0.8%) were other neonatal complications.3 (13.0%) out of 23 newborn were large for gestational age in women with GDM while only 1 (0.8%) neonate was large for gestational age (LGA) in women without GDM. Out of 23 neonates 18 (78.3%) were appropriate for gestational age (AGA) in women with GDM while 122 (96.1%) out of 127 were AGA in women without GDM.

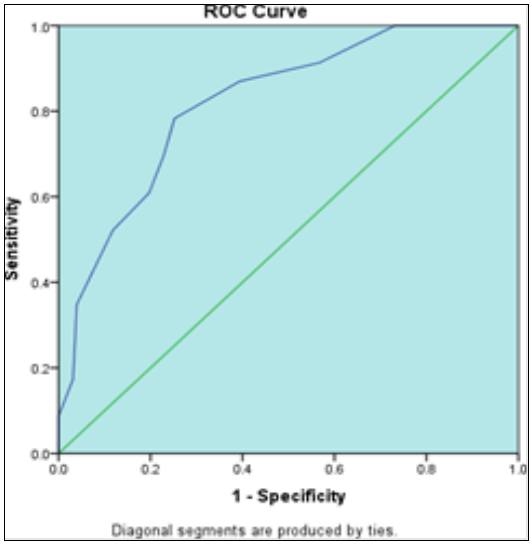
Table 12: Birth weight and APGAR score in women with and without GDM

	With GDM	Without GDM	P value
Birth weight (kgs)	3.31±0.65	2.69±0.46	<0.001
APGAR score at 1 min	7.02±0.59	8.93±0.68	<0.01
APGAR score at 5 min	8.13±0.74	9.04±1.10	0.02

Mean birth weight of baby was significantly higher in pregnant women with GDM (3.31±0.65 kgs) compare to women without GDM (2.69±0.46 Kgs).

Table 13: ROC curve interpretation

Parameter	Value
Area under curve	0.82
95% CI	0.73-0.91
Std error	0.04
P value	<0.001
Cut off value	5.3



A ROC curve was HbA1c for prediction of gestational diabetes mellitus was prepared and analysis showed a significant relationship between the first-trimester HbA1c level and the occurrence of GDM. The optimal diagnostic cut-off value, derived from the ROC analysis was 5.3%. The optimal diagnostic cut-off value is where the highest likelihood ratio is calculated and sensitivity-specificity correlation is the best. The area under the ROC curve was 0.82 (95% CI 0.73-0.91; *p*< 0.01).

Table 14: HbA1c test performance in diagnosing GDM

Cut off value of HbA1c	Sensitivity	Specificity
4.650	1.000	0.079
4.750	1.000	0.142
4.850	1.000	0.268
4.950	0.913	0.433
5.050	0.870	0.606
5.150	0.783	0.748
5.300	0.696	0.772
5.450	0.609	0.803
5.550	0.522	0.882
5.650	0.348	0.961
5.75	0.174	0.969
5.85	0.087	1.000

Table 14 depicts different cutoff level of HbA1c and sensitivity and specificity at that cutoff value which shows that at 5.65% specificity of HbA1c was 96.1% while at 5.05% sensitivity of HbA1c was 87.0% and specificity was 60.6%.

Table 15: Value of first trimester HbA1c for screening of GDM - mid trimester GTT as gold standard for diagnosis

	At cutoff level of 5.3	95% CI
Sensitivity	69.6%	47.1-86.8
Specificity	77.2%	68.9-84.1
Positive predictive value	35.6%	26.6-45.6
Negative predictive value	93.3%	88.2-96.3
Accuracy	76.0%	88.2-96.3
LR+ve	3.05	2-4.63

Patients with an HbA1c >5.3% had a 3.05-fold risk of developing GDM. For the optimal cut-off of the ROC analysis the sensitivity was 69.6% (95% CI- 47.1%-86.8%), the specificity was 77.2% (95% CI – 68.9%-84.1%), the positive predictive value was 35.6% (95%CI- 26.6% -45.6%) and the negative predictive value was 93.3% (88.2%- 96.3%). Overall diagnostic accuracy of HbA1c value >5.3% was 76.0% (95% CI-88.2%-96.2%).

Table 16: Distribution of HbA1c in GDM and non GDM group

	With GDM (n=23)		Without GDM (n=127)		P value
	No.	%	No.	%	
HbA1c >5.3%	16	69.6	29	22.8	<0.01
HbA1c ≤5.3%	7	30.4	98	77.2	

Using the cutoff value of 5.3% HbA1c was able to detect 16 (69.6%) out of 23 cases of GDM while we would have missed the GDM diagnosis in 7 out of 23 women, and 29 of 127 women would have been mistakenly diagnosed with GDM.

Table 17: Correlation of HbA1c with birth weight

	r value	p value
Birth weight	0.19	0.02*

Mild positive correlation was observed between HbA1c (%) level and birth weight (r value=0.19; p value =0.02).

Table 18: Association of different risk factors with raised HbA1c level

Risk factors of GDM	HbA1c ≤5.3 (n=105)		HbA1c>5.3 (n=45)		P value
	No.	%	No.	%	
PCOD	16	15.2	8	17.8	0.69
h/o GDM in previous pregnancy	18	17.1	12	26.7	0.18
Family history of GDM	19	18.1	11	24.4	0.37
h/o IUD	1	1.0	1	2.2	0.53
h/o delivery of neonates >4 kg	9	8.6	6	13.3	0.37

All the risk factors like PCOD, h/o GDM in previous pregnancy, Family history of GDM, h/o delivery of neonates >4 kg and h/o IUD were more commonly observed in women with HbA1c >5.3% compare to women with HbA1c ≤5.3 but no significant difference was observed between both groups.

Discussion

Diabetes mellitus is a common complication of pregnancy. GDM can adversely affect the fetal and neonatal outcomes [19]. However with proper glycemic control and improved monitoring these complications can be significantly reduced. But the ideal degree of glycemic control is still controversial [20, 21]. The purpose of screening, treatment and management of GDM is to prevent stillbirth, and decrease the incidence of LGA babies, thereby reducing maternal and perinatal morbidity and mortality. An HbA1c level represents the summation of glucose variability in the past 3 months and is a reliable determinant of diabetes compared to the one day blood sugar status determined by fasting/post-prandial glucose estimation or OGTT as clarified by the American Diabetes Association [24]. During pregnancy, HbA1c concentration drops below the pre-pregnancy level by at least 0.5%. This may be related to the shorter half- life of red blood cells during pregnancy, resulting in their limited exposure to hyperglycemia [27].

In 2010 ADA recommended HbA1c for diagnosing diabetes mellitus but there are no such guidelines for the use of HbA1c during pregnancy and for diagnosing GDM. The intra-individual coefficient of variation for measuring FBS has been found to be 6.4-11.4% and 14.3-16.7% for measurement of 2-h plasma glucose [21]. Compared to this HbA1c measurement has excellent reliability with intra-individual coefficient of variation of 4.2% over the short term in persons with diabetes and 1.9% over the long term in persons without diabetes [22].

O'Connor *et al* [23]. Formulated a nomogram for first trimester HbA1c in which the normal range was 4.3-5.4%. Other studies reported an upper normal first trimester HbA1c reference of 5.5-5.7% [27]. Hence, as for glucose, it is important to define pregnancy- specific HbA1c values that correlate with the adverse outcomes. This may help clinicians to establish HbA1c as a parameter in GDM risk stratification and prediction.

Demographic characteristics

Out of total 150 pregnant women included in our study, majority were in the age group of 26-30 years (41.3%) followed by 21-25 years (32.0%) and 31-35 years (18.0%). Only 13 (8.7%) women belonged to less than 20 years of age group. Mean age of study subjects was 26.59±4.06 years. In the study by Arbib N *et al* [24], mean age of pregnant women was 34.6±5.80 years which was significantly higher than our study. In the study by Arthy S *et al* [25], most of the pregnant women were between the age group of

21-25 years (62.8%) followed by 16-20 years (18.0%) and 26-30 years (17.5%) which is in concordance with our study. Out of 150 pregnant women, 39 (26.0%) were nullipara while 47 (31.3%) were primipara. 19 (12.7%) women had parity ≥3. In study by Arthy S *et al* [25], 41.2% women were nullipara and 39.6% were primipara.

Out of 150 pregnant women, 80 (53.3%) women had normal BMI while 23 (15.3%) were overweight and 47 (31.3%) were obese. PCOD was present in 24 (16.0%) subjects, h/o GDM in previous pregnancy was reported in 30 (20.0%) subjects while family history of DM was present in 15 (10.0%) subjects. 30 (20.0%) women gave history of delivery of neonates >4 kgs in previous pregnancy. Out of 150 pregnant women 123 (82.0%) were delivered vaginally while LSCS was required in 27 (18.0%) women. In study by Arthy S *et al* [25], 51% women were overweight and 10% were obese. In a study by Arbib N *et al* [24], 64.8% women were delivered vaginally, 6.3% by assisted vaginal delivery while LSCS was required in 28.9% women.

Prevalence of GDM

In our study, out of 150 pregnant women, GDM was developed in 23 pregnant women so the prevalence of GDM was 15.3% in our study. In the study by Amylidi S *et al* [26], the prevalence of GDM was 14.3% which is similar to our study while Arthy S *et al* [25] reported the prevalence of GDM as 29% in their study. Sujithra D *et al* [27] reported that GDM was developed in 27% of pregnant women selected for their study which is very high compared to our study.

Comparison of risk factors between subjects with and without GDM

In our study, history of gestational diabetes mellitus in previous pregnancy was seen in almost half of the women with GDM (52.1%) while it was seen in 14.2% women without GDM. Family history of diabetes mellitus was also seen more commonly in women with GDM (47.8%) compare to without GDM (15.0%) which was also significantly different. Our finding were in concordance to study by Mohanapriya N [28] *et al* reported family history of GDM in 35% mothers in GDM group and 3% members in non-GDM group and history of GDM in previous pregnancy in 5% mothers in GDM group and 1% mother in non-GDM group. 6 out of 23 (26.1%) women who developed GDM informed h/o delivery of neonates >4 kg in previous pregnancy while only 7.1% women without GDM reported >4 kg of neonates delivered in previous pregnancy. h/o IUD was also present in 2 women with GDM while none of the women without GDM gave history of IUD. PCOD was also present in 5 (21.7%) women with GDM and 19 (15.0%) women without GDM. In our study, prevalence of GDM in subjects with normal BMI was 7.5%, in subjects with BMI between 25-29.99 kg/m^2 was 17.4%, in subjects with BMI between 30-34.99 kg/m^2 prevalence of GDM was 25.0% while in Obese class II subjects, prevalence of GDM was 29.0%. This shows that chances of developing GDM in pregnancy increasing with increasing BMI. Out of 23 women with GDM, pre-eclampsia was developed in 2 (8.7%) women while no women without GDM developed pre-eclampsia. This association was found statistically significant (p=0.02).

Maternal Complications

In the present study, out of 27 women with GDM, LSCS was required in 8 (34.8%) women and 19 (15.0%) women without GDM. Many studies have found high caesarean delivery rates in GDM patients despite good maternal blood glucose control during pregnancy [29]. The significantly higher rate of caesarean delivery in GDM patients compared to the controls, is found in this study also. The most common indication for caesarean in this study was previous history of caesarean sections. The caesarean rate of 34.8% in this series is comparatively higher (19-30%) reported in previous studies [28].

Neonatal Complications

In our study, congenital anomaly was seen in 1 (4.3%) (patent ductus arteriosus) neonate of women with GDM while in subjects without GDM congenital anomaly was not seen in any of the neonates.

As unrecognized pre-existing diabetes is associated with an increased incidence of congenital malformations [30], women at risk may benefit from screening early in pregnancy. The general screening policy for GDM using a 75-g OGTT between 24 and 28 weeks of gestation may delay the diagnosis and possibility of early treatment for the high-risk women. There is no doubt that among women with preexisting diabetes, the fetal and neonatal risks are proportional to the degree and duration of maternal hyperglycemia and the pre-conceptional HbA1c level [31]. Indeed, a higher rate of malformations and poor pregnancy outcome have been consistently published in diabetic women with pre-conceptional HbA1c values >7.0% (>53 mmol/mol) [32]. Neonatal hypoglycemia was developed in 9 (39.1%) neonates of women with GDM which was significantly higher compare to neonates of women without GDM (0.8%). Respiratory distress syndrome (n=6; 26.0%) was significantly higher than (n=1; 0.8%) in women without GDM. 3 (13.0%) out of 23 newborn were large for gestational age in women with GDM while only 1 (0.8%) neonate was LGA in women without GDM. Out of 23 neonates 18 (78.3%) were appropriate for gestational age (AGA) in women with GDM while 122 (96.1%) out of 127 were AGA in women without GDM. Mean birth weight of baby was significantly higher in pregnant women with GDM (3.31±0.65 kgs) compared to women without GDM (2.69±0.46 Kgs).

Macrosomia is a known complication of GDM and it is a proven fact that post prandial hyperglycemia is associated with increased incidence of macrosomia. The macrosomia rate in our study (4.3%) was lower than various studies reported in literature like 5.9% in the study conducted by Landon MB *et al* [33] in 2009, 9.7% by Schmidt MI *et al* [34] in 2001, 27.6% by Shefali AK *et al* [35] and 18.90 by Hirst JE *et al* [36]. This observed difference can be due to better glycemic control or due to different genetic, demographic and maternal metabolic factors that are known to affect fetal growth. The difference may also be due to different diagnostic criteria applied in different literatures. Although glycemic control plays an important role in determining fetal size, excessive maternal weight gain and obesity also strongly influence neonatal birth weight, even in women without glucose intolerance [37]. This was a limitation in our study as these confounding factors were not included in our study, shoulder dystocia (n=1; 4.3%) and preterm delivery (n=2; 8.7%) compared to (n=8; 6.3%) in women without GDM.

We had 2 (8.7%) spontaneous preterm delivery in our study which was slightly higher than non GDM patients which was 6.3%, and the rate is in accordance with that quoted in other similar studies [33]. Literature does not show an increased incidence of congenital anomalies in gestational diabetes compared to that of general population, again related to hyperglycemia at peri-conceptional period and during period of organogenesis. This is also reflected in our study and comparable to other studies [35].

Diagnostic value of HBA1C

We prepared ROC curve using HbA1c for prediction of gestational diabetes mellitus and analysis showed a significant relationship between the first-trimester HbA1c level and the occurrence of GDM. The optimal diagnostic cut-off value, derived from the ROC analysis was 5.3%. The optimal diagnostic cut-off value is where the highest likelihood ratio is calculated and sensitivity-specificity correlation is the best.

The area under the ROC curve was 0.82 (95% CI 0.73-0.91; $p<$ 0.01). Patients with an HbA1c >5.3% had a 3.05-fold risk of developing GDM. For the optimal cut-off of the ROC analysis the sensitivity was 69.6% (95% CI- 47.1%-86.8%), the specificity was 77.2% (95% CI - 68.9%-84.1%), the positive predictive value was 35.6% (95%CI-

26.6% -45.6%) and the negative predictive value was 93.3% (88.2%-96.3%). Overall diagnostic accuracy of HbA1c value >5.3% was 76.0% (95% CI-88.2%-96.2%).

Using the cutoff value of 5.3% HbA1c was able to detect 16 (69.6%) out of 23 cases of GDM while we would have missed the GDM diagnosis in 7 out of 23 women, and 29 of 127 women would have been mistakenly diagnosed with GDM.

Conclusion

The optimal diagnostic cut-off value, derived from the ROC analysis was 5.3%. The area under the ROC curve was 0.82 (95% CI 0.73-0.91; $p<$ 0.01). Patients with an HbA1c >5.3% had a 3.05-fold risk of developing GDM. For the optimal cut-off of the ROC analysis the sensitivity was 69.6% (95% CI- 47.1%-86.8%), the specificity was 77.2% (95% CI – 68.9%-84.1%), the positive predictive value was 35.6% (95%CI- 26.6% -45.6%) and the negative predictive value was 93.3% (88.2%-96.3%). Overall diagnostic accuracy of HbA1c value >5.3% was 76.0% (95% CI-88.2%-96.2%). Using 5.65% cut-off value, specificity of HbA1c was 96.1% while at 5.05% sensitivity of HbA1c was 87.0% and specificity was 60.6%. Mild positive correlation was observed between HbA1c (%) level and birth weight (r value=0.19; p value =0.02).

The present study results suggested that HbA1c can be an appropriate biomarker for GDM prediction, probably not in isolation, but rather as a part of a multi-marker algorithm for high-and low-risk populations.

Conflict of Interest

Not available

Financial Support

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