PROSPECTIVE ASSESSMENT OF GLYCOSYLATED HEMOGLOBIN IN EARLY PREGNANCY AS A PREDICTOR OF GESTATIONAL DIABETES MELLITUS

"**Dr. Anil Bhattad**
Assistant Prof. Department of General Medicine
Krishna Institute of Medical Sciences,
Krishna Vishwa Vidyapeeth
"Deemed To Be University", Karad – 415110, Maharashtra"

"**Dr. Ganesh Thorat Assistant**
Prof. Department of General Medicine
Krishna Institute of Medical Sciences,
Krishna Vishwa Vidyapeeth
"Deemed To Be University", Karad – 415110, Maharashtra"

"**Dr. Desai Jabbar V.**
Assistant Department of General Medicine
Krishna Institute of Medical Sciences,
Krishna Vishwa Vidyapeeth
"Deemed To Be University", Karad – 415110, Maharashtra"

ABSTRACT

Glycemic dysregulation increases the risk of developing diabetes in both the mother and the child. Since more women acquire type 2 diabetes mellitus (T2DM) during pregnancy, screening at the first prenatal visit is crucial. GDM is usually diagnosed in the late second or early third trimester because of the first trimester's accuracy. GDM incidence is growing in India, necessitating clinical treatment recommendations. Due to genetic and demographic factors, Indian women are more at risk of developing insulin resistance or diabetes during pregnancy. Analytical stability is improved by HbA1c test uniformity and decreased volatility before analysis. Thus, this study explored glycosylated hemoglobin as a pregnancy GDM diagnosis tool and its impact on fetal outcomes. We come to conclusion that first-trimester HbA1c may identify high-risk GDM patients.

Keywords: T2DM**,** GDM**,** HbA1c, first trimester.

INTRODUCTION

Gestational diabetes mellitus (GDM) was first defined by O'Sullivan in 1961 as a carbohydrate intolerance of varying degrees that manifests itself during pregnancy or is first detected in pregnant

3398

women.[1] Studies have also proved that glycemic dysregulation is a pathological situation that increases the risk of diabetes in both the mother and the child.[2] Due to the surge in the proportion of women with undetected type 2 diabetes mellitus (T2 DM) during pregnancy, screening for pre-existing diabetes at the first prenatal consultation is indicated. GDM is still often diagnosed in the late second or early third trimester because of the inaccuracy of the first trimester diagnosis.

GDM's widespread incidence in India necessitates clinical treatment guidelines. Indian women are more likely to develop insulin resistance or diabetes during pregnancy due to genetic and demographic factors in the Indian population[.3] HbA1c, in turn, has been shown to result from the non-enzymatic, irreversible binding of glucose to plasma proteins such as hemoglobin (Hb). The average plasma glucose level across an erythrocyte's lifespan is related to glycosylation. The HbA1c test has improved analytical stability due to better uniformity across tests and decreased variation before analysis. Therefore , The purpose of this study was to investigate and appraise the utility of glycosylated hemoglobin as a diagnostic tool for GDM in pregnancy as well as its significance for perinatal outcomes.

AIM

The purpose of this study was to investigate and appraise the utility of glycosylated hemoglobin as a diagnostic tool for GDM in pregnancy as well as its significance for perinatal outcomes.

INCLUSION CRITERIIA

1. Patients who were between 8 to 16 weeks of gestation were included in the study.

2. Patient with singleton preganancy were included in the study.

EXCLUSION CRITERIA

1. Patients with overt diabetes 1st trimester glycosylated Hb more than 6.5 g % were excluded fro the study.

2. Patients with haemoglobinopathies, anaemia (Hb<10 g%), chronic renal disease, multiple pregnancies were excluded from the study.

MATERIALS & METHOD

STUDY DESIGN – Our study was prospective type of study.

STUDY SETTING – Our study was conducted on patients attending ANC OPD of tertiary health care centre**.**

STUDY PERIOD – Our study was for around 18 months in total .

ETHICAL CLEARANCE – After receiving clearance from the Institutional Human Ethics Committee as well as the Institute Research Committee we have started with our study.In our study

we have maintained the privacy & confidential details of the patient throughout our research. Furthermore, no additional expenses were incurred for the patient as part of the study.

STUDY SUBJECTS- Antenatal cases attending the antenatal clinic.

DATA COLLECTION TECHNIQUE

After taking informed consent , HbA1c & other investigations were done with 1st trimester patients. Furthermore, proforma were given to all patients meeting the inclusion criteria. Proforma included demographics, obstetric history, past history, family history, 1st trimester HbA1c value, 1st trimester OGCT (8-16 weeks) & scan , 2nd trimester OGCT (24-28 weeks) 3rd trimester OGCT (32-36 weeks), infant details after birth. All the patients included in the study were followed up till their respective delivery. In addition, based on DIPSI criteria they were group as normal & GDM patients.HbA1c investigation was performed using board D 10/HPL while 75 g OGCT was performed by glucose oxidase method .

STASTICAL ANALYSIS

We have used microsoft excel to enlist the data . Further, continuous variables were estimated by using mean & standard deviation. Nominal data were expressed as the frequency. Appropriate statistical tests like t test, chi square test, were done to know the correlation between the variables. ROC curve was constructed to assess discriminative capacity of HbA1c for detection of GDM. Sensitivity, specificity, predictive values were also calculated. Analysis of the data were done using appropriate statistical software (SPSS Trial version).

RESULT

AGE

AGE IN YEARS	FREQUENCY	PERCENT
<20yrs	16	12.9
21-25yrs	59	47.6
26-30yrs	39	31.5
>30yrs	10	8.1
Total	124	100.0

3400

TABLE 1: AGE DISTRIBUTION.

In our study, we have found that out of 124 patients, 12.9 % patients were in < 20 years age group, 47.6% in 21-25 year group, 31.5% were in 26-30 year group and 8.1 % in 30 years and above age group.

PARITY

	Frequency	**Percent**
Multipara	37	29.8
Primi para	87	70.2
Total	124	100.0

TABLE 2: PARITY DISTRIBUTION.

In our study , we have found that out of 124 patients , 29.8% were under multigravidas category & 70.2% were under primi gravidas category.

BMI

BMI (kg/m^2)	**Frequency**	**Percent**
18-24	58	46.8
25-29	60	48.4
>30	6	4.8
Total	124	100.0

TABLE 3: BMI DISTRIBUTION.

In our study we have found that out of 124 patients , 46.8% belonged to 18-24 BMI group, 48.4 %belonged to 25-29 BMI group, 4.8 % belonged to above 30 group.

3401

FAMILY H/O DM

	Frequency	Percent
No	95	76.6
Yes	29	23.4
Total	124	100.0

TABLE 4 : FAMILY H/O DM DISTRIBUTION.

In our study we have found that out of 124 patients , 23.4 % had family history of DM.

GDM

	Frequency	Percent
No	94	75.8
Yes	30	24.2
Total	124	100.0

TABLE 5 : GDM DISTRIBUTION.

In our study we have found that out of 124 patients studied, 30 (24.2%) found to have GDM, 94 (75.8 %) non-GDM .

GESTATIONAL AGE AT GDM

	Frequency	Percent
24-28weeks	29	96.7
32-36weeks	1	3.3
Total	30	100.0

TABLE 6 : GESTATIONAL AGE AT GDM DISTRIBUTION.

In our study we have found that out of 30 GDM patients , 29 (96.7%) were diagnosed in second trimester,1(3.3%) were diagnosed in third trimester.

3402

DIABETIC STATUS

	Frequency	Percent
Non GDM	94	75.8
GDM on MNT	16	12.9
GDM on treatment	14	11.3
Total	124	100.0

TABLE 7 : DIABETIC STATUS DISTRIBUTION.

In our study we have found that out of 30 GDM patients ,16 patients were managed with MNT ,14 patients were managed with oral hypoglycemic agents /Insulin (9 patients with metformin and 5 with insulin).

POLYHYDRAMNIOS DISTRIBUTION

	Frequency	Percent
No	115	92.7
Yes	9	7.3
Total	124	100.0

TABLE 8 : POLYHYDRAMNIOS DISTRIBUTION.

In our study we have found that out of 124 patients , 9 patients (7.3 %) had polyhydramnios.

MODE OF DELIVERY

	Frequency	Percent
FTVD	72	58.1
LSCS	52	41.9
Total	124	100.0

TABLE 9 : MODE OF DELIVERY.

In our study we have found that out of 124 patients studied ,72 (58.1%) delivered vaginally and 52 (41.9 %) underwent LSCS.

BIRTH WEIGHT

	Frequency	Percent
1.5-2.5kgs	26	21.0
2.5-3.5kgs	88	71.0
>3.5kgs	10	8.1
Total	124	100.0

TABLE 10 : BIRTH WEIGHT DISTRIBUTION.

In our study we have found that out of 124 infants delivered , 88 (71%) were belonged to group 2.5 – 3.5 kg , 26 (21%) infants had birth weight around 1.5 – 2.5 kg and remaining 10 (8.1%) infants had birth weight more than 3.5 kgs.

HbA1c level for GDM & N-GDM

HbA1C	Total	GDM	
		Present	**Absent**
N	124	30	94
Mean	5.366	5.85	5.21
Sd	0.34	0.13	0.22
Minimum	4.7	5.6	4.7
Maximum	6.2	6.2	5.8
Median	5.30	5.8	5.2
Q1	5.1	5.8	5.1
Q3	5.7	5.9	5.4

TABLE 11: HbA1c level in GDM & N-GDM.

In our study we have found that patients of 124, mean HbA1c was 5.36% with SD 0.34,minimum value of HbA1c in the study sample was 4.7% and maximum value was 6.2%.Among the group with GDM, mean HbA1c was 5.85% ± 0.13 compared to 5.21% ± 0.22 in patients without GDM.
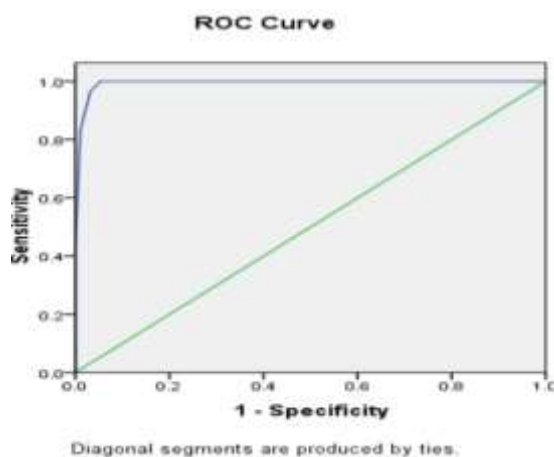
ROC CURVE

FIGURE 1 : ROC CURVE.

Area under the ROC curve (AUC)	0.994
Standard Error	0.00452
95% Confidence interval	0.959 to 1.000
P value	<0.0001

TABLE 12: ROC CURVE CHARACTERISTIC.

Criterion	Sensitivity	Specificity	+LR	-LR	+PV	-PV
>5.6	100.00	94.68	18.80	0.00	85.7	100.0
>5.7	96.67	96.81	30.29	0.034	90.6	98.9
>5.8	83.33	98.94	78.33	0.17	96.2	94.9

TABLE 13 : ROC CURVE CUT OFFS.

In our study, we have found that an ROC curve for optimum cutoff of predicting GDM showed 5.7 % including sensitivity as 97.67% , specidicity as 96.82% , PPV as 90.6% and NPV as 98.9% respectively. This ROC curve was constructed to study estimate cutoff of HbA1c to predict GDM.

ASSOCIATION BETWEEN AGE & HbA1c

		Mean	SD	P value
Age	**HbA1c ≤ 5.7**	24.48	3.359	0.021
	HbA1c >5.7	26.35	4.472	

TABLE 14: LINK BETWEEN THE 2 VARIABLES.

In our study we have found that there was a stastical significant difference between age & HbA1c . Therefore, with advancing in age there was more changes of elevated HbA1c .

ASSOCIATION BETWEEN BMI & HbA1c

BMI	HbA1c ≤ 5.7	HbA1c >5.7	Total
Normal	49	9	58
	50.0%	34.6%	46.8%
Overweight	48	12	60
	49.0%	46.2%	48.4%
Obese	1	5	6
	1.0%	19.2%	4.8%

TABLE 15: LINK BETWEEN 2 VARIABLES.

In our study we have come across that P value was 0.001 , i.e. there was astastical significant difference between BMI & H bA1c . Furthermore, with increased BMI there was increased incidence of elevated HbA1c.

ASSOCIATION BETWEEN FAMILY H/O DM & HbA1c

Family H/o DM	HbA1c ≤ 5.7	HbA1c >5.7	Total
No	83	12	95

	84.7%	46.2%	76.6%
Yes	15	14	29
	15.3%	53.8%	23.4%
Total	98	26	124
	100.0%	100.0%	100.0%

TABLE 16: LINK BETWEEN 2 VARIABLES.

In our study we have found that P value was 0.001 , i.e. there was astastically significant difference found between family h/o & HbA1c . Furthermore, in patients with family history of DM (53.8%) had elevated HbA1c ($\geq$ 5.7%) whereas in patients without family history of DM (46.2%) had HbA1c ($\geq$ 5.7%) . In addition, the association was stastically significant proved. Hence, women with family history DM have 6 times more chance of elevated HbA1c .

ASSOCIATION BETWEEN GDM & HbA1c

GDM	HbA1c $\leq$ 5.7	HbA1c >5.7	Total
No	93	1	94
	94.9%	3.8%	75.8%
Yes	5	25	30
	5.1%	96.2%	24.2%
Total	98	26	124
	100.0%	100.0%	100.0%

TABLE 17 : LINK BETEWEEN GDM & HbA1c.

In our study we have found that P value was 0.001 i.e. there was a stastically significant difference between GDM & HbA1c. Inaddition, patients with HbA1c ($\geq$ 5.7%) showed more risk of developing GDM . Furthermore, (24.3 %) of patients developed GDM, women with HbA1c value (> 5.7 %, 96.2%) developed GDM & (3.8%) did not develop GDM.

ASSOCIATION BETWEEN GESTATIONAL AGE OF DIAGNOSIS OF GDM & HbA1c.

N Gestational age of diagnosis of GDM	HbA1c ≤ 5.7	HbA1c >5.7	Total
24-28wks	4	25	29
	80.0%	100.0%	96.7%
32-36wks	1	0	1
	20.0%	.0%	3.3%
Total	5	25	30
	100.0%	100.0%	100.0%

TABLE 18 : LINK BETWEEN 2 VARIABLES.

In our study we have found that p value was 0.167 i.e. there was no stastically significant difference found between gestational age of diagnosis of GDM & HbA1c.

ASSOCIATION BETWEEN GDM MANAGEMENT & HbA1c.

	HbA1c ≤ 5.7	HbA1c >5.7	Total
On MNT	3	13	16
	60%	52%	12.9%
On Treatment	2	12	14
	40%	48%	11.3%
Total	5	25	30
	100%	100%	100%

TABLE 19 : LINK BETWEEN GDM MANAGEMENT & HbA1c

In our study we have found that P value was 0.743 i.e. there was no ststistically significant difference between GDM management & HbA1c.

3408

ASSOCIATION BETWEEN POLYHYDRAMNIOS & HbA1c

POLYHYDRAMNIOS	HBA1C $\leq$ 5.7	HBA1C >5.7	TOTAL
No	96	19	115
	98.0%	73.1%	92.7%
Yes	2	7	9
	2.0%	26.9%	7.3%
Total	98	26	124
	100.0%	100.0%	100.0%

TABLE 20 : LINK BETWEEN 2 VARIABLES.

In our study we found that P value ws 0.001 , i.e. there was astastically significant difference between polyhydramnios & HbA1c.

ASSOCIATION BETWEEN MOD & HbA1c

	HbA1c $\leq$ 5.7	HbA1c >5.7	Total
FTVD	59	13	72
	60.2%	50.0%	58.1%
LSCS	39	13	52
	39.8%	50.0%	41.9%
Total	98	26	124
	100.0%	100.0%	100.0%

TABLE 21 : LINK BETWEEN MODE OF DELIVERY & HbA1c.

In our study we found that P value was 0.3491, i.e. there was no stastical significant difference between mode of delivery & HbA1c.

ASSOCIATION BETWEEN BIRTH WEIGHT & HbA1c

		Mean	**SD**	**P value**
Birth weight	**HbA1c $\leq$ 5.7**	2.818102	.3998397	0.005

HbA1c >5.7	3.116538	.6741747

TABLE 22: LINK BETWEEN BIRTH WEIGHT & HbA1c

DISCUSSION

To determine whether first-trimester HbA1c predicts GDM, we conducted a study. Tertiary care centers hosted the study. The study included 124 pregnant women between 8 and 14 who were carrying one toddler. GDM affected 24% of those in the study. The study group's first-trimester HbA1c averaged 5.366. Women with GDM had greater HbA1c values compared to women who did not acquire the condition. Subjects with GDM had an average HbA1c value of 5.85+0.13%, compared to 5.21+0.22% in subjects without GDM. The ROC analysis showed that 1 significantly affected GDM prevalence. ROC analysis showed that a 5.7% cutoff best predicted GDM. Patients with HbA1c > 5.7% had six times more diabetes complications. The study's ROC curve has a 95% CI of 0.994. The optimal cutoff of 5.7% has a sensitivity of 96.67%, a specificity of 96.81%, a positive predictive value of 90.6%, and a negative predictive value of 98.9%. The cutoff HbA1c value was compared to maternal, obstetric, and perinatal factors.

AGE

The association between age and HbA1c was stastically signifoicant . Indicating that with increasing age (> 25 years) there is more chance of elevated HbA1c . Further, early detection & management of GDM among this age group can bring doen long term adverse consequences in mother as well as baby.

BMI

Through our study we have found that there was stastiscally significant association between BMI & HbA1c values . Further, women with BMI > 25 had increased incidence of elevated HbA1c.

FAMILY H/O OF DM

The association in our study proved to be statsically significant relation between the 2 variables. Furthermore, patients with family history of GDM have been shown more chance for elevation in HbA1c level.

GDM & HbA1c

In our study, total of 24.3 % of the patients developed GDM . Further , women with HbA1c value > 5.7 % , 96.2% developed GDM & 3.8% did not develop GDM. In the group with HbA1c < 5.7 %,

5.1 % patients developed GDM & 94.9% did not develop GDM. The association should stastically significant (p = < 0.001) relation. Thus , women with HbA1c ≥ 5.7 % have 6 times more risk to develop GDM.

GESTATIONAL AGE OF DIAGNOSIS OF GDM

With the help of our investigation , we found that the 2 variables did not ashow a stastically significant difference .

GDM MANAGEMENT & HbA1c

In our study we found that , 53.4% of GDM patients had blood sugar level that were controlled with medical nutrition therapy & 46.6% women required insulin. 48% women with HbA1c > 5.7 % required therapy / OHA compared to 18.2 % women with HbA1c value < 5.7% . However , the difference was not stastically significant indicating that the level of blood sugar control was not associated with HbA1c values.

3RD TRIMESTER SCAN

In our study, 7.3% women had evidence of polyhydaminos in 3rd trimester scan. 26.9% women with HbA1c values > 5.7 % had polyhydraminos n 3rd trimester scan compared to 2% women with HbA1c values <5.7%. Difference between the two groups was statistically significant with p value <0.001. Hence, women with elevated HbA1c value had more risk of polyhydramnios.

MODE OF DELIVERY

In our study we have found that , 58.1% women delivered vaginally and 41.9% subjects underwent caesarean section.50% of women with elevated HbA1c .Hence, the difference was not statistically significant w.r.t. women with HbA1c.

BIRTH WEIGHT

In our study we found that, majority of the babies born (71%) had birth weight between 2.5-3.5kg . Furthermore,women with HbA1c >5.7%, babies born were macrosomic compared to babies in the group with HbA1c <5.7%.Hence, we have found a statistically significant difference between Birth weight and HbA1c.

RECENT RELEVANT STUDIES

1. According to a 2018 study by Stefanie N. Hinkle et al., there was a significant linear relationship between HbA1c during enrollment (8–13 weeks) and GDM risk (P = 0.001). GDM risk was 2.73 (95% CI 1.59–4.66) times higher in women with a first trimester HbA1c of 5.7% (39 mmol/mol) than in women with a median HbA1c of 5.2% (33mmol/mol).[4]

3411

Eur. Chem. Bull. 2023, 12(Special Issue 4), 3398-3413

2. In a 2019 study by Nissim Arbib et al., the duration of gestation was shown to be negatively associated with HbA1C concentration (r = 0.317, P 0.001).. Gestational diabetes was linked to a higher HbA1C. An HbA1C concentration of 5.45% predicted gestational diabetes with 83.3% sensitivity, 69% specificity, and positive and negative gestational diabetes values of 53.0% and 90.8%, respectively.[5]

3. The optimal cut-off for HbA1C was found to be 5.4960.48% in a study by Shaiesta Amreen et al., as it gives a sensitivity of 80% and a specificity of 55.3% and may be used as a screening tool for GDM.[6]

4. In a study by Rajesh Rajput et al., the mean HbA1c value of women with GDM was significantly higher than that of women without GDM (5.73±0.34 vs. 5.34±0.35). In diagnosing GDM, a HbA (1c) cutoff value of 5.95% had a sensitivity of 28.6% and a specificity of 97.2%, while a HbA (1c) cutoff value of 5.45% had a sensitivity of 85.7% and a specificity of 61.1%. An OGTT is required to appropriately detect GDM in women with a HbA1c value between 5.45 and 5.95. This methodology would have discovered 85.7% of GDM cases, but 2.8% of healthy women would have been wrongly labeled with GDM. Furthermore, for 61.8% of women, this methodology would have removed the requirement for an OGTT.[7]

5. Khalafallah A. and colleagues tested 480 pregnant women for GDM using GlycoHb. They suggested those women with GlycoHb > 5.4% undergo a GTT to reduce the burden of second-trimester universal screening.[8]

6. According to Saleh et al., the sensitivity of HbA1c at the following cut-off points of 5.0%, 5.5%, 6.0%, 6.5%, and 7.0% (i.e., sensitivity values) was 100%, 98.4%, 87.1%, 62.9%, and 39.5%, respectively, and the mean HbA1c of patients with GDM was 6.9+0.8% versus 6.4+0.6% of those without GDM (P 0.006) (P 0.006).[9]

CONCLUSION

First trimester HbA1C 5.7% has a sensitivity of 97.67%, a specificity of 96.81%, a PPV of 90.6%, and a NPV of 98.9% and may identify pregnant women who may develop GDM early in pregnancy so they can get nutritional and lifestyle guidance. The burden of GDM may be decreased if steps are taken early for individuals with certain modifiable risk factors. Maternal age, parity, and pre-pregnant BMI are modifiable risk factors that are substantially related to increased HbA1c. HbA1c values and polyhydraminos are substantially connected. Thus, we conclude that , the first-trimester

3412

HbA1c readings may be used as a diagnostic tool to identify women at high risk of developing GDM or not.

REFERENCE

1. O'Sullivan JB. Gestational diabetes: unsuspected, asymptomatic diabetes in pregnancy. New England Journal of Medicine. 1961 May 25;264(21):1082-5.

2. Swaminathan G, Swaminathan A, Corsi DJ. Prevalence of gestational diabetes in India by individual socioeconomic, demographic, and clinical factors. JAMA network open. 2020 Nov 2;3(11):e2025074-.

3. Bahl S, Dhabhai N, Taneja S, Mittal P, Dewan R, Kaur J, Chaudhary R, Bhandari N, Chowdhury R. Burden, risk factors and outcomes associated with gestational diabetes in a population-based cohort of pregnant women from North India. BMC Pregnancy and Childbirth. 2022 Dec;22(1):1-

4. Hinkle SN, Tsai MY, Rawal S, Albert PS, Zhang C. HbA1c measured in the first trimester of pregnancy and the association with gestational diabetes. Scientific reports. 2018 Aug 16;8(1):12249.

5. Arbib N, Shmueli A, Salman L, Krispin E, Toledano Y, Hadar E. First trimester glycosylated hemoglobin as a predictor of gestational diabetes mellitus. International Journal of Gynecology & Obstetrics. 2019 May;145(2):158-63.

6. Amreen S, Suneel A, Shetty A, Vasudeva A, Kumar P. Use of glycosylated HbAlc and random blood sugar as a screening tool for gestational diabetes mellitus in first trimester. International Journal of Reproduction, Contraception, Obstetrics and Gynecology. 2018 Feb 1;7(2):524-9.

7. Rajput R, Rajput M, Nanda S. Utility of HbA1c for diagnosis of gestational diabetes mellitus. Diabetes research and clinical practice. 2012 Oct 1;98(1):104-7.

8. Khalafallah A, Phuah E, Al-Barazan AM, Nikakis I, Radford A, Clarkson W, Trevett C, Brain T, Gebski V, Corbould A. Glycosylated haemoglobin for screening and diagnosis of gestational diabetes mellitus. BMJ open. 2016 Apr 1;6(4):e011059.

9. Aldasouqi SA, Solomon DJ, Bokhari SA, Khan PM, Muneera S, Gossain VV. Glycohemoglobin A1c: a promising screening tool in gestational diabetes mellitus. International journal of diabetes in developing countries. 2008 Oct;28(4):121.