

**Which can predict Pregnancy-induced Insulin Resistance and Gestational Diabetes Mellitus; Glycated Albumin or Glycated Hemoglobin?**

Abd El Ghaffar Saeed Dawood<sup>a</sup>, Ahmed M.E. Ossman<sup>a\*</sup>, Nareman Elhamamy<sup>a</sup>.

<sup>a</sup>Department of Obstetrics & Gynecology, Faculty of Medicine, Tanta University, Tanta, Egypt.

**Abstract**

**Background:** Aberrant gestational glucose homeostasis initiates a cascade of events that end in the development of gestational diabetes mellitus (GDM). Glycated albumin (GA) is a promising sensitive plasma marker for detecting early disturbed glucose homeostasis.

**Objectives:** To evaluate the ability of trimester-course estimated plasma glycated hemoglobin (HbA1c) and GA levels to identify women vulnerable to developing GDM.

**Patients and methods:** Blood samples were obtained from 272 newly pregnant women for the 75-g oral glucose tolerance test (OGTT), estimation of fasting blood glucose (FBG), and serum insulin to calculate the homeostasis model assessment of insulin resistance (HOMA-IR) score and estimation of HbA1c and GA levels at the 12<sup>th</sup>, 24<sup>th</sup>, and 36<sup>th</sup> gestational weeks (GW).

**Results:** At 24-GW, 56 women developed GDM. FBG levels at 24-GW were positively correlated with a significant ( $P = 0.001$ ) coefficient to the 12-GW body mass index (BMI), HbA1c ( $P < 0.001$ ), and GA levels ( $P < 0.001$ ). HOMA-IR score determined at 24-GW showed positive significant ( $P = 0.001$ ) correlation with the 12-GW BMI, HbA1c ( $P < 0.001$ ), and GA levels ( $P < 0.001$ ). ROC curve analysis defined the estimated level of GA at the 12-GW as a significant ( $P < 0.001$ ) identifier of normoglycemic liable to develop GDM and IR ( $P = 0.001$ ).

**Conclusion:** GA plasma levels start to increase earlier during pregnancy than HbA1c levels and so could be used as an early predictor for abnormal OGTT at 24 GW and can detect liability to have IR irrespective of the BG level.

**Keywords:** Gestational diabetes mellitus; Glycated albumin; Glycated hemoglobin A1c; Insulin resistance; Body mass index.

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**Correspondence:** [ahmed.mE.ossman99@gmail.com](mailto:ahmed.mE.ossman99@gmail.com)

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## Introduction

Metabolism during pregnancy undergoes numerous changes that can lead to gestational diabetes mellitus (GDM), a disease with heterogeneous pathogenesis that is increasing in prevalence and is associated with the modern lifestyle (Omazić et al., 2021). Pregnant women afflicted with GDM are prone to both maternal and neonatal complications; thus, it is of utmost importance to discriminate women liable to get GDM and to sustain glycemic control during pregnancy (Zhang et al., 2021).

The glycation of protein entails the non-enzymatic addition of carbohydrate moieties to protein-reactive residues (Rondeau et al., 2010). Early glycation includes the interaction of reducing sugars, such as glucose, with free amino groups of lysine and arginine residues, leading to the formation of Schiff's bases and Amadori products, and upon oxidation, the advanced glycated end products are formed (Arasteh et al., 2010).

The standard monitoring of diabetic patients depends on the estimation of glycated hemoglobin (HbA1c), which represents the glycemic status within the preceding 2-3 months, which is too infrequent for managing GDM (Mendes et al., 2019). Frequent estimation of blood glucose (BG) levels is subjected to multiple daily variations and are unnecessary for women with mild to moderate GDM in addition to its inconvenience (Belsare and Coté, 2021). Multiple studies assured the need for an intermediate biomarker that can be used effectively to monitor the glycemic status of diabetic patients, especially women with GDM (Mendes et al., 2019; Mihaela et al., 2019; Belsare and Coté, 2021).

This study aims to evaluate the ability of trimester-course estimation of plasma HbA1c and GA to predict

the oncoming GDM in normoglycemic pregnant women.

## Patients and methods

**Design :** Prospective multicenter comparative study.

**Setting :** Departments of Obstetrics and Gynecology, Faculty of Medicine, Tanta and Menoufia Universities.

**Ethical Approval:** The Ethical Committee at the Faculty of Medicine, Tanta University approved the study protocol.

Women who presented with manifestations suggestive of being pregnant were evaluated for the requirements of inclusion in the study. Pregnancy was diagnosed chemically and assured at the 6<sup>th</sup> gestational week (GW) by abdominal ultrasonography on detection of a viable intrauterine gestational sac.

**Inclusion criteria:** Newly diagnosed pregnant normoglycemic women who had a BMI < 35 kg/m<sup>2</sup> at the time of diagnosis were eligible for enrolment after signing the fully informed written consent.

**Exclusion criteria:** Current diabetes mellitus (DM), history of GDM for multipara, history of DM that was running in the family, endocrinopathy-inducing hyperglycemia or obesity, body mass index (BMI) of >35 kg/m<sup>2</sup> at time of attending the clinic, chronic liver, kidney, or cardiac diseases, autoimmune diseases or maintenance on autoimmune therapy, current or previous attack of COVID-19 disease, recent vaccination for COVID-19 disease, refused to participate in the study.

**Study protocol:** Women's demographic and previous obstetric and clinical data were registered, and blood samples were obtained to estimate random blood glucose (BG) to ensure being normoglycemic. Then, fasting (at least 6 hr) blood samples were withdrawn to undergo a full

spectrum of assigned investigations and determination of their glucose homeostatic status.

### **Diagnostic tools**

1. **Determination of booking BMI:** the weight and height of attendants were determined, and BMI was calculated according to Bray's equation (**Bray, 1992**):  $BMI = \text{weight (in kg)}/\text{height (in m}^2\text{)}$ . Women were classified as regards BMI according to the guidelines of **WHO (1995)**, as average BMI ( $\leq 25 \text{ kg/m}^2$ ), overweight ( $25\text{-}29.9 \text{ kg/m}^2$ ), and obese grade I ( $30\text{-}34.9 \text{ kg/m}^2$ ), women with  $BMI > 35 \text{ kg/m}^2$  were excluded from the study.
2. **Determination of booking glucose tolerance:** using the 75-oral glucose tolerance test (OGTT) that entails the estimation of fasting and postprandial blood glucose (FBG and PPBG) concentrations at two hours after taking a 75-gm oral glucose load. The 75-OGTT results were interpreted for diagnosis of GDM according to the recommendations of the International Association of Diabetes and Pregnancy Study Groups (**IADPSG, 2010**) as follows: FBG of  $\geq 92 \text{ mg/dl}$  and PPBG of  $\geq 153 \text{ mg/dl}$  indicate GDM.
3. **Determination of booking insulin resistance (IR):** Serum fasting insulin was estimated in the same sample obtained for estimation of FBG and the IR was evaluated using the homeostasis model assessment of IR (HOMA-IR) score that was calculated according to the formula:  $\text{fasting serum insulin } (\mu\text{U/ml}) \times [\text{FBG (mg/ml)}/18]/22.5$ ; HOMA-IR score of  $>2$  is considered abnormal (**Matthews et al., 1985**).

**Laboratory investigations:** Blood samples (5 ml) were aseptically

collected at the 6<sup>th</sup>, 12<sup>th</sup>, 24<sup>th</sup>, and 36<sup>th</sup> GW:

1. One ml of blood was mixed with 2 mg sodium fluoride in a single tube for estimation of BG using the glucose oxidase method on an automated chemistry analyzer (**Tinder, 1969**).
2. Another part of the blood sample was mixed with EDTA in a separate tube for estimation of HbA1c and GA levels.
3. The remaining part of BS was allowed to clot, centrifuged, and the resultant serum was frozen at  $-20^\circ\text{C}$  for estimation of serum insulin levels.

### **Estimated parameters**

- a. HbA1c levels were estimated using latex turbidimetry (LINEAR CHEMICALS S.L. Joaquim Costa, Montgat, Barcelona, Spain) (**Tietz, 1999**).
- b. Serum insulin levels were measured using ELISA kits (Cat-No. ab200011, Abcam Inc., San Francisco, USA) according to the manufacturer's instructions (**Gordon et al., 1985**). This kit was sensitive down to  $< 4 \mu\text{U/mL}$  within a range of  $4.69 - 300 \mu\text{U/mL}$ .
- c. Plasma GA levels were measured using a liquid enzymatic method with the Lucica® method for GA, manufactured by Asahi Kasei Pharma Corporation; a specific test for GA (EKF USA, San Antonio, Taxis, USA). GA analysis was carried out using an automated biochemical instrument (Glamour2000; Molecular Devices, Sunnyvale, CA, USA) with inter-assay and intra-assay coefficient variations of  $< 3$  and  $5.1\%$ , respectively, according to the precision test. The test principle is briefly described as hydrolysis of GA to amino acids by an albumin-specific proteinase and was then

oxidized by ketoamine oxidase to produce hydrogen peroxide, which was measured quantitatively. The GA value was calculated as the percentage of GA relative to the total albumin (glycated and non-glycated), and it was measured using the bromocresol purple method on the same sample (Paroni et al., 2007).

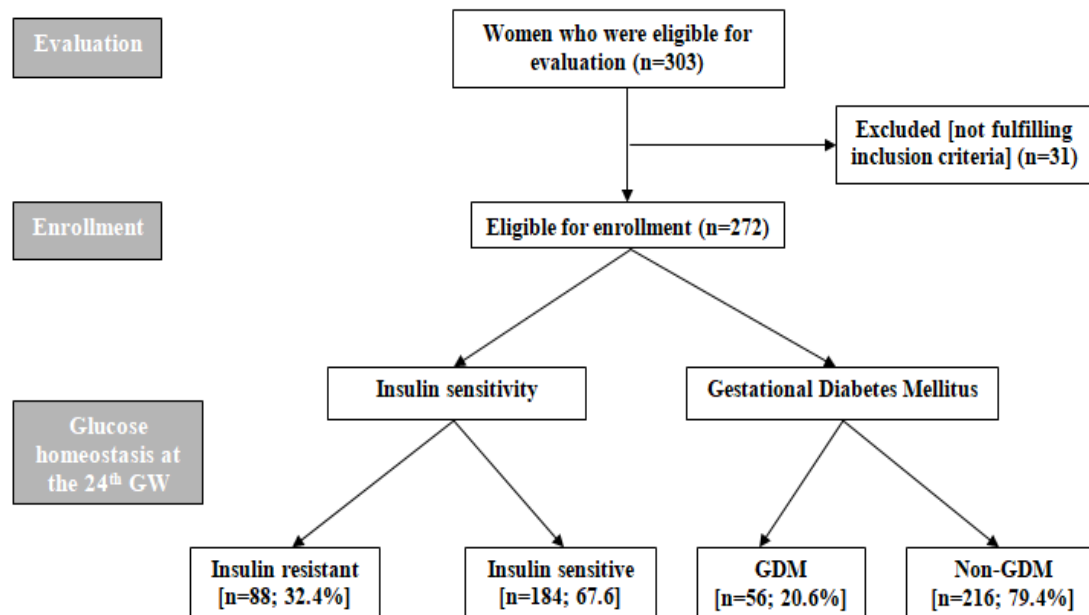
### Statistical analysis

The data normality was assessed using the Kolmogorov-Smirnov test. The data are presented as mean, standard deviation (SD), numbers, and percentages. The significance of the inter-group differences was assessed using the unpaired t-test, and the intra-group difference using the paired t-test, Mann-Whitney test, and Chi-square test ( $X^2$  test). Pearson's correlation analysis was applied to evaluate correlations between studied variables. Receiver characteristic curve (ROC)

analysis was used to define the identifiers for the development of GDM at 24<sup>th</sup> GW FBG levels of  $\geq 92$  mg/dl (IADPSG, 2010) among the 12<sup>th</sup> GW BMI, HbA1c, and GA as judged by the area under the curve (AUC) with its significance evaluated versus the area under the reference line curve (AUC = 0.5). Statistical analysis was conducted using IBM® SPSS® Statistics (Version 22, 2015; Armonk, USA) for the Windows statistical package. P value  $<0.05$  was considered statistically significant.

### Results

Preliminary evaluation excluded 31 women and 272 women were enrolled in the study. At 24-GW, 88 women (32.4%) developed IR with a HOMA-IR score of  $>2$ , and of these IR women, 56 women (20.6%) progressed to have GDM (Fig. 1). There were insignificant differences between women baseline data as shown in (Table.1).



**Fig.1. Consort Flow sheet**

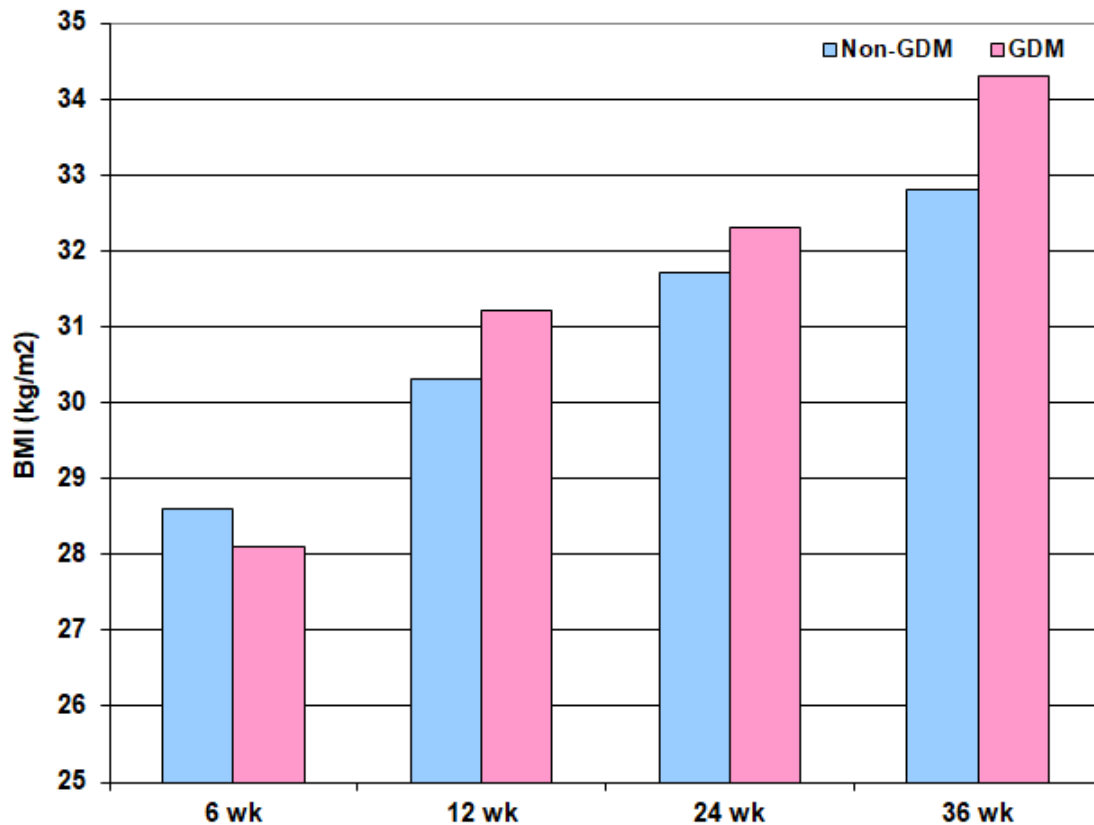
BMI of women of both groups showed non-significant difference at the 6<sup>th</sup> GW, but at 12-, 24- and 36-GW the BMIs of GDM women were

significantly higher BMI at the 12<sup>th</sup> GW (P = 0.001, 0.022, and  $<0.001$ , respectively) than non-GDM women (Fig. 2).

**Table 1. Patients' enrollment data**

Variables Group	Non-GDM (n=216)	GDM (n=56)	P-value
Age (years)	28.1±2.5	27.8±2.9	0.485
Weight (kg)	81.8±4	81.6±4.9	0.714
Height (cm)	169.3±3.4	170.4±4	0.079
BMI (kg/m <sup>2</sup> )	28.6±1.6	28.1±2.3	0.120
Gravidity*	2 [1-2]	2 [1-2]	0.711
Parity*	1 [0-1.75]	1 [0-2]	0.984
Systolic blood pressure (mmHg)	106.4±8.6	107.7±10.9	0.341
Diastolic blood pressure (mmHg)	70.1±4.1	71.5±4.6	0.051

Data are presented as mean, standard deviation, median, and interquartile range; P < 0.05 indicates significant Unpaired t-test and Mann-Whitney test\*

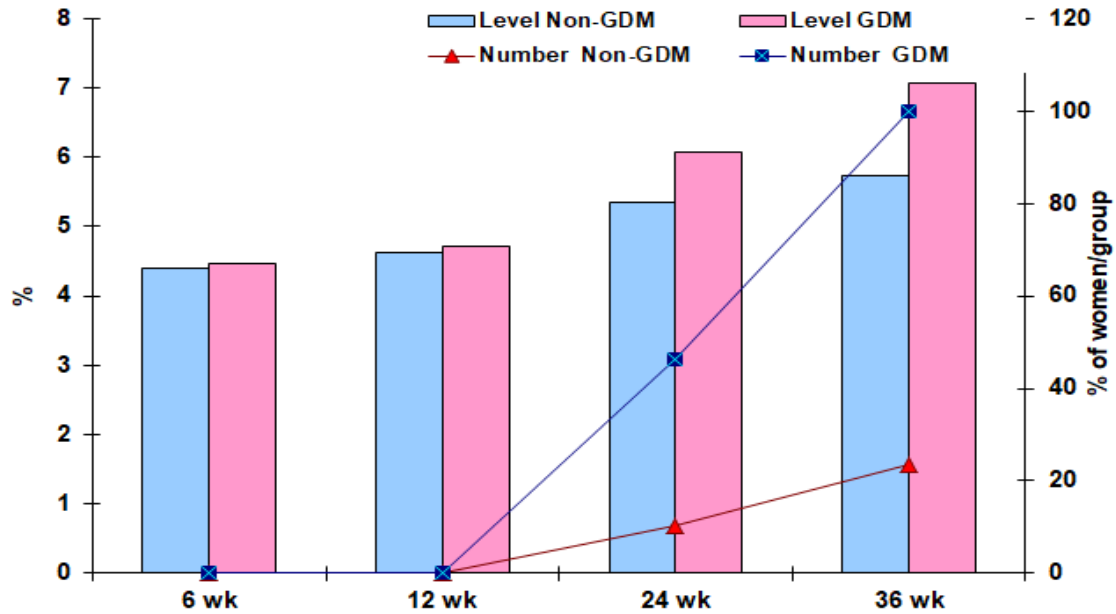
**Fig.2. Trimester-course BMI of women of both groups**

At booking time (6<sup>th</sup> GW), all enrolled women were normoglycemic and insulin sensitive with non-significant differences between women of both groups regarding the estimated results of 75-OGTT or HOMA-IR scoring and levels of glycosylated proteins. At the 24<sup>th</sup> GW, the results of 75-OGTT and HOMA-IR scorings were significantly higher in all women in

comparison to their levels determined at the 6<sup>th</sup> GW with significantly higher FBG and 2-hr PPBG in samples of GDM women in comparison to non-GDM women. Also, the calculated HOMA-IR score was significantly higher among GDM than non-GDM women. All GDM women and 32 women (14.8%) of non-GDM women were IR with significant intergroup

differences. Similarly, estimated levels of HbA1c progressively increased during pregnancy in all women with non-significant differences between GDM and non-GDM women at the 6<sup>th</sup> and 12<sup>th</sup> GW, but the differences were significant at the 24<sup>th</sup> and 36<sup>th</sup> GW. Interestingly, among women of the non-GDM group, 22 women and 51

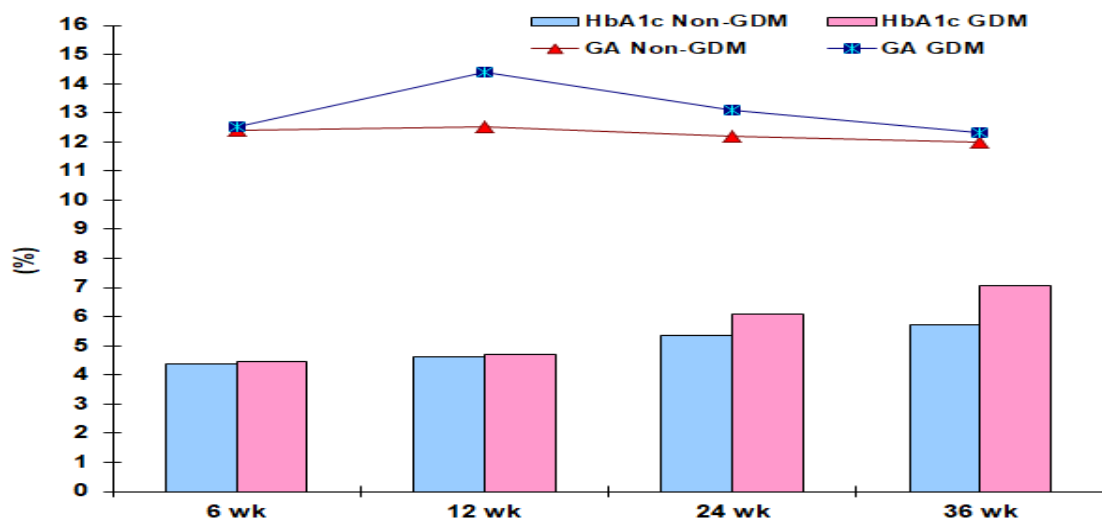
women had HbA1c levels >6 at the 24<sup>th</sup> and the 36<sup>th</sup> GW, respectively despite having within normal FBG and 2-hrPPBG levels using the 75-OGTT performed at the 24<sup>th</sup> GW. On the other hand, 30 women diagnosed with GDM according to the results of the 75-OGTT at the 24<sup>th</sup> GW had HbA1c levels of ≤ 6 (Fig. 3).



**Fig.3. Trimester-course mean value of estimated level of HbA1c and percentage of women had level >6% among women of both groups**

The trimester-course changes in plasma GA levels entail increased levels at the 12<sup>th</sup> GW in samples of all women. However, the estimated levels at the 24<sup>th</sup> and 36<sup>th</sup> GW samples were

decreased to a level lower than that estimated at the 6<sup>th</sup> GW and this was contradictory to the behavior of HbA1c as shown in (Fig. 4).



**Fig.4. Comparison of the trimester-course change in the percentage of glycated proteins estimated in women of both groups**

Estimated plasma GA levels at the 6<sup>th</sup> and 36<sup>th</sup> GW showed non-significant differences between GDM and non-GDM women, despite being higher in GDM women. On the contrary, estimated GA plasma levels

at the 12<sup>th</sup> and 24<sup>th</sup> GW were significantly ( $P < 0.001$  &  $= 0.00006$ , respectively) higher in GDM women in comparison to levels estimated in non-GDM women (**Table.2, Fig. 4**).

**Table 2. Patients' glycemic data and levels of glycosylated proteins estimated during pregnancy**

Variables Group		Non-GDM (n=216)	GDM (n=56)	P-value	
75-OGTT	FBG	6-GW	80.2±5.4	81.8±6	0.059
		24-GW	82.3±4.2	121.6±8.3	<0.001
	P1 value		0.001	<0.001	
	2-hr PPBG	6-GW	119.6±7.1	106.9±8.6	0.072
		24-GW	128.6±9.5	184.3±21.1	<0.001
	P1 value		<0.001	<0.001	
HOMA-IR score	Score	6-GW	0.83±0.28	0.88±0.35	0.225
		24-GW	1.25±0.42	2.78±0.4	<0.001
	P1 value		<0.001	<0.001	
	Frequency of IR at 24-GW	Yes	32 (14.8%)	56 (100%)	<0.001
No		184 (85.2%)	0		
HbA1c level (%)	6-GW		4.39±0.39	4.47±0.45	0.122
	12-GW		4.63±0.41	4.71±0.48	0.097
	24-GW		5.35±0.45	6.07±0.54	<0.001
	36-GW		5.74±0.49	7.07±0.29	<0.001
GA level (%)	6-GW		12.4±1.45	12.5±1.5	0.646
	12-GW		12.5±1.58	14.4±1.7	<0.001
	24-GW		12.2±1.62	13.1±1.53	0.00006
	36-GW		12±1.56	12.3±1.54	0.198

Data are presented as mean±standard deviation, numbers, and percentages; P-value indicates the significance of intergroup difference using the unpaired t-test; P1: indicates the significance between values estimated at the 6<sup>th</sup> and 24<sup>th</sup> GW using the paired t-test; P-value <0.05 indicates a significant difference

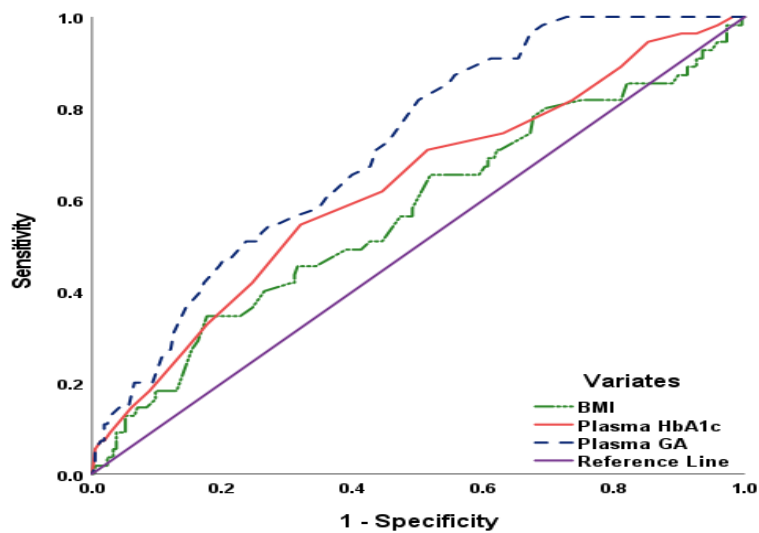
Estimated FBG and HOMA-IR scores determined at the 24-GW showed a positive significant correlation with the 12<sup>th</sup> GW BMI ( $r = 0.196$  &  $0.201$ , respectively,  $p = 0.001$ ). FBG at the 24<sup>th</sup> GW also was positively correlated with a significant coefficient to the 12<sup>th</sup> GW HbA1c and GA levels ( $r = 0.336$  &  $0.430$ , respectively,  $p < 0.001$ ). Similarly, the HOMA-IR score determined at the 24<sup>th</sup> GW was in positive significant correlation with the 12<sup>th</sup> GW HbA1c

and GA levels ( $r = 0.235$  &  $0.382$ , respectively,  $p < 0.001$ ).

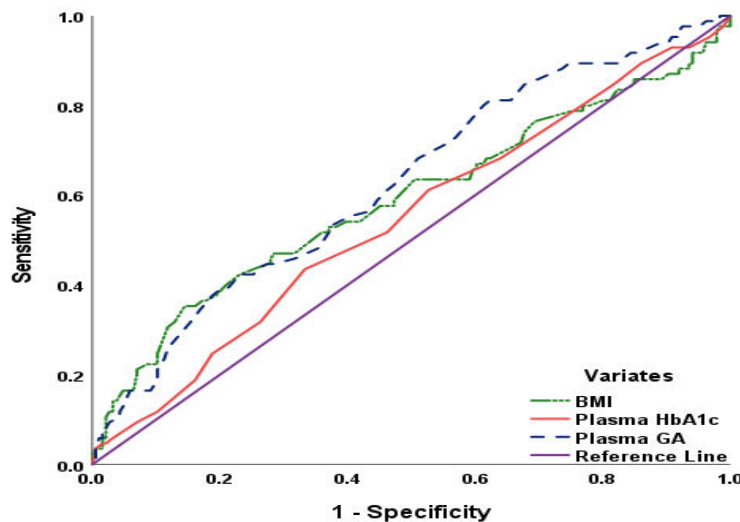
ROC curve analysis defined the estimated level of GA at the 12<sup>th</sup> GW as a highly significant predictor for oncoming GDM ( $p < 0.001$ ) and IR ( $P = 0.001$ ) in previously insulin sensitive normoglycemic pregnant women. High plasma levels of glycosylated hemoglobin and BMI at the 12<sup>th</sup> GW as predictors for GDM and IR, respectively as shown in (**Table.3**) and (**Figs. 5 & 6**).

**Table 3. ROC curve analysis of the BMI and plasma levels of glycated hemoglobin and albumin as predictors of oncoming GDM and IR at the 24<sup>th</sup> GW**

Parameters	Variates	Area under ROC curve	Standard error	P-value	95% Confidence interval
GDM	BMI	0.571	0.045	0.106	0.482-0.660
	Plasma HbA1c	0.626	0.043	0.004	0.542-0.710
	Plasma GA	0.714	0.035	<0.001	0.646-0.782
IR	BMI	0.589	0.040	0.019	0.511-0.667
	Plasma HbA1c	0.545	0.038	0.235	0.470-0.620
	Plasma GA	0.626	0.037	0.001	0.555-0.689



**Fig. 5. The ROC curve for analysis of BMI and glycated hemoglobin and albumin as predictors of GHT at the 24<sup>th</sup> GW**



**Fig. 6. The ROC curve for analysis of BMI and glycated hemoglobin and albumin as predictors of IR at the 24<sup>th</sup> GW**



## Discussion

The current study illustrated the extent of the influence of pregnancy on glucose homeostasis as shown by the significantly higher fasting and postprandial BG levels estimated in studied women irrespective of the development of GDM. This could be attributed to pregnancy-induced insulin resistant (IR); at the 24<sup>th</sup> GW 88 women (32.4%) became IR; 56 women (20.6%) progressed, and 32 IR women did not progress to GDM despite being normoglycemic and insulin sensitive at the 6<sup>th</sup> GW. The reported figures for IR and GDM go hand in hand with **Bano et al. (2021)**, who reported incidence rates for IR and GDM of 27.9% and 22.05%, respectively, and with **Chume et al. (2021)**, who detected a prevalence of GDM by OGTT according to the IADPSG criteria of 18.8%.

The reported disturbed glucose homeostasis could be attributed to the detected progressive increase of BMI throughout the pregnancy course, as evidenced by the positive significant correlation between the 12<sup>th</sup> GW BMI and the 24<sup>th</sup> GW FBG and HOMA-IR score, and statistical analyses defined BMI as an important predictor for oncoming IR and GDM. In line with these data and suggestions, **Corrales et al. (2021)** found that sustained overnutrition during pregnancy causes excessive maternal weight gain leading to changes in the adipose tissue cellular and lipid composition that predispose to IR, GDM, and other metabolic disorders and **Lewandowski et al. (2021)** also, detected IR among pregnant women and found women who developed GDM showed greater IR than pregnant women without GDM. Moreover, **Akgöl et al. (2021)** detected a positive relation between abdominal subcutaneous fat thickness and severity of GDM as reflected by BG levels and found patients with high

thickness were more liable to need antenatal insulin therapy than GDM women with less fat thickness.

Recently, **Aye et al. (2022)** attributed pregnancy-induced IR to obesity which induces adipose tissue inflammation and endoplasmic reticulum stress which promote adiponectin ubiquitination and degradation in adipocytes with subsequent increase in body weight and IR which induces further degradation of adiponectin and a vicious circle initiate and progresses with the progress of pregnancy.

The current study detected 88 IR women, of whom 56 women progressed to GDM, while 32 did not progress to GDM. Such selective progression was attributed by **Li et al. (2021)** to the detection of co-expression of long non-coding RNA RPL13P5, which forms a co-expression chain with the tubulin gene through the phosphatidylinositol 3-kinase/protein kinase B signaling *pathway* that is involved in the regulation of multiple cellular physiological processes and thus becomes a part of the process of IR that progresses to GDM.

The plasma levels of glycated proteins estimated at the 6<sup>th</sup> GW showed a non-significant difference between women who developed GDM and those who did not. At the 12<sup>th</sup> GW, the estimated levels of glycated hemoglobin and glycated albumin were increased in all women, with a significant difference between GDM and non-GDM women regarding GA levels. The reported earlier significant increase in GA level in GDM in comparison to non-GDM women, despite increased levels in both groups, illustrated the importance of estimating of GA level as an early predictor for increasing BG and earlier initiation of the process of protein glycation and indicated the feasibility of using GA as

predictor for oncoming diabetic state earlier than HbA1c. This difference between both proteins could be attributed to the properties of albumin, which has a short half-life of about 12-19 days in the human body, so its glycated form can reflect BG control in the preceding 2–3 weeks (**Kouzuma et al., 2004**), while HbA1c can reflect BG control status within the preceding 3 months, which is inconvenient for follow-up during pregnancy (**Mendes et al., 2019**). Moreover, albumin has a higher sensitivity to glycemic fluctuations than HbA1c due to its multiple intramolecular disulfide bonds, which makes it more suitable and liable to modifications (**Yuwen et al., 2017**), its short life span, and rapid turnover; thus, it can provide useful renewed information about BG especially when HbA1c does not accurately reflect the glycemic status (**Aleks et al., 2021**).

The high earlier predictability of plasma GA levels as a sensitive marker, as documented statistically, versus HbA1c levels, coincided with previous studies that documented the ability of GA to provide a significantly better measure for glycemic control in diabetic hemodialysis patients, while HbA<sub>1c</sub> levels in these patients might lead to underestimation (**Inaba et al., 2007; Nagayama et al., 2009**). Also, **Huh et al. (2018)** documented the superiority of GA as a glycation index over HbA1c for reflecting renal tubulopathy in T2DM patients, even those who have normal estimated glomerular filtration rate and normo-albuminuria. Recently, **Li et al. (2021)** documented that using ROC analysis, GA plasma level at a cutoff point of 15.15% was an efficient marker for detecting diabetes. Moreover, **Zhang et al. (2021)** documented that only GA levels, not HbA1c were associated with increased rates of operative delivery and macrosomia in GDM and

recommended GA as an appropriate glycemic control marker for pregnant mothers.

HbA1c levels estimated at the 24<sup>th</sup> and 36<sup>th</sup> GW were progressively increased with the progress of pregnancy, with significantly higher levels in samples of GDM women, while the corresponding plasma GA levels were decreased with the progress of pregnancy, and the difference between both groups was significant at the 24<sup>th</sup> but non-significant at the 36<sup>th</sup> GW. The reported trimester-course figures for plasma glycated proteins coincided with the reference intervals documented by **Zhang et al. (2021)** and **Agnello et al. (2021)** who also detected gradual decreases of plasma GA with gradual increases of plasma HbA1c levels with the progress of pregnancy from the 1<sup>st</sup> to the 3<sup>rd</sup> trimester, and a weak negative correlation was found between GA levels and BMI (**Agnello et al., 2021**).

**Limitations:** Evaluation of the relationship between disturbed plasma levels of glycated proteins and maternal and neonatal outcomes was missed and needed to be evaluated.

**Recommendations:** Time-course estimation of plasma GA since the start of pregnancy might be a valuable discriminative modality for pregnant women as IR and/or GDM before being clinically manifest.

### **Conclusion**

Pregnancy is a diabetogenic state irrespective of being manifest or not, and normal BG levels at the start of pregnancy could not exclude the liability for the development of GDM. GA plasma levels start to increase earlier during pregnancy than HbA1c levels and so could be used as an early predictor for abnormal OGTT at the 24<sup>th</sup> GW. Increased GA plasma levels could predict women liable to have IR

irrespective of their BG level or development of GDM.

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