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The role of serum afamin in prediction of gestational diabetes mellitus in high risk patients

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Abstract

Background: Gestational diabetes mellitus (GDM) is defined as onset of first recognition of abnormal glucose tolerance during pregnancy. This condition is associated with adverse pregnancy outcomes, including fetal macrosomia, stillbirth, neonatal metabolic disturbances. Aim of this study is to assess the prognostic capability of Afamin to predict gestational diabetes mellitus (GDM) in the 1st trimester.

Methods: This prospective cohort study was conducted in the department of Obstetrics of Tanta University. It included 60 women with first trimester singleton pregnancy that were recruited from prenatal outpatient clinic of Tanta University Hospital in the period from November 2018 till November 2021.

The selected cases were divided in two groups:

Group I: (High-risk group): 40 cases who had risk factors for the occurrence of GDM.

Group II: (Control "low-risk" group): Apparently healthy 20 pregnant women

Results: Maternal concentrations of serum afamin in the first trimester in both studied groups were higher among cases in the high-risk group than women of the low-risk group but there was no statistical significance difference between them and cut-off value is 73.5 mg/L. Also, maternal serum afamin levels in the second trimester were significantly higher in high-risk with GDM than high-risk without GDM and in low-risk groups (P1 =0.008 and P2 <0.001) but they were insignificantly different between high-risk without GDM and low-risk groups.

Conclusions: First trimester maternal serum afamin concentrations could be used as a new cost-effective and easily applicable biomarker for early prediction of gestational diabetes mellitus. Afamin can be used as a screening test that can determine which pregnant woman are at high risk for developing GDM and to prescribe the best management to improve maternal and fetal outcome.

Keywords: Serum afamin, diabetes mellitus, gestational

Introduction

The World Health Organization (WHO) defined diabetes mellitus (DM) is a chronic, metabolic disease characterized by elevated levels of blood glucose (or blood sugar), which leads over time to serious damage to the heart, blood vessels, eyes, kidneys and nerves. The most common is type2 diabetes, usually in adults, which occurs when the body becomes resistant to insulin or doesn't make enough insulin [1].

Gestational diabetes mellitus (GDM) is defined as onset of first recognition of abnormal glucose tolerance during pregnancy. This condition is associated with adverse pregnancy outcomes, including fetal macrosomia, stillbirth, and neonatal metabolic disturbances [2].

Also, offspring of mothers with GDM are at increased risk for diabetes and obesity [3]. Furthermore, metabolic changes including obesity, diabetes mellitus and hyperlipidemia contribute to an increased additive risk for potential cardiovascular diseases, thus preeclampsia and pregnancy-related hypertension or metabolic disorders have been discussed as the 'metabolic syndrome of pregnancy' [4].

Human Afamin (AFM) is a glycoprotein that is present in biological fluids such as plasma, ovarian follicular, cerebrospinal and seminal fluids [5]. Also, afamin is a vitamin E-binding protein and vitamin E is an important antioxidant that protects against oxidative stress [6].

Plasma concentrations of afamin are independent of fasting status, age, and sex but it increase linearly approximately two-fold during an uncomplicated pregnancy probably due to changing the hormonal status and subsequent hormonal regulation of afamin gene expression in human liver and drops to pre-pregnant values immediately after delivery [7, 8].

Moreover, the plasma glycoprotein afamin was previously found to be associated with the prevalence and development of insulin resistance (IR) and metabolic syndrome in the general population [9].

Afamin concentrations are strongly correlated with clinical and laboratory parameters of the metabolic syndrome, such as elevations in body mass index (BMI) and plasma glucose concentrations, dyslipidemia, and hypertension [10].

It was subsequently shown in a population-based study upon more than 20,000 individuals that afamin concentrations are also associated with the prevalence and incidence of type 2 diabetes mellitus (T2DM) as well as insulin resistance (IR) [11].

In a pilot study done by Dieplinger and his colleagues, they found that higher serum concentration of afamin in women with pregnancy complications associated with vascular insufficiency and multisystemic conditions of pregnancy. Aim of this study is to assess the prognostic capability of Afamin to predict gestational diabetes mellitus (GDM) in the 1st trimester.

Patients and Methods

This prospective cohort study was conducted in the department of Obstetrics of Tanta University. It included 60 women with first trimester singleton pregnancy that were recruited from prenatal outpatient clinic of Tanta University hospital in the period from November 2018 till November 2021.

The selected cases were divided in two groups

Group I: (high-risk group): 40 cases who had risk factors for the occurrence of GDM.

Group II: (control "low-risk" group): Apparently healthy 20 pregnant women.

The Inclusion criteria to all selected cases

Maternal age ranged from 19 to 39 years old. Singleton living fetuses. Gestational age were 11 to 14 weeks calculated from the first day of last menstrual cycle or confirmed by the first ultrasonography performed. The selected criteria of high-risk women for developing GDM according to National Institute for Health and Care Excellence (NICE) guidelines were women with one or more of the following risk factors.

Previously having GDM

History of previously delivered macrocosmic neonate.

A first-degree relative with diabetes mellitus.

History of polycystic ovarian syndrome (PCO).

History of fetal congenital anomalies.

History of polyhydramnios.

The Exclusion Criteria

Pregestational diabetes (Either type 1 or 2).

Multiple pregnancy.

Patients with chronic diseases e.g., hypertension, thyroid dysfunction and auto immune diseases.

Informed written consent was taken from each participant before sharing of the study and after explaining the purpose and the procedures of the study.

Methods

Study candidates were subjected to the following.

History taking including.

Full personal history, menstrual history, details of obstetric history including history of previous gestational diabetes, grand multipara, history of delivery of a macrosomic baby, history of repeated abortions, unexplained IUFD or baby with congenital malformations of unknown cause and any previous obstetric complications.

Past history of drugs or medical disorders.

Family history: history of first degree relative has diabetes.

The 75gm OGTT was done at booking (11-14 wks) and repeated at 24-28 weeks; the women were asked not to eat or drink (other than sips of water) for 8 hours before the test then they were asked to drink a liquid that contained 75gm glucose, three blood samples were withdrawn one before drinking the liquid and again two times every 60 minutes after drinking it (1 hour and 2 hours) for measuring the blood glucose levels.

The diagnosis of gestational diabetes (GDM) by 2 hours 75gm oral glucose tolerance test was made according to the guidelines of IADPSG (22).

Fasting: 95 mg/dl or 5.3 mmol/L

1-hour post prandial: 180 mg/dl or 10.0 mmol/L

2-hour post prandial: 155 mg/dl or 8.6 mmol/L

At least one of these thresholds must be equaled or exceeded to make a diagnosis of GDM.

Measurement of serum afamin levels

Serum Afamin concentrations were measured at booking (11-14 wks) and again between 24 to 28 weeks and were compared with the results of OGTT.

Venous blood (5ml) was withdrawn from each participant woman for estimation of serum afamin concentrations.

Samples were stored immediately at 4 oC for four hours to avoid cell lysis then collected in a serum separator tube and allowed to clot for two hours at room temperature, centrifugated for 20 minutes at the speed of 2000-3000 r.m.p., the supernatant was extracted then kept in aliquot at -20oC to preserve till afamin measurement.

Serum afamin concentrations were measured by a double-antibody sandwich enzyme-linked immunosorbent ELISA kits (Shanghai Sunred Biological Technology Company).

Assay procedure

All reagents, samples and standards were prepared. Afamin was added to monoclonal antibody enzyme which is pre-coated with Human Afamin monoclonal antibody. Incubated 1 hour at 37oC Added Afamin antibodies labeled with biotin and combined with Streptavidin-HRP to form immune complex. Incubated and washed again to remove the uncombined enzyme. Added Chromogen Solution A, B the color of the liquid changed into blue and at the effect of acid the color finally became yellow. The chroma of color and the concentration of AFM of samples were positively correlated.

Calculation

Table 1: Standard dilution.

320 ng/ml	120 µ l Original Standard + 120 µ l Standard diluents
160 ng/ml	120 µ l Standard No.5 + 120 µ l Standard diluents
80 ng/ml	120 µ l Standard No.4 + 120 µ l Standard diluent
40 ng/ml	120 µ l Standard No.3 + 120 µ l Standard diluent
20 ng/ml	120 µ l Standard No.2 + 120 µ l Standard diluent

Standard density was taken as the horizontal, the OD value for the vertical and the standard curve was drawn on graph paper (Figure 1).

Corresponding density was found out according to the sample OD value by the Sample curve (the result is the sample density)

With the standard density, OD value, and the sample OD value in the equation, the sample density was calculated.

The normal cut off values were 73.5 mg/L at 11-14 weeks and 96.5 mg/L at 24-28 weeks.

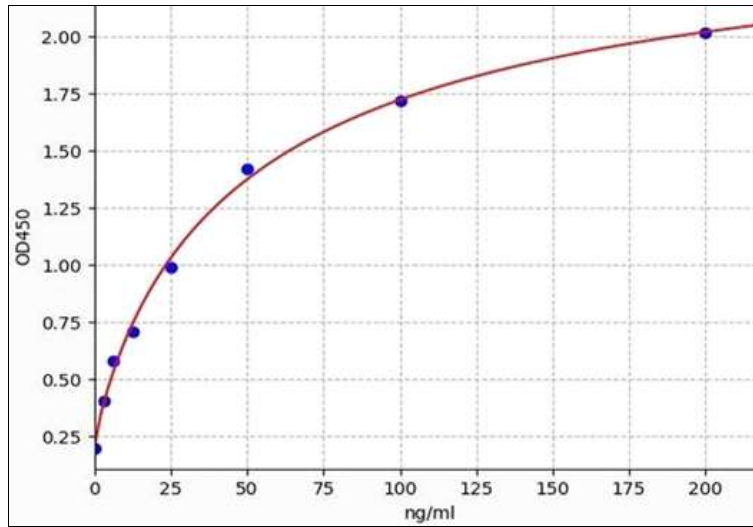


Fig 1: Standard curve of afamin.

Statistical analysis

SPSS statistics for windows (Statistical Package for the Social Sciences) version 26 (IBM, Armonk, NY, USA) was used for statistical analysis of the collected data. Shapiro-Wilk test was used to check the normality of the data distribution. All tests were conducted with 95% confidence interval. P (probability) value < 0.05 was considered statistically significant. Quantitative variables were expressed as mean and standard deviation while categorical variables were expressed as frequency and percentage. One-way ANOVA with Bonferroni post hoc analysis and Kruskal Wallis with Dunn’s post hoc analysis tests were used for inter-group comparison of

parametric and non-parametric continuous data respectively. Categorical Group differences with Fisher exact and Chi square tests were used for inter-group comparison of nominal data. Bivariate Correlations were assessed using Pearson’s or Spearman’s correlation coefficient depending on the nature of data. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated using the receiver operating characteristic (ROC) curve. A binary logistic regression model was conducted to determine the value of platelet indices in prediction of abortion (R2).

Results

Table 2: Patients’ characteristics of the studied groups.

		High-risk group (n= 40)	low-risk (control) group (n= 20)	95% CI	P
Age (years)	Range	19.0-39.0	20.0-34.0	-0.78 - 3.53	0.206
	Mean ± SD	24.83±4.138	23.45±3.456		
Occupation	Housewife	25 (62.5%)	11 (55.0%)	-0.34 - 0.19	0.576
	Worker	15 (37.5%)	9 (45.0%)		
Residency	Urban	11 (27.5%)	7 (35.0%)	-0.18 - 0.33	0.550
	Rural	29a (72.5%)	13 (65.0%)		
Gravidity	Range	1.0-5.0	2.0-5.0	-0.33 - 0.83	0.283
	Mean ± SD	2.85±1.099	2.60±0.995		
Parity	Range	0.0-4.0	1.0-3.0	-0.34 - 0.59	0.565
	Mean ± SD	1.88±0.911	1.75±0.716		
BMI (kg/m2)	Range	28-40	26.1-32.7	-4.43 – -1.72	<0.001*
	Mean ± SD	32.5±3.39	29.33±1.979		
History of PCOS		8 (20.0%)	0	-0.32 – -0.08	0.043*
Previously having gestational diabetes		23 (57.5%)	0	1.53 - 3.09	< 0.001*

95% CI: 95% confidence interval of the mean difference between both groups. P is significant when $p < 0.05$.

BMI: body mass index.

PCOS: poly cystic ovarian syndrome.

Table (2) shows that demographic and clinical characteristics (age, occupation, residency, gravidity, and parity) were

statistically insignificantly different between the two studied groups.

On the other hand BMI, history of PCOS, and previously had gestational diabetes, It was found that they were significantly higher in the high-risk group than the low-risk group ($p < 0.001$, 0.043, and $p < 0.001$ respectively).

Table 3: Results of 75 g oral glucose tolerance test at first trimester.

		High-risk group (n= 40)	low-risk (control) group (n= 20)	95% CI	P
Fasting blood glucose (mg/dL)	Range	79.0-95.0	75.0 - 90.0	-0.21 - 5.56	0.068
	Mean ± SD	85.32±5.27	82.65±5.17		
One-hour postprandial blood glucose (mg/dL)	Range	142.0-175.0	138.0-153.0	-21.52 – -11.88	<0.001*
	Mean ± SD	163.35±13.21	146.6±5.33		
Two-hours postprandial blood glucose (mg/dL)	Range	102.0-152.0	99.0-136.0	-25.73 – -13.07	<0.001*
	Mean ± SD	141.45±10.09	122.05±11.92		

95% CI: 95% confidence interval of the mean difference between both groups. P is significant when $p < 0.05$.

Table (3) showed that first trimester fasting blood glucose concentrations were statistically insignificantly different

between the high-risk group and low-risk groups.

Also, there was a significant difference in blood glucose levels after one and two hours between both studied groups in spite of fasting glucose levels within the normal range ($p < 0.001$).

Table 4: First trimester maternal serum afamin levels in both studied groups.

		High-risk group (n= 40)	low-risk (control) group (n= 20)	95% CI	p
Maternal serum afamin (mg/L)	Range	44.0 - 115.0	38.0 - 81.0	-3.60- 14.15	0.239
	Mean \pm SD	74.08 \pm 18.268	68.80 \pm 10.754		

95% CI: 95% confidence interval of the mean difference between both groups.

P is significant when < 0.05 .

Table (4) shows that in spite of, maternal concentrations of

serum afamin in the first trimester in both studied groups were higher among cases in the high-risk group than women of the low-risk group but there was no statistical significance difference between them and cut-off value is 73.5 mg/L.

Table 5: Results of second trimester 75 g oral glucose tolerance test in women of both participating groups.

		High-risk group (n= 40)	low-risk (control) group (n= 20)	95% CI	p
Fasting blood glucose (mg/dL)	Range	80.0-115.0	83.0-94.0	6.11-16.74	0.001*
	Mean \pm SD	98.88 \pm 11.532	87.45 \pm 3.790		
One-hour postprandial blood glucose (mg/dL)	Range	158.0-215.0	134.0-174.0	19.52-35.53	< 0.001*
	Mean \pm SD	182.47 \pm 18.23	154.95 \pm 12.33		
Two hours postprandial blood glucose (mg/dL)	Range	124.0-202.0	116.0-155.0	15.57-39.98	< 0.001*
	Mean \pm SD	163.82 \pm 25.371	136.05 \pm 13.87		

95% CI: 95% confidence interval of the mean difference between both groups.

P is significant when < 0.05 .

Table (5) shows that fasting, one and two-hours postprandial

blood glucose levels in the second trimester were significantly higher in the high-risk group than women in the low-risk group ($p = 0.001$, < 0.001 , < 0.001 respectively).

Table 6: Maternal serum afamin levels in the second trimester in both studied groups.

		High-risk group (n= 40)	low risk (control) group (n= 20)	95% CI	p
Maternal serum afamin (mg/L)	Range	67.0-126.0	74.0-103.0	3.62-15.28	0.002*
	Mean	96.30 \pm 13.79	86.85 \pm 8.616		

95% CI: 95% confidence interval of the mean difference between both groups. P is significant when < 0.05 .

Table (5) shows that fasting, one and two-hours postprandial blood glucose levels in the second trimester were significantly higher in the high-risk group than women in the low-risk group

($p = 0.001$, $p < 0.001$, $p < 0.001$ respectively).

Table (6) shows that when comparing maternal serum afamin levels in the second trimester between the two groups, it was found that they were significantly higher in the women in the high-risk group than the women in the control group ($p = 0.002$).

Table 7: Results of 75g oral glucose tolerance test in the first trimester in high-risk women who developed gestational diabetes & who did not develop diabetes and in low-risk groups.

		High-risk group (n= 40)		low-risk (Control) group (n= 20)	P
		High-risk with GDM (n= 18)	High-risk without GDM (n= 22)		
Fasting blood glucose (mg/dL)	Range	80.0 - 95.0	79.0-93.0	75.0-90.0	0.023* P1: 0.077 P2: 0.025* P3: 0.843
	Mean \pm SD	87.17 \pm 6.99	83.82 \pm 2.59	82.65 \pm 5.17	
One-hour postprandial blood glucose (mg/dL)	Range	151.0-179.0	142.0-174.0	121.0-166.0	<0.001* P1: 0.005* P2: <0.001* P3: 0.01*
	Mean \pm SD	169.56 \pm 11.27	158.27 \pm 12.70	138.4 \pm 14.76	
Two-hours postprandial blood glucose (mg/dL)	Range	112-152	102.0-149.0	99.0-139.0	<0.001* P1: 0.233 P2: <0.001* P3: <0.001*
	Mean \pm SD	144.72 \pm 12.73	138 \pm 11.43	122.40 \pm 14.25	

P is significant when < 0.05 , P1: significance between high-risk with GDM and high-risk without GDM, P2: significance between high-risk with GDM and low-risk (control) group, P3: significance between high-risk without GDM and low-risk (control) group.

GDM: Gestational diabetes mellitus. Table (7) Shows that in the first trimester, there was a statistically significant difference in fasting blood glucose, one-hour postprandial blood glucose, and two-hour postprandial blood glucose among the studied groups ($p = 0.023$, < 0.001 , and < 0.001 respectively).

Fasting blood glucose levels at the first trimester were

insignificantly different between the high-risk group with GDM and the high-risk group without GDM

Also they were insignificantly different between high-risk without GDM and the control group. But it was significantly higher in women of high-risk group with GDM than in the control group ($P2 = 0.025$).

Regarding one-hour postprandial blood glucose levels at the first trimester, they were significantly higher in the high-risk group with GDM than the high-risk group without GDM and in low-risk groups ($P1 = 0.005$, $P2 < 0.001$), and also, they were significantly higher in the high-risk group without GDM than in low-risk group ($P3 = 0.01$).

After two hours, postprandial blood glucose levels were insignificantly different between women with GDM and without

GDM but were significantly higher in women with GDM and without GDM than in the control group (P2 and P3 <0.001).

Table 8: Maternal serum afamin concentrations at first trimester in high risk who developed gestational diabetes & who did not develop gestational diabetes and in low-risk (control) groups.

		High-risk group (n= 40)		low risk (control) group (n= 20)	P
		High-risk with GDM (n= 18)	High-risk without GDM (n= 22)		
Maternal serum afamin (mg/L)	Range	53.0-115.0	44.0-95.0	38.0-81.0	0.002* P1:0.001* P2:0.028* P3: 0.172
	Mean ± SD	81.50±16.878	62.94±14.503	68.80±10.754	

P is significant when < 0.05, P1: significance between high-risk with GDM and high-risk without GDM, P2: significance between high-risk with GDM and low-risk (control) group, P3: significance between high-risk without GDM and low-risk (control) group.

GDM: Gestational diabetes mellitus.

Table (8) shows that there was a significant difference in maternal afamin concentrations in the first trimester among the

studied groups (p =0.002).

There was a statistically significant elevation in maternal afamin concentrations in the first trimester in patients who developed GDM compared to women without GDM in the high-risk group and in the control group (P1 =0.001 and P2 =0.028). But they were insignificantly different between women in high-risk without GDM and low-risk (control) groups.

Table 9: Results of the second trimester 75g oral glucose tolerance test in all participating women.

		High risk group (n= 40)		low-risk (control) group (n= 20)	P
		High-risk with GDM (n= 18)	High-risk without GDM (n= 22)		
Fasting blood glucose (mg/dL)	Range	101.0-118.0	80.0-94.0	82.0- 97.0	< 0.01* P1:<0.001* P2:<0.001* P3: 0.644
	Mean ± SD	107.25±5.285	86.31±4.729	87.45±3.790	
One-hour postprandial blood glucose (mg/dL)	Range	164.0-215.0	158.0-200.0	130.0-174.0	< 0.001* P1:<0.001* P2:<0.001* P3:<0.001*
	Mean ± SD	194.11±18.07	172.95±11.91	154.20±11.68	
Two-hours postprandial blood glucose (mg/dL)	Range	153.0-202.0	124.0-158.0	116.0-155.0	< 0.001* P1:<0.001* P2:<0.001* P3: 0.653
	Mean ± SD	180.17±15.656	139.31±15.11	136.05±13.87	

P is significant when < 0.05, P1: significance between high-risk with GDM and high-risk without GDM, P2: significance between high-risk with GDM and low-risk (control) group, P3: significance between high-risk without GDM and low-risk (control) group.

GDM: Gestational diabetes mellitus.

Table (9) Shows that there was a statistically significant difference in fasting blood glucose, one-hour postprandial blood glucose, and two-hour postprandial blood glucose among the studied groups (p <0.001).

Fasting blood glucose levels in the second trimester were significantly higher in the high-risk with GDM group than high-risk without GDM and control groups (P1 and P2 <0.001). But it was insignificantly different between the high-risk without

GDM group and the control group.

On the other hand, it was observed that one-hour postprandial blood glucose levels in the second trimester were significantly higher in the high-risk with GDM group than high-risk without GDM and low-risk groups (P1 and P2 <0.001).

Moreover, it was significantly higher in the high-risk without GDM group than the control group (P3 <0.001).

Two-hour postprandial blood glucose levels in the second trimester were significantly higher in the high-risk with GDM group than high-risk without GDM and low-risk groups (P1 and P2 <0.001).

Although the blood glucose levels after two hours were higher in women in high risk without GDM group than the control group, there was no significant difference between them.

Table 10: Maternal serum afamin levels in the second trimester in both participating groups.

		High-risk group (n= 40)		low-risk (control) group (n= 20)	P
		High-risk with GDM (n= 18)	High-risk without GDM (n= 22)		
Maternal serum afamin (mg/L)	Range	78.0-126.0	67.0-113.0	74.0 - 103.0	0.001* P1:0.008* P2:<0.001* P3: 0.530
	Mean ± SD	100.92±13.465	89.38±11.459	86.85±8.616	

P is significant when < 0.05, P1: significance between high-risk with GDM and high-risk without GDM, P2: significance between high-risk with GDM and low-risk (control) group, P3: significance between high-risk without GDM and low-risk (control) group.

GDM: Gestational diabetes mellitus.

Table (10) Shows that there was a statistically significant

difference in maternal serum afamin in the second trimester among the studied groups (p<0.001).

Also, maternal serum afamin levels in the second trimester were significantly higher in high-risk with GDM than high-risk without GDM and in low-risk groups (P1 =0.008 and P2 <0.001) but they were insignificantly different between high-risk without GDM and low-risk groups.

Table 11: Correlation between serum afamin in the first trimester and blood glucose in the second trimester.

Second trimester 75-g oral glucose tolerance test	Serum Afamin at 1 st trimester	
	r	P-value
Fasting blood glucose(mg/dL)	0.365	0.004*
One-hour postprandial blood glucose (mg/dL)	0.343	0.007*
Two-hours postprandial blood glucose (mg/dL)	0.327	0.011*

Table (11): There was a significant positive moderate correlation between serum Afamin at 1st trimester and fasting blood glucose (r =0.365, p =0.004), one-hour postprandial blood glucose (r =0.343, p =0.007), and two-hours postprandial blood glucose (r =0.327, p =0.011).

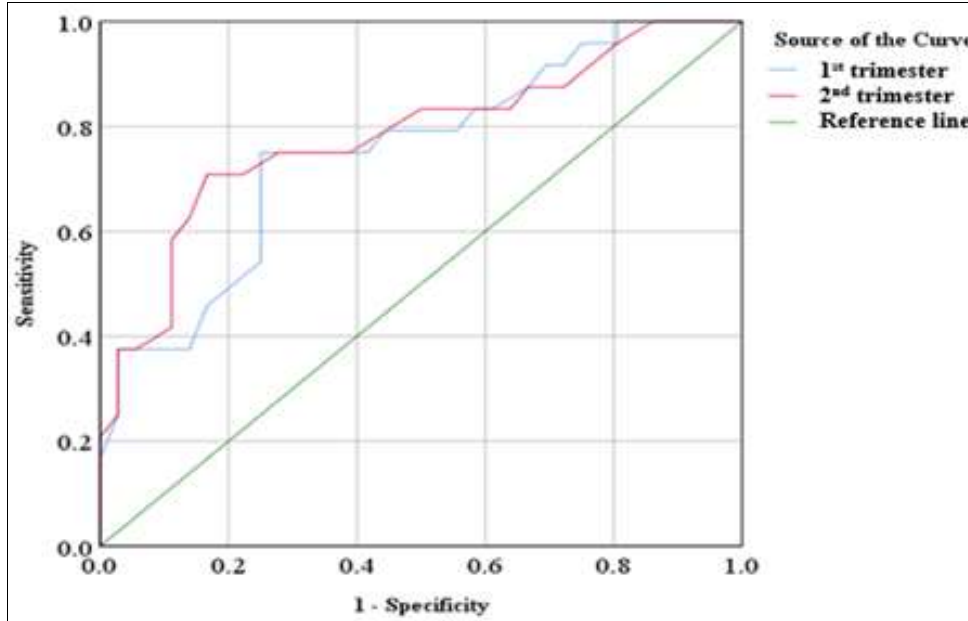


Fig 2: ROC curve for the diagnostic profile of Serum Afamin for detection of the development of gestational diabetes.

Figure (2) Shows that maternal serum afamin in the first trimester is a valid test for the prediction of GDM.

Discussion

During pregnancy, a woman adapts her body systems to support nutrient and oxygen supply for fetus growth and subsequent lactation. Inappropriate adaptation of maternal physiology may lead to severe complications during pregnancy, such as GDM [12].

In the present study, it was observed that demographic characteristics of the selected cases (age, occupation, residency, gestational age, gravidity, and parity) were matched and no significant different between the data of studied groups. These results are in agreement with the findings, Parast and Paknahad who carried out a case-control study in 80 pregnant women, comprising 40 women with definite diagnosis of GDM, and 40 healthy pregnant women (Control group) and the results showed that there were no significant differences about age, number of pregnancies, gestational age, interval from last pregnancy [13].

In the current study, the selection of cases who had risk factors for developing GDM was preferred as those were considered as a good candidate for the occurrence GDM and can be early preventable.

This selection is enforced by the study of Benhalima *et al.* who carried out a multi-centric cohort study based on performing different European selective risk factors screening guidelines compared to the universal IADPSG screening for diagnosis GDM and the results showed that; 1811 women received universal screening with a 75 g OGTT with prevalence GDM in

12.5% (n =231) compared to retrospectively applying the English, Irish, French and Dutch guidelines for selective screening, respectively 28.5% (n = 526), 49.7% (n = 916), 48.5% (n = 894) and 50.7% (n = 935) with GDM prevalence 10.2%, all participants had at least one risk factor, so the number of missed cases was reduced [14].

Regarding the levels of serum afamin, in current study, it was observed that cases who had increased serum afamin levels and developed GDM had higher BMI than the other participating cases.

These results are in agreement of the work of Lorenzo-Almorós *et al.* who concluded that preconception high BMI was associated with increase serum afamin and high risk for developing GDM. This explained by adipose tissue production of cytokine as tumor necrosis factor α (TNF- α) that play the most important role in IR [15].

Furthermore, Saranya K. *et al.* highlighted that higher BMI was significantly associated with GDM. Ladies having BMI > 30 kg/m² constituted 30.8 and 13.9% of subjects in the GDM and non GDM groups respectively (p =0.001) [16].

Additionally, Ozanne *et al.* stated that excessive gestational weight gain is associated with an increased risk of impaired glucose tolerance during pregnancy [17].

Also, in the current study, it was found that women with history of polycystic ovary (PCO) had elevated serum afamin levels in both first and second trimester which were higher than cases without PCO. Also, we noticed that they had the liability for development of GDM and impaired 75 g OGTT.

These data were in accordance with the results of Anttila *et al.* [18], Kousta *et al.* [19], Boomsma *et al.* [20], Wang *et al.* [21],

Ashrafi *et al.* [22], Pan *et al.* [23], Aktun *et al.* [24] Köninger A [25], who found that, an increase incidence and relationship and higher prevalence of developing GDM in women with history of PCO. They explained these data due to the elevated risk of metabolic and inflammatory disorders, IR, glucose tolerance disorders and lower sex hormone binding globulin levels.

Regarding the results of 75g oral GTT in the present study, it was observed that fasting blood glucose levels at the first trimester was insignificantly difference between high-risk group and control group while one and two-hours postprandial blood glucose were in the upper normal range and significantly higher in the high-risk group than the control group.

This results are in agreement with Sivaraman *et al.* [26] who attempted to determine the magnitude of the long term risk of progression to diabetes and identifying factors that predict the development of gestational diabetes. It was found that the risk of developing gestational diabetes was 21.1%. One and two hours post-prandial glucose levels during pregnancy were high and associated with future risk of diabetes.

In the present study, it was found that (31%) 18 cases out of 60 cases, from the high-risk group, who developed GDM in mid trimester had first trimester high serum afamin concentrations. Also, second trimester serum afamin concentrations were significantly higher in cases developed GDM than non-diabetic in high-risk group and control group.

Also, there was a statistically significant difference between the elevated maternal serum afamin concentrations in the second trimester pregnancy and impaired 75 OGTT among cases of high-risk group who developed GDM.

This results in accordance with Köninger *et al.* [27] who explained the patho- mechanism of GDM as serum afamin concentrations probably reflect and increase IR and oxidative stress results in occurrence of GDM.

Additionally, Tramontana *et al.* [28] Conducted a case control study to assess the correlation of first trimester serum afamin levels with three-dimensional placental bed vascularization in pregnant women and its prognostic value for predicting pre-eclampsia, GDM and future fetal and maternal complications during pregnancy. About 764 women was correlated to 5 pregnancy outcome groups: gestational hypertension (n=76), pre-eclampsia (n=33), IUGR (n=91), pre-term birth (n=39), GDM (n=170). the results showed significantly higher serum afamin levels in women with pre-eclampsia (P<0.05) and GDM (P<0.05) compared to healthy pregnant women.

Moreover, Tramontana *et al.* [29] who aimed to assess the prognostic capability of afamin to predict pregnancy complications where first-trimester screening was consecutively performed in 4948 pregnant women, of whom 474 women developed pregnancy complications [gestational hypertension (n = 84), pre-eclampsia (n = 30), IUGR (n = 107), preterm birth (n = 44), and GDM (n = 209)]. Afamin serum concentrations were measured in 948 pregnant women at the second-trimester screening. It was found that median afamin concentrations were significantly higher in women developing pre-eclampsia or GDM when compared to women with uncomplicated pregnancies (76 mg/L vs. 65 mg/L, p = 0.001 and 80 mg/L vs. 69 mg/L, p< 0.001). There was no difference in median afamin values between all other pregnancy complications and their matched controls. Increased afamin (i.e. > 65 mg/L) was a strong and independent predictor for the development of pre-eclampsia (risk ratio, 24.58; 95% CI, 2.82–214.12; p = 0.004) as well as GDM (Risk ratio, 2.07; 95% CI, 1.33–3.22; p = 0.001).

In the present study it was observed that, there was a significant positive correlation between serum afamin at 1st trimester and

fasting blood glucose, one-hour postprandial blood glucose, and two-hours postprandial blood glucose.

The present study showed that first trimester maternal serum afamin levels are good predictor for GDM (AUC =0.750, p value =0.001). At diagnostic point 73.5 mg/L, it has 78% sensitivity, 75% specificity, 66.7% PPV, and 81.8% NPV.

The strength points of this study were

- Prospective cohort study.
- Controlled and comparative study.
- Strict in inclusion and exclusion criteria.

Limitations of the present study were

- Small sample size.
- Single center study.
- Lack of follow up the participating women for pregnancy outcome and the relation between serum afamin and other pregnancy complications.

Conclusions

From the results of the current study, it can be concluded that:

- First trimester maternal serum afamin concentrations could be used as a new cost-effective and easily applicable biomarker for early prediction of gestational diabetes mellitus.
- Afamin concentrations during the first trimester of pregnancy positively correlated with the results of 75g OGTT during the second trimester of pregnancy.
- Afamin can be used as a screening test that can determine which pregnant woman are at high risk for developing GDM and to prescribe the best management to improve maternal and fetal outcome.
- Maternal risk factors in combination with serum afamin measurements may improve the predictive power compared to risk factors alone.

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