Relationship between Maternal Serum Betatrophin Levels and Gestational Diabetes Mellitus

Zainab Akram Mohammed Ali, Thuraya Hussamuldeen Abdullah

ABSTRACT:

BACKGROUND:

Betatrophin has been reported to have a role in beta cell talk about insulin resistance states. Betatrophin levels association with gestational diabetes mellitus (GDM) in comparison to normal glucose tolerance need to be evaluated.

AIM OF THE STUDY:

Assessment of betatrophin level in pregnant women with gestational diabetes in comparison to those with no gestational diabetes.

PATIENTS AND METHODS:

Case control study .The study included 100 pregnant women divided in to 2 groups.

1st group –included 50 pregnant women diagnosed to have GDM.

2nd group –included 50 pregnant women with no GDM as control group.

For all included women measurement of maternal serum betatrophin level was performed.

RESULTS:

The Mean ±SD of betatrophin in women with GDM was (295.78 pg/ml ±193.03pg/ml) and in control group was (157.04 pg/ml ±77.62pg/ml) it was significantly higher in association with GDM at p value <0.001. In GDM, betatrophin level were significantly correlated with maternal age, parity, HbA1c(r=0.455, p=0.001), (r=0.413, p=0.003), (r=0.287, p=0.044) respectively. No significant correlation with BMI (r=0.163, p=0.258) nor with gestational age (r=0.065, p=0.654). ROC curve for betatrophin level as diagnostic aid for GDM demonstrated that AUC was 0.692 at p value 0.001, sensitivity 62.0%, specifity 66.0% cutoff value 185.5 ng/ml.

CONCLUSION:

Betatrophin is significantly higher in pregnant women who have gestational diabetes in comparison with normal healthy pregnant women and it is significantly correlated with maternal age, parity, and HbA1c.

KEY WORDS: Gestational diabetes mellitus, body mass index, hemoglobin HbA1c**.**

INTRODUCTION:

Gestational diabetes: is defined as carbohydrate intolerance of variable severity with onset or first recognition during the present pregnancy. This definition applies whether or not insulin is used for treatment and undoubtedly includes some women with previously unrecognized overt diabetes. [1] Diabetes is the most medical condition encountered during pregnancy with about 5% of pregnancies being complicated by either pre-existing or gestational diabetes [2]. The increasing prevalence of type 2 diabetes in general and in younger people in particular had led to an increasing number of pregnancies with this complication [3]. The greater majority of women with carbohydrate intolerance during pregnancy do not have signs or symptoms; so, it should be suspected in patients with known risk factor for Gestational Diabetes Mellitus (GDM) according to the national institute for health and care excellence (NICE) criteria 2015 which include[4] .1- BMI >30kg/m^2.2- GDM in previous pregnancy.3- Previous macrosomic baby >4.5kg. 4- Family history (first degree relative with diabetes).5- Ethnicity: family origin with a high prevalence of diabetes. Optimal glycaemic control prior to conception and throughout pregnancy improves pregnancy outcome [5]. Any degree of glucose intolerance during pregnancy is associated with adverse maternal and fetal outcome [6]. Betatrophin belongs to family of angiopoietin-like protein and it is known under various names: angioprotein like protein 8 (ANGPTL8), lipasin, hepatocellular carcinoma associated protein [7]. The ANGPTL protein family contains 7 typical members which are characterized by the presence coiled-coil domain at the N-terminus, a fibrinogen-like domain at the C-terminus and a signal peptide for protein secretion [8]

Al-Imamain Al-Kadhimain Medical City, Baghdad, Iraq

Betatrophin is a new but atypical member of the ANGPTL family, because it lacks the fibrinogen-like domain [9]. It was initially detected in 2004 as a tumor-associated antigen in patient serum, in 2012, betatrophin was shown to correlate with the serum triglyceride (TG) level and regulate lipase activity [10].The gene for betatrophin lies on human chromosome 19 and encodes a protein composed of 198 amino acid with molecular weight of 22 KDa. Active form of betatrophin is a dimer. Betatrophin is absent in non-mammalian vertebrates and in invertebrates. The majority of betatrophin is produced in the liver Diabetes mellitus develops as a result of the failure of beta-cells to compensate for the increased insulin demand caused by hyperglycemia and insulin resistance[11]. The search for agents that promote beta-cell proliferation has been very active yet elusive [12]. The discovery of betatrophin as a hormone that is capable of increasing beta-cell proliferation has been hailed as a scientific breakthrough [13]. It has been shown that betatrophin was increased under states of insulin resistance to increase beta-cell proliferation and increase insulin production. Interestingly, betatrophin also correlated with estrogen and progesterone level raising the possibility of appositive regulation of betatrophin production which may contribute to remarkable betatrophin elevation during pregnancy.

PATIENTS AND METHODS:

This is a case control study which was carried out in the department of Obstetrics and Gynecology of AL-Emamein Alkadhimain Medical City, Baghdad, Iraq, during the period from first of February 2019 to the first of December 2019. It was approved by scientific council of Obstetrics and Gynecology/ Iraqi Board for Medical Specializations. The study included 100 pregnant women divided into 2 groups:-

1st group included 50 pregnant women who were diagnosed with gestational diabetes and admitted for follow up and they were on treatment for their condition.

2nd group included 50 healthy pregnant women with no GDM, with normal blood sugar and normal OGTT as control group GDM were excluded in control group by 75gm oral GTT according to NICE 2015 criteria (0 mint =5.6mmol/l, 120mint =7.8mmol/l). Inclusion criteria:-1- Maternal age (20-40).2- Party (0-8).3- Gestational age (24-36).Exclusion criteria:-1- Previous history of diabetes (type 1, type2). 2- past medical history of liver disease.3- Previous history of polycystic ovarian syndrome. 4- Past medical history of metabolic disease. Evaluation of all included women were done by full history including maternal age, parity, gestational age, previous history or family history of diabetes, history of gestational diabetes in previous pregnancies. Examination of women (general and obstetric examination) included:

-BP, PR, Temperature

- Abdominal examination

-Obstetric ultrasound examination was done and confirmation of gestational age was done by LMP and corresponding early pregnancy ultrasound scan.

- BMI calculated by dividing body weight (kg)/height (M) ^{2}. Blood sample were collected after 8hr of fasting, four milliliters of venous blood was collected from each patient by vein- puncture using the disposable syringe the blood was kept in plastic tubes. After incubation at room temperature for 10-20min, tubes are centrifuged for 20 mint. Then, the samples were transferred to the laboratory for measurement of betatrophin by ELIZA method. Two milliliters of venous blood was collected from each patient in EDTA tube and mixing sample and send to laboratory for HbA1c measured by Hemoglobin A1c test kit, (Clover A1C Analyzer).

Statistical analysis

Data were presented as mean ± standard deviation, and comparison between means of study groups done by using unpaired student t test. Pearson correlation was done between betatrophin with other variables of each group. ROC (Receiver operating characteristics) curve was used to calculate sensitivity and specificity of betatrophin. P value less than 0.5 was considered as significant. Microsoft excel 2019 and SPSS (statistical package for social sciences) version 23 were used as software to do the statistics.

RESULTS:

The present study included 100 pregnant women divided into 2 groups:

1 st group- included 50 pregnant women with GDM (patients group).

2 nd group- included 50 pregnant women without GDM as control group.

Table (1) shows comparison of included parameters between GDM group and control group, Regarding maternal age (years) the mean ±SD in patient group was (27.84±4.81) and was (27.82±6.18) in control group .no significant difference in maternal age between 2 groups (P value =0.986).The mean ±SD of parity in patient group was (2.98±1.49) and was

(2.62±2.33) in control group. No significant difference in maternal parity between 2 groups (p value =0.360). The mean ±SD of BMI (kg/m2) was (28.14±4.28) in GDM group which is significantly higher than (24.94±5.47) in control group. (P value=**0.002**). The mean ± SD of gestational age (week) (31.32±2.18) in patient group and was (30.68 ± 2.76) in control group. No significant different between 2 groups (P value =0.201). Mean ± SD of HbA1c was (5.01±0.88) in patient group and mean ±SD was (4.94±0.71) in control group no significant different between 2 group (p value =0.646).

Table 1: Comparison of study parameters between patients and control by unpaired t test.

Parameters	Patient group N=50 Mean±SD	Control group N=50 Mean±SD	P value
Age (year)	27.84±4.81	27.82±6.18	0.986
Parity	2.98±1.49	2.62±2.33	0.360
BMI (Kg/m^2)	28.14±4.28	24.94±5.47	0.002
GA (week)	31.32±2.18	30.68±2.76	0.201
HbA1c %	5.01±0.88	4.94±0.71	0.646

BMI=Body mass index, GA=Gestational age

Table (2) shows the distribution of maternal serum betatrophin level in all study cases. The mean±SD was (295.78±193.03), median (200), Range (100-794) in patient and mean±SD (157.04±77.62), median (157.5), Rang (12-333) in control group is a significant (p value<0.001).

Table 2: Comparison of serum betatrophin level between patients and control by unpaired t test

Betatrophine (pg/ml)	Patients N=50	Control N=50	P value
Mean±SD	295.78±193.03	157.04±77.62	<0.001
Median	200	157.5	
Range	100-794	12-333	

In table (3) the level of betatrophin categorized into three groups according to their betatrophin concentration (<300 pg/ml), (300-600 pg/ml), (>600 pg/ml) in patient and control group.

Table 3: Association of different betatrophin levels with risk of gestational diabetes mellitus in patient and study group.

Level of betatrophin	OR (95% CI)	P value
<300 (pg/ml)	1	
300-600 (pg/ml)	0.04 (0.005-0.313)	<0.001
>600 (pg/ml)	0.091 (0.005-1.821)	0.065

CI Confidence interval, OR Odd ratio

Figure (1) and table (4) the ROC curve for betatrophin as diagnostic aid for gestational diabetes during pregnancy show that (AUC) was 0.692, p value (0.001), sensitivity (62.0%), specificity (66.0%) cutoff value 185.5 ng/ml.

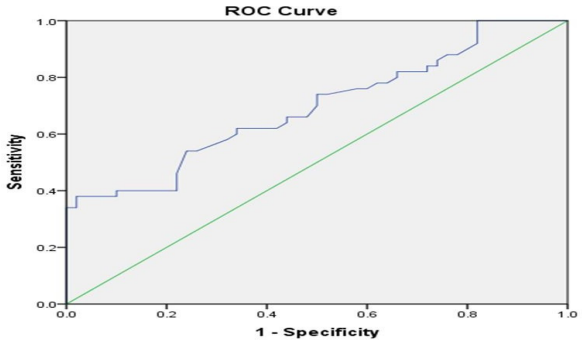

Figure 1: ROC curve for serum betatrophin

Table 4: Sensitivity and specificity of serum betatrophin.

AUC	P value	Sensitivity	Specificity	Cutoff value
0.692	0.001	62.0%	66.0%	185.5

AUC=Area under curve

In table (5) the patient group betatrophin levels were found to be significant correlated with maternal age (r=0.455 ,p=0.001), parity (r = 0.413, p=0.003), HbA1c (r=0.287,p=0.044). no correlation was found with (BMI) and (GA) in control group betatrophin level were significantly correlated with GA (wk) (r=0.006 , p=0.969) no significant correlation with other parameter.

Table 5: Correlation between betatrophin and other parameters in 2 study groups.

Parameter		Betatrophin	
		Patients	Control
Age (yr)	r	0.455	0.044
	P	0.001	0.763
BMI (Kg/m^2)	r	0.163	-0.058
	P	0.258	0.691
Parity	r	0.413	-0.043
	P	0.003	0.768
HbA1c%	r	0.287	0.136
	P	0.044	0.347
GA (wk)	r	0.065	0.006
	P	0.654	0.969

BMI=Body mass index, GA=Gestational age.

DISCUSSION:

The present study evaluated the association between maternal serum betatrophin level and GDM. It is found that betatrophin Mean± SD in women with GDM was (295.78 pg/ml ±193.03pg/ml) which is significantly higher than its level in women with normal glucose tolerance which was (157.04pg/ml ±77.62pg/ml) at p value (**<0.001**). These results go with what was found by (Ruirong Pan etal, 2019) [14] who found that betatrophin level in GDM group was significantly higher in women with GDM in comparison to control group. (Fei-Juan Kong etal, 2015)[15] In Their Meta-Analysis reported that overall circulating betatrophin level in GDM were higher than that in healthy control group with (95% CI: 0.41-1.68) at p value =0.001 and this goes with what was found in our study. Many studies reported association of higher betatrophin level with GDM in comparison to level in women with no GDM and this may indicate that augmented insulin demand in GDM may be the cause of up regulation of betatrophin level [16].

(Wang et al, 2016)[17,18] Reported that in addition, cord blood betatrophin levels also were increased in GDM patients and betatrophin concentration in cord blood was higher than that in maternal serum, which might suggest its role in promoting β-cell proliferation during intrauterine life. The alteration of betatrophin has been reported to be influenced by multiple factors, such as age, sex, duration of diabetes and BMI, as well as environmental and genetic factors. In this study categorization of betatrophin concentration into 3 groups (<300pg/ml, 300 – 600 pg/ml and >600 pg/ml) and association of GDM with these levels were evaluated. It is found that higher levels were associated with higher prevalence of GDM (<300 pg/ml =38.75%, 300-600pg/ml = 94.12%, > 600pg / ml =100%). ROC curve for betatrophin level as diagnostic aid for GDM demonstrated that AUC was 0.692 at p value 0.001, sensitivity 62.0%, specifity 66.0% cutoff value 185.5 ng/ml. (Lana Kosi et al, 2015)[19] in their study concluded that circulating betatrophin concentration are significantly higher in GDM versus normal glucose tolerance state and, in addition, they reported that in the light of betatrophin role in lipid metabolism, betatrophin may represent a noval endocrine regulator of lipid in pregnancy. Regarding correlation between betatrophin level and other parameters in GDM group. In the present study, it is found that there is statistically significant correlation between betatrophin and maternal age, parity, HbA1c (r=0.455 ,p=0.001),(r=0.413 ,p=0.003) , (r=0.287 ,p=0.044) respectively and no significant correlation with BMI (r=0.163 ,p=0.258) ,or with gestational age (r=0.065 ,p=0.654). (Yilmaz, et al, 2015)[20] Reported that betatrophin levels increased with age and that old age may be contributing factors for increased betatrophin levels in GDM. (Kohzo Takebayashi et al 2017)[21] In their study found that betatrophin level has positive significant correlation with HbA1c and fasting plasma glucose and this goes with the finding of the present study regarding HbA1c. Recently, an increasing number of studies evaluated the relationship between betatrophin level and obesity but the results are controversial. (Chen X et al, 2015)[22] found that betatrophin levels are lower in association with BMI >40 kg/m^2 but no significant change in those with BMI (30-40) kg /m^2. While (Jing Zheng et al, 2017) [23] demonstrated that Serum betatrophin levels are significantly elevated in over weight patients but not in obese. (Abu Farha et al, 2016)[24] reported higher levels in obese than non-obese population .These controversial findings are explained that BMI estimate total fat mass but cannot accurately distinguish the distribution of body fat and possibly only adipose tissue in some parts of body can synthesis betatrophin rather than all adipose tissue. (Ruirong et al, 2019)[25] Demonstrated that betatrophin levels were positively associated with BMI and insulin resistance and they found that BMI and age of women with GDM were higher than in control group indicating that incidence of GDM decline with a good health status and younger age.

CONCLUSION:

From the result of present study

1- Betatrophin is significantly increased in pregnant women who have gestational diabetes in comparison with normal healthy pregnant women.
2- Betatrophin levels are significantly correlated with maternal age, parity, HbA 1c but no significant correlation with BMI and GA.
3- Betatrophin can be used as a diagnostic aid in GDM.

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