

RESEARCH ARTICLE

Insulin Resistance and Other Adipokines as Clinical Predictors of Gestational Diabetes Mellitus among Pregnant Women

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Abstract

BACKGROUND: Gestational diabetes mellitus (GDM) has a strong relationship with an increased risk of maternal and perinatal complications. However, in Basrah, Iraq, studies regarding GDM are still limited. In current study, we aimed to investigate the association between insulin resistance and some clinical predictors of GDM among pregnant women in 1st and 3rd trimesters of gestation.

METHODS: This case-control study was conducted on 44 pregnant women with GDM and 45 without GDM aged 20 to 40 years who applied for GDM screening during the first (9-13 week) and third trimester (24-28 week) of pregnancy. Demographics, blood glucose, HbA1c, insulin, homeostatic model assessment for insulin resistance (HOMA-IR), spexin, nesfatin-1, orexin-A, vaspin and lipid profile levels were compared between groups.

RESULTS: Subjects with GDM showed a higher level of glucose, insulin HOMA-IR, HbA1c, spexin, vaspin in the

first and third trimesters of pregnancy ($p<0.01$) compared to the healthy subjects. Meanwhile in the first and third trimester, subjects with GDM showed significantly lower level of nesfatin-1 and orexin-A compare to the control. In third trimester, oral glucose tolerance test (OGTT) outcomes for fasting glucose at 1 hour, 2 hours, and 3 hours after glucose load were significantly higher ($p<0.01$). According to the area under the receiver operating characteristics (ROC) curve (AUC) findings, HOMA-IR, spexin, and vaspin may be more effective predictors biomarkers for GDM in pregnant subjects, while orexin-A and nesfatin-1 were ineffective.

CONCLUSION: The correlation of insulin resistance and adipokines in the first and thrid trimester was not significantly different, which may cast new light on the possible role as an etiological cause of GDM and might be a better monitoring parameter in women with GDM.

KEYWORDS: gestational diabetes mellitus, insulin resistance, vaspin, spexin, orexin-A, nesfatin-1

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Introduction

Pregnancy is a physiological state associated with insulin resistance, hyper-insulinemia and may predispose developed diabetes mellitus in some women.(1,2) Gestational diabetes mellitus (GDM), a complex disease characterized by elevated blood glucose, can be defined as any degree of carbohydrate intolerance of varying severity with onset or

first recognition during pregnancy. Given the possibility that unrecognized glucose intolerance may have preceded pregnancy, the use of the term hyperglycemia during pregnancy seems more appropriate as recently indicated by the Endocrine Society.(3) Some recent studies reported that GDM may has immediate and lasting consequences for both mother and fetus, some of which continue throughout the life of the mother and child. Hence, women with GDM may have a risk of many diseases later in life such as type

2 diabetes mellitus (T2DM), hypertension, hyperlipidemia, urinary tract infection and electrocardiogram abnormalities which may cause to a higher mortality. On the other hand, the fetus of women with GDM are at a significant likely to be obese, develop impaired glucose tolerance or T2DM during childhood or in early adulthood.(3-4)

Some evidence indicates that during the past 20 years, the prevalence of GDM has increased in a number of racial/ethnic groups. The prevalence of GDM was 7% in a 2014 prospective study on 100 pregnant women from Iraq. Preterm birth, cesarean section, and hypertension during pregnancy were all more likely in GDM patients. The risk factors for acquiring GDM were growing old, having a family history of diabetes, having more children, and having a higher body mass index (BMI). A recent study on 120 women between the ages of 20-45 years old discovered that 13.3% of them have GDM.(5-7)

Noted that a variety adipokines are produced by adipocytes, hence the number of these chemical messengers in the blood serum and placenta may change throughout pregnancy.(5) It has been reported that these bioactive adipokines, such as nesfatin-1, vaspin, orexin-A and spexin, have an influence on both T2DM and GDM result that might be related to any dysregulation of these adipokines and insulin resistance.(8-13)

In the province of Basrah, southern Iraq, there has been no previous study analyzing the association between homeostatic model assessment for insulin resistance (HOMA-IR) and the adipokines (nesfatin-1, orexin-A, spexin, and vaspin). Therefore, in this study we examined and compared the association between insulin resistance and the the previously mentioned adipokines as a clinical predictor for the development of GDM among pregnant women in first and third trimesters of gestation.

Methods

Study Design and Subjects Recruitment

The current study was a case-control clinical trial conducted between October 2021 to April 2022. Subjects were recruited from a Diabetic and Endocrine Glands Center at Al-Mawany Teaching Hospital and Basrah Hospital for Obstetrics and Children in Basrah Province, Iraq. For addition, some subjects were also recruited from a private clinics run by Dr. Fatima Hashem Makhour in Abu-Al-Khaseeb General Hospital. Total 89 subjects aged between 20-40 years were included in the study and classified into 2 main groups. The first group consisted of 44 pregnant

women with GDM that were divided into two subgroups according to age of gestational, namely 22 women at the first trimester (9-13 weeks) of gestation and 22 women at the third trimester (24-28 weeks) of gestation. While the second group included 45 healthy pregnant women were divided into two subgroups according to age of gestational, namely 23 women at the first trimester of gestation and 22 women at the third trimester of gestation.

Diagnosis of GDM patients was based on the recommendation of American Diabetes Association (14), that at <24 weeks of gestation, fasting blood glucose (FBG) was used to identify GDM, while at 24-28 weeks of pregnancy based the diagnosis was based on the oral glucose tolerance test (OGTT). Ethical clearance for this study was obtained from Ethical Committee of Basrah University (No. 7/54/2505), and each participant signed an informed consent form following a thorough description of the methods based on The Helsinki Declaration year 2000.

Inclusion and Exclusion Criteria

For the GDM subjects, GDM patients with no pre-existing glucose intolerance were included in this study. While for the control subjects, we included healthy pregnant women with no disease or family history of GDM, and not taking any drug that have an effect on serum glucose level.

The exclusion criteria for this study were women aged under 20 and above 40 years old, subjects with type I or II DM, GDM in previous pregnancy, smoking in the current pregnancy, presence of active infection, liver disease, heart diseases, hypertension, kidney disease and thyroid disorders or other endocrine diseases. Furthermore, women who took hormone replacement therapy or corticosteroid therapy were also excluded.

Samples Collection

After 12 hours of fasting and 30 minutes of rest in the supine position, samples were collected in the morning between 09:00 and 10:00 am. Five mL of blood was drawn from the vein of the forearm of the subjects then divided into two parts, the first part (1 mL) was added into ethylenediaminetetraacetic acid (EDTA) containing polypropylene tubes and was shook gently to be utilized for the determination of the level of HbA1c. The second part (4 mL) was moved into gel tube then moved into a centrifuge at 402 x g for 20 minutes to obtain the serum. The collected serum immediately utilized in the estimation of variables in this study, while the rest were stored in plain tube at deep freezing at -70°C until used.

Biochemical Quantification

The following procedures were used to analyzed blood samples for biochemical parameters: BMI was calculated as the following formula [BMI (kg/m²) = Wt in kg/Ht in m²].(15)

HbA1c measurements were determined using the Bio-Rad D-10® HPLC analyzer (Bio-Rad Laboratories, Hercules, CA, USA). Serum glucose was assayed on UV-Vis Spectrophotometer (UV-EMC-LAB, Duisburg, Germany) by using the kit (Cat No. GL2279/UK, Randox, Crumlin, UK). Insulin level was determined using the (Cat No. E0010Hu, BT-Lab, Shanghai, China) kit which was a solid phase enzyme-linked immunosorbent assay (ELISA) based on the sandwich principle. Serum vaspin was quantified by kit (Cat No. E0921Hu, BT-Lab), nesfatin-1 was estimated by kit (Cat No. E3063Hu, BT-Lab), spexin was estimated by kit (Cat No. E3507Hu, BT-Lab), orexin-A was estimated by kit (Cat No. E1296Hu, BT-Lab).

Serum total cholesterol was determined by automated enzymatic cholesterol oxidase-peroxidase aminoantipyrin (CHOD-PAP) method using kit (Cat No. 052168A1, Biolabo, Maizy, France). Serum triglyceride was determined using kit (Cat No. 042131A1, Biolabo) and the high-density lipoprotein (HDL) cholesterol was determined using kit (Cat No. 02160, Biolabo). The low-density lipoprotein (LDL) cholesterol was calculated according to the Friedewald formula [LDL cholesterol (mmol/L) = Total cholesterol – (Triglycerides/2.2 + HDL Cholesterol)].(16) IR was calculated by the HOMA-IR equation [HOMA-IR = Fasting insulin (μIU/mL) × Fasting glucose (mg/dL)/405].(17)

Statistical Analysis

Statistical analysis was performed using SPSS software version 26 (IBM Corporation, Armonk, NY, USA). The data were distributed normally and the comparison between groups was analyzed using the analysis of variance followed by Dunnett's t-test to find the statistical significance. The receiver operating characteristics (ROC) curve, which is formed by graphing sensitivity (y-axis) against 1- specificity (x-axis) and calculating the area under the ROC curve (AUC), was used to calculate the sensitivities and specificities, as well as the 95% confidence interval. Correlations were determined using Pearson correlation. A $p < 0.05$ was considered statistically significant, $p < 0.01$ highly significant, and an AUC value near 0 (or 1) implies a strong diagnostic value, the values of one group were mainly greater (or lower) than the values of the comparison group in this circumstance.

Results

There was no significant differences of age, gestational age, and BMI in GDM subjects and healthy control either in the first or third trimesters. The mean age of GDM subjects and healthy control in first and third trimester were 31.41 ± 5.2 vs. 31.65 ± 5.3 and 32.05 ± 4.6 vs. 31.82 ± 4.9 , respectively. All the baseline characteristics of the subjects and the controls were summarized in Table 1.

According to the results, subjects with GDM showed a higher level of HOMA-IR, glucose, insulin, and vaspin in the first and third trimesters of pregnancy ($p < 0.01$) compared to healthy controls (Table 2). Levels of HbA1c and spexin were significantly higher in the GDM subjects ($p < 0.05$ and $p < 0.01$) in the first and third trimesters, respectively. In subjects with GDM, the levels of triglyceride and very low-density lipoprotein (VLDL) were not statistically different ($p > 0.05$) in the first trimester and were elevated ($p < 0.05$) in the third trimester, whereas the level of total cholesterol was elevated ($p < 0.05$) in both trimesters of pregnancy compared to the control group. Moreover, the comparison of the third trimester between the GDM subjects and the healthy controls revealed that the levels of nesfatin-1 and orexin-A were significantly lower ($p < 0.05$), whereas OGTT (fasting glucose, 1-h glucose, 2-h glucose, and 3-h glucose) were significantly higher ($p < 0.01$).

The obtained AUC results indicated that insulin, HOMA-IR, HbA1c, spexin and vaspin could potentially be used as greater predictive biomarkers in pregnant women at the first trimester (AUC = 0.994, 0.915, 0.978, 0.749, 0.810, respectively) and at the third trimester (AUC = 1.00, 1.00, 0.987, 0.777, 0.946, respectively). While, nesfatin-1 and orexin-A could not be used as predictive biomarkers in pregnant women at the first trimester (AUC = 0.409, 0.571, respectively) as well as at the third trimester (AUC = 0.312, 0.074, respectively), as illustrated in Figure 1.

Table 3 showed that the correlations between HOMA-IR level and insulin, HbA1c, spexin, and vaspin were positive and highly significant ($p < 0.01$) ($r = 0.708$ vs. $r = 0.824$; $r = 0.683$ vs. $r = 0.764$; $r = 0.566$ vs. $r = 0.708$; and $r = 0.629$ vs. $r = 0.798$, respectively). Additionally, HOMA-IR showed a significant negative correlation with nesfatin-1 ($r = -0.652$ vs. $r = -0.971$, $p < 0.01$), a negative correlation with non-significance ($r = -0.186$, $p > 0.05$), and a negative correlation with significant negative values ($r = -0.622$, $p < 0.01$) between the levels of serum HOMA-IR and orexin-A in the first and third trimester.

Table 1. The demographic characteristics of the subjects (n=89).

The Characteristics	GDM Subjects		Healthy Control	
	First Trimester (n=22)	Third Trimester (n=2)	First Trimester (n=23)	Third Trimester (n=22)
Age (years), mean±SD	31.41±5.2	32.05±4.6	31.65±5.3	31.82±4.9
Gestational age (weeks), mean±SD	11.77±1.2	26.23±1.4	11.74±1.2	26.23±1.4
Family History, n (%)	10 (45.45)	8 (36.36)	3 (13.04)	6 (27.27)
Demographic Area, n (%)				
Urban	19 (86.36)	18 (81.82)	16 (69.57)	14 (63.64)
Rural	3 (13.64)	4 (18.18)	7 (30.43)	8 (36.36)
Educational Background, n (%)				
Learned	17 (77.27)	18 (81.82)	21 (91.30)	20 (90.91)
Illiterate	5 (22.73)	4 (18.18)	2 (8.70)	2 (9.09)
Smoking Habits, n (%)				
Positive	0 (0)	0 (0)	0 (0)	0 (0)
Negative	22 (100)	22 (100)	23 (100)	22 (100)
Food Habits, n (%)				
Vegetarian	4 (18.18)	2 (9.09)	4 (17.39)	5 (22.73)
Non-Vegetarian	18 (81.82)	20 (90.91)	19 (82.61)	17 (77.27)
Employment Status, n (%)				
Employed	17 (77.27)	18 (81.82)	21 (91.30)	19 (86.23)
Not- Employed	5 (22.73)	4 (18.18)	2 (8.70)	3 (13.64)

Table 2. The levels of all parameters measured in serum of GDM subjects and healthy control.

Parameter	Mean±SD			
	GDM Subjects		Healthy Control	
	First Trimester	Third Trimester	First Trimester	Third Trimester
BMI (kg/m ²)	29.78±4.16	29.26±3.93	29.61±4.08	29.02±3.52
Fasting glucose (mg/dL)	128.59±5.74**	143.73±6.49**	97.70±4.55	102.45±4.22
1h-glucose (mg/dL)	-	213.73±4.37**	-	153.73±3.23
2h-glucose (mg/dL)	-	186.36±4.54**	-	128.50±3.15
3h-glucose (mg/dL)	-	148.73±6.49**	-	106.27±4.32
Fasting insulin (μIU/mL)	9.65±1.52**	12.63±1.89**	5.66±1.15	6.22±1.46
HOMA-IR	2.77±1.00**	4.50±1.05**	1.36±0.31	1.49±0.50
HbA1c (%)	6.34±0.74*	7.10±0.77**	4.79±0.48	4.85±0.50
Total cholesterol (mg/dL)	214.86±5.07*	222.73±5.86*	184.00±4.33	192.77±4.48
Triglycerides (mg/dL)	161.95±4.26	181.32±4.69*	132.35±3.44	140.95±3.52
HDL (mg/dL)	34.59±7.98	34.32±6.75	36.17±6.38	35.77±9.00
LDL (mg/dL)	125.69±39.84	152.14±56.35	116.76±43.97	150.90±52.11
VLDL (mg/dL)	32.49±11.99	13.92±36.14*	26.51±9.94	28.27±10.76
Nesfatin-1 (ng/mL)	16.54±1.43*	15.19±2.09**	18.22±4.18	18.11±4.49
Orexin-A (pg/mL)	374.25±110.07	260.05±41.31**	386.76±57.99	396.30±85.60
Spexin (ng/L)	749.80±156.4*	898.44±237.6**	622.08±124.31	683.18±201.13
Vaspin (ng/mL)	1.61±0.40**	1.90±0.36**	1.12±0.35	1.11±0.33

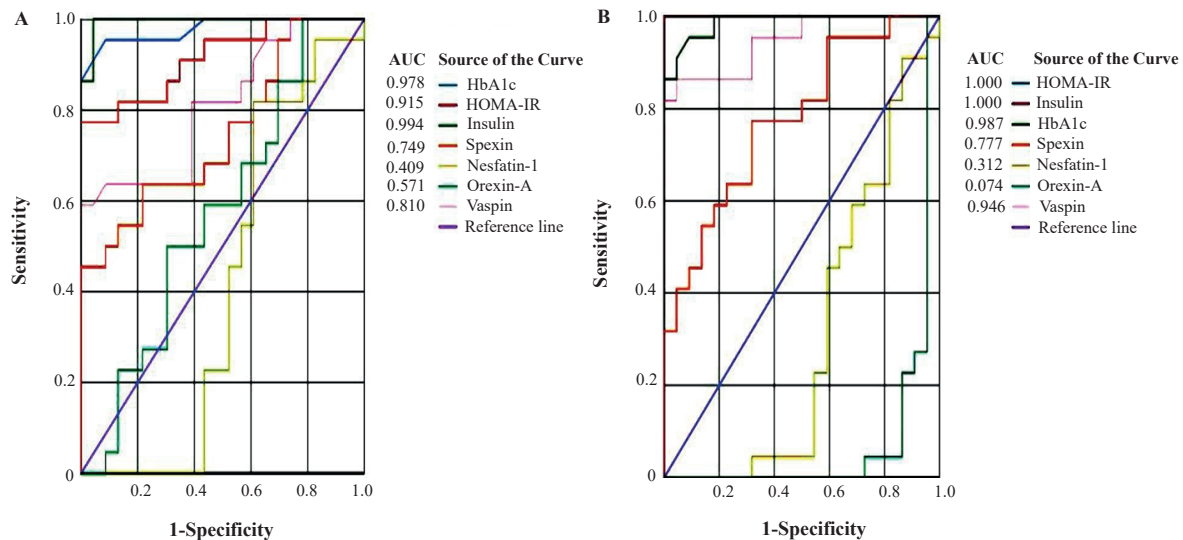


Figure 1. The ROC curve for serum HbA1c, HOMA-IR, insulin, spexin, nesfatin-1, orexin-A and vaspin levels in first and third trimester of GDM subjects. A: First trimester (9-13 weeks); B: Third trimester (24-28 weeks).

Discussion

Most of subjects in this study were from urban areas, they all had a good education and had a good workplace as well as non-smokers. On the other hand, studies have proven that urban residents have some important differences with rural residents such as differences in pollution, environments, social, psychological, genetic, nutritional and other factors, which are increasing dramatically in urban areas. Furthermore, work stress and requirements had the potential to affect the psychology of the female volunteers. Family and marital factors are also stress factors and lead to an increased oxidant/antioxidant state problem. Previous studies have found that residing in a depressed environment is linked to GDM.(17,18)

Increased level of insulin resistance could be result from reduce in sensitivity of insulin which may generally found through pregnancy to spare the glucose for the fetus. Hence, this is credited to the effects of hormones secret from placenta, the physiological changes in a some women throughout pregnancy outcome in glucose tolerance damage which might lead to GDM.(19-22) On the other hand, some scientific reports postulated that the main reason of insulin resistance throughout GDM is post-cellular damage manifested by reduced tyrosine phosphorylation remains in receptors of insulin and insulin receptor substrate-1 whereas serine phosphorylation is raised which reduce signalling of insulin from activating glucose transporter type 4 (GLUT4)-translocation.(23-26) Furthermore, pregnant women with

GDM may had both increased peripheral insulin resistance for the most part in skeletal muscle and impaired secretion of insulin as well as decreased in insulin sensitivity 30-40% in pregnant with GDM contrasted with healthy pregnant. Moreover, the secretion of insulin is considerably weaken in hyperglycaemia answer, this recommend main beta cell lack that makes return for raised insulin resistance hard to perform and implies several deficiency in insulin action the length of impaired compensatory secretion of insulin in the aetiology of gestational diabeteses.(27-30)

Decreased levels of nesfatin-1 in pregnant women with GDM may be related to insulin secretion dysregulation and insulin resistance, both of which may contribute to the pathogenesis of GDM. During pregnancy, insulin sensitivity decreases.(31) Previous studies demonstrated that nesfatin-1 promotes insulin release by Ca^{+2} influx through L-type Ca^{+2} channels independently of protein kinase A (PKA) and phospholipase A2 (PLA2), suggesting that nesfatin-1 dysregulation may be related to metabolic diseases, notably in diabetic patients.(6) Additionally, knowing how the central nervous system affects insulin resistance and how it relates to the emergence of GDM may provide a clearer picture of the underlying and include the following mechanism: An increase in the level of insulin resistance may effect on nerve impulses, reduce the action of the hormone α -melanotropin, and increase the distortion of MC3 receptors and MC4, and reduces sensitivity to insulin, and thus reduces the level of nesfatin-1.(7) As compared to pre-pregnancy condition, the immune system changes throughout pregnancy. Because of these adjustments,

Table 3. Correlations coefficient of HOMA-IR vs. other clinical parameters in first and third trimesters of GDM subjects.

Parameters	Correlation Coefficient (r)	
	First Trimester	Third Trimester
Insulin (μ IU/mL)	0.708**	0.824**
HbA1c (%)	0.683**	0.764**
Spexin (ng/L)	0.566*	0.792**
Nesfatin-1 (ng/mL)	-0.652**	-0.971**
Orexin-A (pg/mL)	-0.186	-0.622**
Vaspin (ng/mL)	0.629**	0.798**

Tested with Spearman's correlations test.*Significant, $p < 0.05$, **Highly significant, $p < 0.01$.

Nesfatin-1 levels may be negatively impacted, and weight may be gained because of a low nesfatin-1 level.(31)

Due to its critical function as an insulin-sensitizing adipocytokine, increased levels of vaspin in pregnant women with GDM compared to healthy pregnant women may be caused by this. Therefore, its production may increase possibly as a compensatory mechanism in insulin-resistant conditions and obese subjects.(5) Additionally, it may have biological effects on the metabolism of carbohydrates and lipids, operate as an insulin sensitizer with anti-inflammatory effects, and maybe work as a particular visceral fat protease inhibitor that controls energy metabolism.(8) Additionally, in a healthy pregnancy, this adipokine may be expressed in the placenta and considerably rise throughout gestation, peaking at the end of the third trimester of pregnancy, which may be related to fetal development. It has been noted that vaspin levels are positively connected with insulin levels, the HOMA-IR, and triglycerides in people with gestational diabetes during the third trimester of pregnancy.(32)

Because of hyperglycemia, insulin resistance, and hyperinsulinemia, orexin-A levels in pregnant women with GDM may be lower than those in healthy pregnant women. According to multiple studies that also demonstrated it can guard against insulin resistance, boost insulin sensitivity, and decrease glucagon secretion, it may play a role in glucose metabolism in normal to obese patients. The ratio of fat-tissue hormones like leptin and adiponectin to pro-inflammatory and anti-inflammatory cytokines, all of which have been associated with enhanced insulin sensitivity, may also be altered, reducing insulin resistance.(11) Therefore, it improves the rise in adipocyte basal and insulin-stimulated glucose absorption while also modulating the influence of the autonomic nervous system on gluconeogenesis in the

liver and antagonizing the effects of endoplasmic reticulum stress in this organ.(10) However, it was discovered that reduced levels of orexin-A may alter the insulin signaling pathway through Akt/protein kinase B in skeletal muscle and the liver, which could lead to insulin resistance by conjugated down-regulation of leptin and insulin receptors in adipose tissue.(5) Hence, it is possible that the decreased level of orexin-A may lead to hyperglycemia, basal levels of hypothalamic Akt phosphorylation are increased throughout the aging process, and the long-term phosphorylation disrupts the hypothalamic insulin action. Furthermore, hypothalamic insulin signaling may be required for the systemic insulin to suppress the hepatic glucose production. Therefore, any alteration in the hypothalamus liver circuit can bring in diabetic hyperglycemia.(33)

The increased level of spexin in pregnant women with GDM compared to healthy pregnant may be due to progressive insulin resistance, which begins in the mid-trimester and progresses throughout the term of pregnancy. Insulin resistance during pregnancy may be a result of insulin-desensitizing effects of hormonal products of the placenta, increased maternal adiposity, inflammation, and oxidative stress. Also, the development of maternal diabetes during gestation may cause various short and long-term maternal and fetal complications that could extend beyond birth.(34) Hence, increased maternal adipose tissue during gestation and the development of insulin resistance due to the anti-insulin effects of placental hormones (*i.e.*, progesterone, estrogen, placental lactogen), may be proposed as the main factors for the emergence of GDM. Furthermore, higher levels of spexin may positively associate with changes in glucose levels during pregnancy in women with GDM but not in healthy controls, and for this reason, it could be adopted as a potential biomarker for this condition.(13)

The results of the present study confirmed that HOMA-IR level was positively and highly significantly correlated with insulin ($r=0.708$ vs. $r=0.824$, $p < 0.01$) in the first and third trimester of pregnancy, respectively. These findings could be attributed to abdominal obesity, abnormalities in pregnant women's glucose and insulin metabolism, and beta-cell proliferation and hypertrophy, which increase beta-cell mass. Along with this, hormonal changes include rising hyperinsulinemia, which is associated with higher levels of estrogen, progesterone, cortisol, chorionic gonadotrophin, and placental lactogen hormones among other markers, further increasing insulin resistance.(22) Furthermore, increased lipolysis and decreased triglyceride storage may result in greater circulating levels of non-esterified fatty acids and triglycerides due to increased insulin hormone

levels, decreased insulin signaling pathways, and tissue resistance to insulin. This leads to ectopic lipid build up and impaired insulin-stimulated glucose uptake in skeletal muscle, which is thought to be the root of insulin resistance. (21) Moreover, larger amounts of non-esterified fatty acids, as well as excess fatty acids in the liver, may reduce the responsiveness of hepatic cells to insulin hormone. (34) Also, serum HOMA-IR was positively and highly significantly correlated with HbA1c level ($r=0.683$ vs. $r=0.764$, $p<0.01$) in the first and third trimester of pregnancy, respectively.

These results may be associated with substantial induction in insulin secretion, decreased of insulin sensitivity and in β -cell dysfunction which lead to hyperglycemia and an elevated in the level of glycation pathway of hemoglobin and increased release of free iron from glycated proteins like hemoglobin. As a result, the increased abundance of iron in the pool will boost the oxidant production, resulting in biomolecule destruction. (23) Furthermore, increased iron build up impairs insulin production and release from the pancreas, as well as the liver's ability to absorb insulin. Because of muscular injury, iron accumulation in the muscle reduces glucose absorption. (35) However, it may be increasingly used as a diagnostic criterion for diabetes in non-pregnant women with a cut-off point of 6.5% or above. The HbA1c level at the start of a pregnancy can help predict the likelihood of negative pregnancy outcomes and postpartum diabetes. However, HbA1c has not been used as a monitoring marker in women with GDM during the first trimester of pregnancy, possibly because it is altered by a variety of variables. (24)

Our data revealed that there was a significant positive correlation ($r=0.566$ vs. $r=0.708$, $p<0.01$) between level of serum HOMA-IR and level of spexin in the first and third trimester of pregnancy, respectively. In pancreatic islets, however, spexin and insulin may interact physiologically, therefore the much higher spexin levels in patients GDM may indicate the significance of insulin resistance (hyperinsulinemia) in the pathophysiology of GDM. (13) The results of this study reported that there was a positively and highly correlated ($r=0.629$ vs. $r=0.798$, $p<0.01$) between level of serum HOMA-IR and level of vaspin in the first and third trimester of pregnancy, respectively. These findings imply that an increase in blood vaspin levels, as well as an increase in vaspin mRNA expression in adipose tissue, might represent a compensatory counter-effect to unknown up-regulated proteases that may be elevated in obesity and insulin resistance conditions. (9)

Obesity, adipose tissue dysfunction, hyperglycemia, and hyperinsulinemia may therefore play a role in metabolic

abnormalities and their repercussions in disorders like GDM. In other words, the release of adipokines like vaspin from adipocytes may result in a chronic inflammatory state that contributes to the development of insulin resistance. (36-38) Moreover, our work showed that there was a negatively and highly significantly correlated ($r=-0.652$ vs. $r=-0.971$, $p<0.01$) between level of serum HOMA-IR and level of nesfatin-1 in the first and third trimester of pregnancy, respectively.

The role of nesfatin-1 in improving both hepatic and peripheral insulin sensitivity, as it enhances glucose uptake by peripheral tissues, decreases glucagon secretion and inhibits gluconeogenesis via different pathways, may explain the negative correlation between insulin resistance and nesfatin-1. As a result, a considerable drop in serum nesfatin-1 may be linked to reduced insulin sensitivity, implying that insulin resistance, hyperglycemia, and hyperinsulinemia may block nesfatin-1. (38)

Adipokines, on the other hand, play an important role in maternal-fetal needs and actively participate in various metabolic processes. (39) Furthermore, insulin resistance is linked to dysregulated adipokine synthesis or secretion in the late second and third trimesters of pregnancy. Therefore, hyperinsulinemia, the dysregulation of the insulin secretion and insulin resistance might be the result from impaired synthesis or release of nesfatin-1 during pregnancy which play a role in the pathophysiology of in GDM. (7) Finally, the present work indicated that there was a significant negative correlation ($r=-0.622$, $p<0.01$) between HOMA-IR and orexin-A in the third trimester of pregnancy.

The hyperglycemia were shown to reduce its secretion from the islet cells in the pancreas, especially in the third trimester of pregnancy for women with GDM. (11) In turn, decreased level of orexin-A may play an important role in dysregulating of the feeding system via stimulate insulin secretion, inhibited glucagon secretion and increased blood glucose level as well as development of high-fat-diet-induced insulin resistance. (10) Furthermore, obesity, glucose intolerance, and insulin resistance were more prevalent in females GDM during the third trimester of pregnancy, possibly implying that it plays a role in glucose metabolism and the development of gestational diabetes due to lower orexin levels and expression because of hyperglycemia caused by insulin resistance. (40)

Although the present study could not yield a statistically significant pattern of the parameters observed which may be due to the relatively contribution of a small number of GDM women subjects included, we believed that it pointed to a connection between some of the parameters.

Conclusion

Our results indicated that the correlation of insulin resistance with studied adipokines may cast new light on the possible role as an etiological cause of gestational diabetes mellitus and might be a better monitoring index in women with GDM. Despite the necessity and importance of diagnosing diabetes in pregnant women in the third trimester, it does not improve pregnancy outcomes, but it may increase the rate of elective cesarean delivery. There is an urgent need that justifies further studies on the importance of diagnosing and treating GDM during pregnancy.

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Authors Contribution

AJMA contributed in the design of the study, the supervision of this manuscript and data analysis. RAA carried out the experiments. All authors wrote the paper, read and approved the final manuscript.

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