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Research Article

Evaluation Of Serum Level Of Pentraxin 3 As A Biomarker For Prediction Of Gestational Diabetes Mellitus.

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Abstract

Background: Gestational diabetes mellitus is associated with adverse perinatal outcome. Screening for gestational diabetes mellitus and applying adequate interventions may reduce the risk of adverse outcome. However, the diagnosis of gestational diabetes mellitus depends largely on test performed in late second trimester. The discovery of new biomarker buildup a simple model to predict gestational diabetes mellitus in early pregnancy one of them is Pentraxin 3.
Objective: In this study we aimed, to evaluate the potential relationship between Pentraxin 3 and occurrence of gestational diabetes at 24-28 weeks of gestation and to evaluate the significance of Pentraxin 3 as early predictor of gestational diabetes.
Study design: prospective case-control study.
Setting: Department of Obstetrics and Gynecology, Al-Yarmouk Teaching Hospital, Baghdad / Iraq.
Patient and methods: The study involved 150 pregnant women with singleton pregnancy, 75 of them with risk factors for gestational diabetes mellitus as a case group(group 1) and the other group have no risk factor as a control group (group 2)
Each participant was given an appointment at 14-18 weeks of gestation .Blood sample was taken from all after fasting for 8 –hours. Unfortunately, we missed a lot of them. However Pentraxin 3 concentration, fasting plasma glucose, glycosylated hemoglobin and fasting plasma insulin were all tested and analyzed subsequently to those who continue the study. Furthermore, there was another appointment at 24—28 weeks of gestation for 75 g OGTT.
Results: Pentraxin 3 was significantly higher in participants of Group (1) who had risk factors (p-value=0.01) .And there is significant association between high body mass index and gestational diabetes mellitus of a p-value 0.05. Oral glucose tolerance test was significantly higher on first, second and third readings in Group (1) who had risk factor (p value were 0.028, 0.05 and 0.01 respectively).
Conclusion: Serum Pentraxin 3 level was significantly higher in patient with gestational diabetes mellitus, The increase in oral glucose tolerance test was significant associated with an increase in the PTX-3.

Keywords : *gestational diabetes mellitus, biomarkers, pregnancy.*

INTRODUCTION

Gestational diabetes mellitus can be defined as carbohydrate intolerance of variable severity with onset or first recognition in pregnancy (1).

GDM is of clinical importance because it increases the risk of poor pregnancy outcome such as accelerated fetal growth, late stillbirth, birth trauma, and neonatal hypoglycemia with long term health risk for child obesity and further risk of type 2 diabetes mellitus all increase with increasing maternal hyperglycemia [(2)].

During healthy pregnancy, the mother's body undergoes a series of physiological changes in order to support the demands of the growing fetus. These include adaptations to the cardiovascular, renal, hematologic, respiratory, and metabolic systems. One important metabolic adaptation is in insulin sensitivity. Over the course of gestation, insulin sensitivity shifts depending on the requirements of pregnancy. During early gestation, insulin sensitivity increases, promoting the uptake of glucose into adipose stores in preparation for the energy demands of later pregnancy [(3)] However, as pregnancy progresses, a surge of local and placental hormones, including estrogen, progesterone, leptin, cortisol, placental lactogen, and placental growth hormone together promote

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a state of insulin resistance [4]. As a result, blood glucose is slightly elevated, and this glucose is readily transported across the placenta to fuel the growth of the fetus. This mild state of insulin resistance also promotes endogenous glucose production and the breakdown of fat stores, resulting in a further increase in blood glucose and free fatty acid (FFA) concentrations [5].

GDM is usually the result of β-cell dysfunction on a background of chronic insulin resistance during pregnancy and thus both β-cell impairment and tissue insulin resistance represent critical components of the pathophysiology of GDM. In most cases, these impairments exist prior to pregnancy and can be progressive representing an increased risk of T2DM post-pregnancy [6].

Some of the most important regulators of neurohormonal metabolic control are adipokines-cell signaling proteins that are secreted primarily by adipose tissue. These include leptin and adiponectin [7].

Pentraxin

The pentraxin family is a superfamily of proteins that shares the same domain and is made from monomers arranged in pentameric structures with a discoid shape [8]. The members of the family are characterized by a 205 amino acids (AA) long conserved sequence located at C-terminal called the pentraxin domain. Members of the pentraxin family share a similar 8 AA (His-x-Cys-x-Ser/Thr-Trp-x-Ser, in which x represent any AA) long conserved sequence called the pentraxin signature within the pentraxin domain [9]. Based on the length of the protein sequence, the pentraxin family can be classified into two subfamilies: the short and long pentraxins. The short pentraxins are comprised of C-reactive protein (CRP) and serum amyloid P component (SAP), whereas the long pentraxins are composed of neuronal pentraxin 1(NPTX1), neuronal pentraxin 2 (NPTX2), neuronal pentraxin receptor (NPTXR), pentraxin 3 (PTX3), and pentraxin 4 (PTX4) [10].

The member of the short pentraxin family, CRP, and SAP were previously reported as mediators in human immune system regulation [11,12]. Their functions in immune regulation include acting against pathogen invasion, removing mutant cells, and triggering inflammation [13]. The neuronal pentraxins are involved in the development of the central nervous system and neurodegenerative diseases [14]. PTX3 not only participates in immune system activation but also affects tumor progression [15].

In recent years, chronic subclinical inflammation is considered to have a potential role in the pathogenesis of hyperglycemia. Pentraxin 3 a recently identified multimeric inflammatory mediator, is correlated with the process of insulin resistance and its level is also increased in diabetes mellitus and diabetic nephropathy which serum PTX3 concentrations are related to glucose levels in pregnant women with GDM [16].

Pentraxin 3 has also been implicated as a predictor of adverse clinical outcomes in patients with heart failure, increased in patients with acute myocardial infarction, good marker for the response to treatment of patients with obstructive sleep apnea, PTX3 is expressed in response to proinflammatory signals as a result, inflammation diseases, especially disorders of the immune system such as rheumatoid arthritis ,progressive systemic sclerosis, Chug-Straus syndrome, Wegener's granulomatosis, and microscopic polyangiitis , as well as systemic inflammatory response syndrome , result in increased expression of plasma PTX3[17]. Chronic kidney disease is also known to increase the level of plasma PTX3. Therefore, it was also of interest to determine the PTX3 expression patterns in inflammatory bowel diseases such as Crohn's disease and ulcerative colitis [18].

The aim of this study is to explore the potential relationship between serum level of Pentraxin 3 and occurrence of gestational diabetes at 24-28 weeks of gestation and to evaluate the significance of Pentraxin 3 a biomarker as a predictor of gestational diabetes.

MATERIALS AND METHODS

Study design and setting

A prospective case-control study performed at ALYarmouk Teaching Hospital and National Institute of Diabetes, between 1st of March 2021 to the 1st of October 2021. involved 150 pregnant women with singleton pregnancy, 75 pregnant women with risk factors as cases group (group 1). and the other 75 with no risk factors for GDM as a control group (group 2).

The first visit was held at outpatient clinic of the Obstetrics and Gynecology Department of Al-Yarmouk Teaching Hospital which is a tertiary center that received thousands cases per year. In addition these cases were also accounted from such a private clinic in Baghdad city too. Maternal characteristics were recorded to all participant and gestational age which was calculated for those with reliable LMP and confirmed by early first trimester ultrasound, body mass index calculated. The medical, obstetric, gynecological and family histories were all taken and recorded.

General examination including the measurement of the vital signs was done to all participants. An appointment was given for each participant at 14 - 18 weeks of gestation by contacting, through phone number, and asking them for eight hours fasting before the day of blood sampling. Unfortunately some for them didn't follow up or even didn't come to complete this examination. This due to the occurrence of complications or fair of Covid 19 affection.

Five ml of venous blood specimen were collected from each pregnant woman and the blood serum were then separated and stored at −80 °C. The levels of fasting serum PTX3

concentrations, fasting plasma glucose (FPG), glycosylated hemoglobin (HbA1c) and fasting plasma insulin (FINS) were all tested and analyzed subsequently. Serum PTX3 was analyzed by using commercial sandwich ELISA kits (Human Pentraxin 3 ELISA Kit) in Al-Shameem lab.

Additionally another appointment was given for the remaining participants in the National Institute of Diabetes at 24–28 weeks; asked them for eight hours fasting and 75 g OGTT was also done for all participants.

Exclusion criteria

1. Type 1 or 2 Diabetes mellitus before pregnancy.
2. Multiple pregnancies.
3. Inflammatory and infectious disease.
4. Those with hepatic, renal, cardiovascular disease (association between Pentraxin 3 level and these diseases).
5. Cancers.
6. Smoking.

Ethical Consideration

Informed consent was taken from all participant after full explanation of aim of the study and ensuring of confidentially.

Statistical analysis

The data was analyzed by the aid of SPSS (Statistical Package for Social Sciences) version 24.

Chi-Square test was used to demonstrate the association between categorical data, and T-test was used to analyze the relationship between numerical data.

Pearson correlation was used to analyze the association among numerical data.

The diagnostic characteristics as sensitivity, and specificity were analyzed through the use of ROC, P value of less than 0.05 was considered to be significant.

RESULTS

The total number of the participated pregnant women was 150, were divided in to two groups; the first one was the study group with 75 pregnant ladies who had one or more risk factors for gestational diabetes; along with another 75 women as a control group without risk factors for gestational diabetes.

Non- significant associations were found when comparing the study and control groups in terms of age, gravida & blood pressure.

Ladies of the study group with risk factors (group 1) had significantly higher BMI (>30(Kg\m2)) than those of the control (group20 (p-value=0.05).

Group (1) participants have significantly higher BMI, (p-value=0.05).History of previous macrosomia was significantly higher in those of Group (1).

Also, Group (1) participants have significantly positive family history of gestational diabetes (p-value=0.0001).

Non- significant association was found in comparing the two groups in terms of previous IUD though it was higher in Group (1).

women of Group (1) have significantly higher levels of FBS, SI, & HOMA than women of the second control group (p-values were 0.039, 0.037&0.001) respectively.

HBA1C (%) was non-significantly higher in Group (1) patients (p-value=0.554).

PTX-3 was significantly higher in participants of Group (1) with a mean of (4.096 ±4.4) compared to group (2) with a mean of (2.58 ±3.31), this difference was statistically significant (p-value=0.01).

PTX-3 was positively and significantly associated with (Base line and 1 hour OGTTs) respectively; meaning that the increase in OGTT was associated with an increase in the PTX-3 and vice versa, but non-significantly associated with OGTT at 2 hours post-prandial.

HBA1C also was associated non-significantly and negatively with the marker (PTX-3).

SI& FBS both were associated positively, but non-significantly with PTX-3; indicating that whenever there is an increase in either SI or FBS; there will be an increase in the marker (PTX-3)

ROC analysis of PTX 3 levels resulted in cut off value of (0.6705), which has sensitivity of 93% & specificity of 16% for the prediction of gestational diabetes.

DISCUSSION

It is evident that GDM represents a major endocrine–metabolic disorder that has a profound effect on maternal and fetal health. It is of multifactorial etiology, where the genetic and environmental factors are the main risk factors. A better understanding of the pathophysiology of GDM can result in the improvement of the outcome of pregnancy. Unfortunately, there is no approved clinical or laboratory screening or diagnostic tool for GDM early in pregnancy, but the discovery of new biomarkers has revolutionized the prediction of this syndrome. In the current study, the relationship between the levels of PTX3 and GDM has already been studied and evaluated [19] .

An increasing number of studies on the relationship between PTX3 and hyperglycemia associated with insulin resistance have been published that suggest potential involvement of PTX3 in diabetes mellitus pathology. PTX3 is a good predictor because its level in early pregnancy increases. Furthermore, because PTX3 is related with the inflammation of vascular, PTX3 has been considered to associate with preeclampsia and type I diabetes. PTX3 levels are related to future cardiovascular disease risk .So in the first trimester, the level

of PTX3 as an inflammatory marker involved in pathogenesis of diabetes related comorbidities could be correlated with the development of GDM during pregnancy [20].

GDM and demographic characteristic: In current study there was no significant association between neither GDM and age of the patients nor the parity in the study groups as the P value was> 0.208, 0.183 respectively in contrast to the study at 2006 in china by Terence T.Lao et al, which revealed that there is association between GDM and maternal age; and prevalence of GDM becomes significantly and progressively increased from 25 years onwards [21] . Meta-analysis study performed at 2015 in America by Naama Schwartz et al. suggested that prevalence of gestational diabetes mellitus recurrence affect by ethnicity and parity with a high recurrence in a multiparty women of p-value 0.0001 .This discrepancy can be explained by the small sample size involved in our study [22].

GDM and BMI

not surprisingly, we found a greater prevalence of GDM among groups with increasing prepregnancy BMIs. Group (1) participants have significantly higher BMI, (p-value=0.05).This fact supported by many studies such as a study at 2013 in California by Amy Shah et al, identified that BMI > 25 Kg /m2 a risk for developing GDM of (P value = 0.001)[23].

GDM and HT

in current study , the mean for systolic and diastolic blood pressure was higher in group (1) than group (2) though it did not reach significant association as the p-value 0.11, 0.18 of systolic and diastolic respectively. However, the results disagreed by a study at 2011 by Deirdre K. Tobias et, al,at whose study assumed that women with GDM were at a significant high risk of developing hypertension of p-value 0.0004.This can be explained by the small sample size involved in our study[24] .

GDM and OGTT

OGTT was significantly higher in first, second , and third readings in Group (1) who had risk factor (p value were 0.028, 0.05 and 0.01) respectively, this is fact which is improved by many studies such as a study done by Maria I. Schmidt et al. aims to diagnosis of GDM With a 2-h 75-g Oral Glucose Tolerance Test 2001 in Brazil with a sample size 4,216 participants using WHO criteria of diagnosis of gestational diabetes [25].

GDM and biochemical parameters

regarding the fasting blood sugar in group 1of p-value 0.039, it has significantly higher levels which are similar in a study done by S.Liao et al, at 2014 which reveals that fasting glucose diagnostic criterion on the prevalence and outcomes of gestational diabetes mellitus in Han Chinese women is observed with sample size 5360 participants in china [26].

The fasting insulin level in group 1 of (p-value 0.037) has been significantly higher which is similar in study done by A.Seval Ozgu et al, at 2014 in Turkey who investigates the development of a predictive index based on high sensitivity C-reactive protein, fasting plasma glucose and fasting plasma insulin measurements for early diagnosis of gestational diabetes mellitus. So his study concludes that FPG and CRP in the first trimester are correlated with later development of GDM in the pregnancy. Which provides FPG a better sensitivity while CRP exhibited a better specificity for prediction of GDM [27] .

Hüsnü Alptekin et al, at 2014 in Italy examines the predictability of gestational diabetes mellitus during the first trimester using the degree of insulin resistance and anthropometric measurements of HOMA of a sample size 240 participants [28] which supports the current study with HOMA in group 1of p-value 0.001 which has significantly higher levels.

PTX 3 and GDM: PTX-3 was significantly higher in participants of Group (1) who had risk factors (p-value=0.01), which is similar in study done by Xiaoxian Qu et al,S hanghai, China;2019 . It revealed the relationship of maternal PTX3 serum concentrations in early pregnancy with GDM , and explored its potential in the prediction of GDM of a sample size 824 participants [29].At 2013 in Vienna, Austria; Jelena Todoric et al, revealed the relationship of pentraxin 3 with insulin sensitivity in gestational diabetes [30].

M.Amini et al,at 2020 in California investigated the diagnostic accuracy of maternal serum multiple marker screening for early detection of gestational diabetes mellitus in the absence of gold slandered test. This was done by using B-hCG , unconjugated estriol and alfa-fetoprotein values which were considered as an acceptable predictors for detecting GDM [31] .

PTX-3 was positively and significantly associated with (Base line and 1 hour OGTTs) respectively. It means that the increase in OGTT was associated with an increase in the PTX-3 and vice versa, but none was significantly associated with OGTT at 2 hours post-prandial.

HBA1C has no relationship with PTX-3., Both SI & FBS were associated positively, but not significantly with PTX-3; which indicate that whenever there is an increase in either SI or FBS; there will be an increase in the marker PTX-3 too .The cut of value is 0.6705 with sensitivity of 93% and specificity of 16%.

CONCLUSION

1. Serum Pentraxin 3 level increases in patients with gestational diabetes mellitus .
2. Pentraxin 3is significantly associated to (Base line and 1 hour OGTTs) respectively; meaning that the increase in OGTT is associated with an increase in the PTX-3 and vice versa.

Recommendations

1. It is recommend the use of Pentraxin 3 as a diagnostic marker for GDM.
2. We recommend Pentraxin 3 level of 0.6705 as the best cut-off point for the diagnosis of GDM.

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