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Oxidative stress with Gestational diabetes mellitus in first, second and third trimester

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ABSTRACT— It is becoming a public health concern to predict which pregnant women may develop gestational diabetes mellitus (GDM). The goal of this case control research is to investigate the role of maternal oxidative stress levels in the first, second, and third trimesters, as well as other factors, in the development of GDM. During October and December 2021, 142 women participated in this study. The 101 GDM patients were separated into three groups based on their trimester (T1, T2, and T3), and 41 healthy pregnant women were chosen as the control group. Levels of oxidative stress were determined by measurement of Total Antioxidant status (TAS) and Total oxidant status (TOS) using colorimetric methods while oxidative stress index (OSI) was calculated. Advanced oxidation protein products (AOPP), xanthine oxidase (XO) and dehydrogenase (XDH) activities were measured. The TOS levels were higher in all GDM groups compared with control (p=0.000) and high significant between patients groups in the order (T3>T2>T1), while high significant of TAS in GDM than control but in the order (T3<T2<T1). The mean levels of OSI were higher significantly in women with GDM in all trimester (T1=73.79 ± 18.43, T2=81.28 ± 18.06, T3=96.70 ± 20.69) in comparison with control (37.28 ± 18.95) with statistical significance (P = 0.000). Oxidative stress levels were higher significantly in the order T3>T2>T1, and the same results were found in the measured AOPP, Xanthine oxidase, XO\XDH ratio levels. On the other hand, Total protein, Albumin, Globulin, and Alb\Glo ratio levels showed non-significant difference (P>0.05) in all GDM groups when compared with that of healthy pregnant women. The correlation of oxidative stress with TOS in T1, T2, and T3 groups was positive with significance, while negatively correlated with TAS in T1, T2, T3 groups. From the findings of this study, a significant increase in total oxidant demonstrated by overall lower antioxidant level in GDM patients tend to heighten oxidative stress.

KEYWORDS: Oxidative stress, Gestational diabetes mellitus, Trimesters, Xanthine oxidase, Xanthine dehydrogenase, Advanced oxidation protein products.

1. INTRODUCTION

Gestational diabetes mellitus" (GDM) refers to glucose intolerance that first manifests or is initially diagnosed during pregnancy. It is a metabolic disorder of the carbohydrate metabolism characterized by hyperglycemia and insulin resistance. Globally, the prevalence of GDM varies and is now believed to range between 7 and 10% [1]. GDM is linked to poor maternal, fetal, and neonatal outcomes [2]. A prior diagnosis of GDM is a recognized risk factor for developing T2DM in later life [3]. The primary risk factors for developing GDM are obesity, progressive overweight, a high-fat, low-carb diet, a sedentary lifestyle, and a family history of diabetes. GDM often develops in a spontaneous hyperglycemic state [4]. Although, GDM usually goes away after delivery, later-pregnant women are more likely to have T2DM 40–50% of the time. The high level of glucose in the blood during pregnancy may cause a multitude of problems affecting the growth of the fetus and discomfort if not treated precisely and properly [5].

Oxidative stress (OS) results from an imbalance between oxidant and antioxidant defense systems, which

produces reactive oxygen species (ROS) [6]. Although, the majority of ROS are produced during metabolic processes, and a variety of enzymes and substances with antioxidant properties work to reduce their effects, however uncontrolled production of ROS, including singlet oxygen ($O_2^{\bullet}$), hydrogen peroxide (H_2O_2), hydroxyl radicals ($HO^{\cdot}$), peroxyl radicals, and superoxide anion ($O_2^{\bullet}$), causes them to attack any biomolecules in their surroundings and change their structure and function, including DNA and proteins [7].

Many diseases, including accelerated aging, diabetes, cancer, hypertension, and coronary heart disease are associated with the OS [8]. A significant burden of maternal and fetal morbidity and death results from illnesses such as abortion, preeclampsia, fetal embryopathy, premature labor, and GDM, among others [9]. Throughout pregnancy, the growing infant is exposed to a variety of endo and ecto-exposome factors, most notably oxidative stress, nutrition, and inflammation, a pregnancy problem in which the exposome is implicated. Placental oxidative stress is clearly linked to a range of adverse pregnancy outcomes, and maternal spiral artery conversion appears to be mechanistically linked. Miscarriage, early delivery, pre-eclampsia, eclampsia, gestational diabetes, and other problems may be enhanced if the pro-oxidant situation is pushed further throughout pregnancy. Additionally, these insults may have an effect on fertility [10].

The aim of this study, was to explore the association between value of oxidative stress concentrations during first, second and third trimester and the development of GDM in pregnant women.

2. Methods

A case control study was conducted by enrolling 142 participants who visited Al-Alawiyeh Maternity Teaching Hospital/ Baghdad during the period between October to December 2021. 101 patients with GDM were subdivided to three groups according to their pregnancy semester (T1=34, T2=34, T3= 33), and 41 healthy pregnant women as a control group. The diagnosis of GDM was done after running fasting /random blood sugar blood analysis by physician according to ADA criteria. The period of sample collection was for all trimesters of pregnancy. All participant were informed and approved to participate in this study, as well the approval from the scientific and ethical committee was obtained.

The inclusion criteria were pregnancy of one fetus. Participants with chronic inflammatory disease, metabolic diseases, hypertension, coronary heart disease, and family history of T2DM or previous GDM were excluded.

After taking venous blood samples, a direct HbA1c analysis was done while the remaining blood was centrifuged after clotting to collect serum which was stored in Eppendroff tubes at -20 ^{o}C. Serum TAS [11], TOS [12], were measured to calculate the oxidative stress index (OSI), also total serum protein, Albumin, and Globulin measured by using Spectrophotometer PD-303 for colorimetric methods (Japan), the AOPP [13], xanthine oxidase and dehydrogenase [14], were measured by using UV-Visible spectrophotometer (Japan).

Also Fasting and random glucose concentrations, were measured by colorimetric methods using kits from HUMAN (Germany), HbA1C was measured using DCA® analyzer Siemens (Ireland).

Statistical analysis: SPSS version 26 was used for all statistical analyses. Data that is descriptive were presented as mean and standard deviation (SD). To make a comparison between groups, one-way ANOVA, post hock was applied. Pearson correlation analysis was utilized to define the relationship between oxidative stress levels with other parameters. The significance level when (P value <0.05) was applied for all statistical analysis.

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3. Results

The findings from measurement of the biochemical parameters are presented in Table 1 where the results of first, second, and third trimester of fasting/Random blood glucose and HbA1c levels revealed noticeably higher levels in GDM than that of controls (P = 0.043, P <0.001, and P < 0.000) respectively. The HbA1C levels were higher in T1 of GDM than T3 with statistical significance (P = 0.032). Non-significant differences were found in levels of S.Protein, Albumin, Globulin levels, Alb\Glo ratio, and XDH activity between the four studied groups.

The mean levels of AOPP, XO, XO\XDH ratio, TAS, TOS, and OSI were higher in GDM patients at three trimesters than control with statistical significance (P =0.000), also higher significant were observed in GDM group who were in T3 than in T2 and in T1 with statistical significant for three semester (P = 0.000).

Table1: The characteristics of the biochemical parameters levels between GDM patients (three semesters) and control groups.

Parameters	Control n=41	T1 n=34	T2 n=34	T3 n=33	P value
Age range (year)	16-43	19-45	18-43	20-45	---
FBG mg\dL	79.45 ± 5.22	113.68 ± 32.38[a]	116.22 ± 34.27[a]	113.61 ± 25.01[a]	0.043
RBG mg\dL	99.25 ± 17.20	148.80 ± 61.87[a]	126.73 ± 42.80[a]	133.53 ± 42.93[a]	0.001
HbA1C %	3.56 ± 0.38	6.13 ± 0.91[a]	6.00 ± 0.91[a]	5.74 ± 0.63[ab]	0.000
S.Protein g\dL	8.23 ± 0.83	8.35 ± 0.87	8.44 ± 1.23	8.52 ± 1.20	0.657
Albumin g\dL	4.60 ± 0.55	4.48 ± 0.77	4.61 ± 0.61	4.65 ± 0.54	0.714
Globulin g\dL	3.63 ± 0.92	3.86 ± 1.17	3.82 ± 1.33	3.87 ± 1.39	0.797
Alb\Glo ratio	1.43 ± 0.79	1.37 ± 0.83	1.40 ± 0.65	1.40 ± 0.72	0.986
AOPP (µmol\L)	32.06 ± 8.11	53.03 ± 12.18[a]	58.32 ± 13.05[ab]	69.63 ± 9.05[abc]	0.000
XO U\L	30.79 ± 5.65	55.32 ± 9.16[a]	70.13 ± 6.52[ab]	78.31 ± 6.53[abc]	0.000
XDH U\L	0.55 ± 0.14	0.55± 0.10	0.56 ± 0.14	0.57 ± 0.14	0.902
XO\XDH	58.39 ± 15.19	102.11 ± 22.91[a]	130.10 ±32.20[ab]	143.93 ± 37.35[abc]	0.000
TOS (mmol H_2O_2 Eq\L)	46.18 ± 15.95	66.49 ± 13.43[a]	74.72 ± 15.42[ab]	82.60 ± 15.08[abc]	0.000
TAS (mmol glutathioneEq\L)	1.41 ± 0.51	0.92 ± 0.26[a]	0.94 ± 0.22[a]	0.88 ± 0.19[a]	0.000

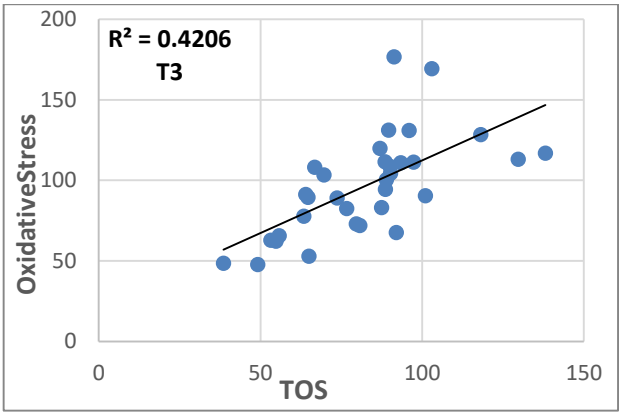
OSI	37.28 ± 18.95	73.79 ± 15.43[a]	81.28 ± 18.06[ab]	96.70 ± 20.69[abc]	0.000

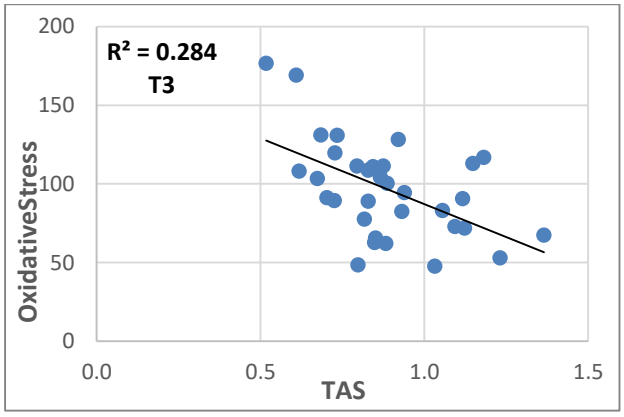
Statistical analysis using ANOVA, significant difference when P< 0.05. a: significant when compared with control group, b: significant when compare T1 with T2 and T3 group, c: significant when compare T2 with T3 group. FBG: fasting blood glucose; RBG: Random blood glucose.

Serum oxidative stress level in T1, T2 and T3 group shows significantly negative correlation with TAS levels (r = -0.379*; P =0.030), (r = -0.482**; p=0.004), (r= -0.533**; p=0.001), respectively. While it was positively associated with TOS levels in T1, T2, and T3 (r = 0.641**; P = 0.000), (r = 0.599**; P = 0.000), and (r= 0.649**; P= 0.000) respectively. No other correlations were found between oxidative stress level with other parameters, as shown in Table 2 and Fig 2.

Table 2: Pearson correlation coefficients of oxidative stress with other biochemical parameters in the first, second, and third trimester groups.

Groups	Parameters	r	P
T1	**TOS** (mmol H_2O_2 Eq\L)	**0.641****	**0.000**
	TAS (mmol glutathione Eq\L)	**-0.379***	**0.030**
T2	**TOS** (mmol H_2O_2 Eq\L)	**0.599****	**0.000**
	TAS (mmol glutathione Eq\L)	**-0.482****	**0.004**
T3	**TOS** (mmol H_2O_2 Eq\L)	**0.649****	**0.000**
	TAS (mmol glutathione Eq\L)	**-0.533****	**0.001**





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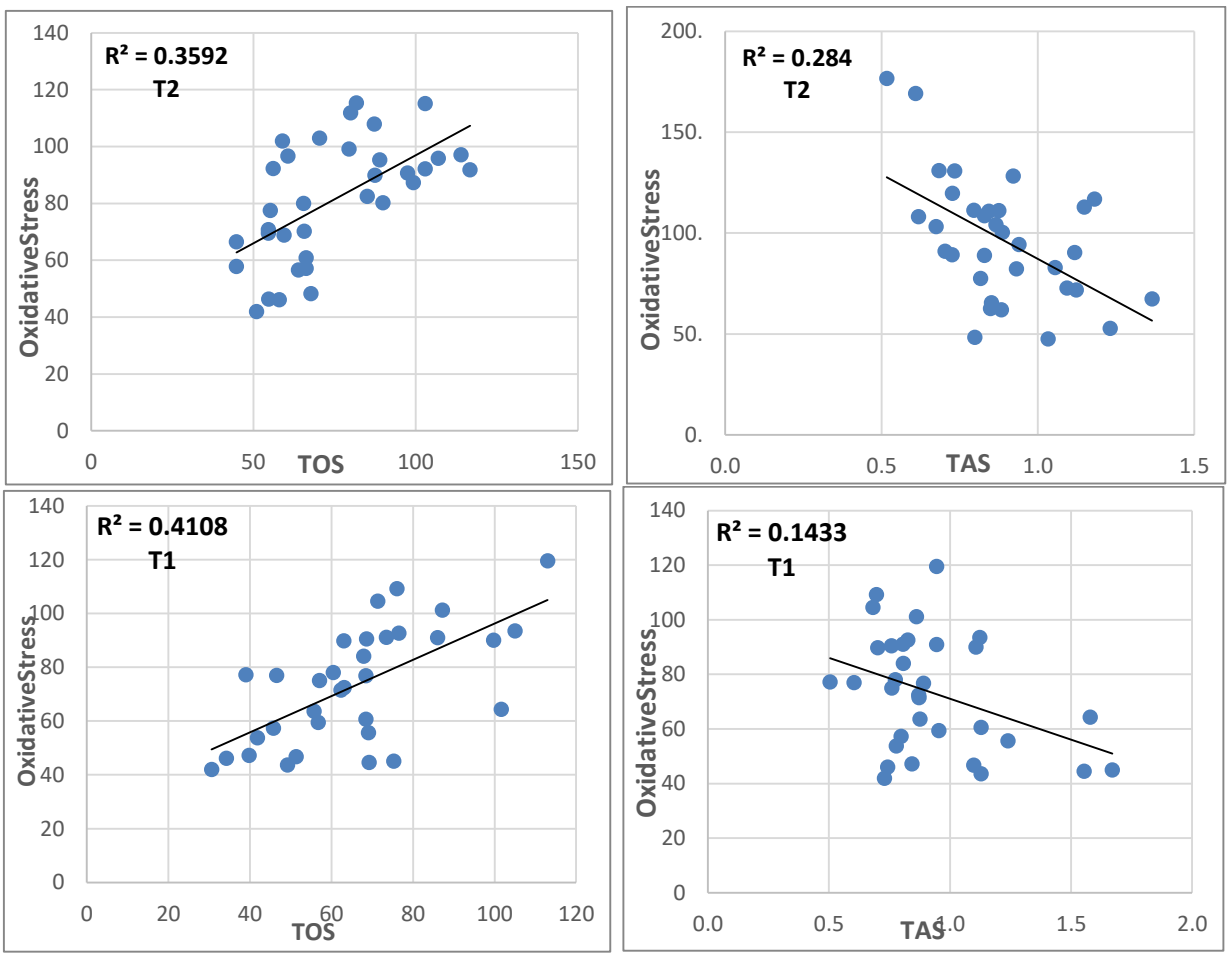

Figure 2: Pearson correlation analysis of oxidative stress with other biochemical parameters

4. Discussion

Despite strong evidence that oxidative stress has an influence on pregnancy and reproduction, PCOS, subfertility, and endometriosis may all be caused by an imbalance in the body's pro-oxidant and antioxidant agents. Miscarriages, gestational diabetes and preeclampsia, fetal growth limitation, and early birth may be caused by oxidative stress. According to some hypotheses, hyperglycemia is the primary source of oxidative stress in GDM [15- 17].

In comparison to healthy pregnant women, individuals with GDM had higher levels of oxidative stress, and antioxidant levels in these patients dropped as gestation progressed [18]. Since inflammatory reactions induce oxidative stress, and oxidative stress prolongs an inflammatory response, inflammation and oxidative stress are intimately related [19], [20]. Oxidative stress may rise in response to inflammatory stimuli that cause a shift from immunological tolerance to immune effector activation, and subsequently a harmful immune response, increasing the probability of poor pregnancy outcomes [21].

Oxidative stress predominates in a regular pregnancy due to the placenta's presence of transitional metals like iron and its mitochondrial richness [22]. Nonetheless, the majority of body cells have the ability to enhance the activity of antioxidants in order to successfully combat a minor rise in oxidative stress. If this capability is achieved, however, rising ROS levels might cause severe, irreparable damage to cellular components [23]. Because of hyperglycemia, which promotes high ROS generation and increases the progression of diabetes, oxidative stress is much higher in patients with GDM [24].

According to research by [25], [26] plasma from women with GDM had significantly more protein carbonyls than that of preeclamptic or control women. Moreover, [27] have shown a significant increase in OS in GDM. They came to the conclusion that oxidative stress, which frequently affects GDM patients, is caused by an imbalance between the body's overall free radical production and its antioxidant defenses.

There was a significant difference in XO between groups T1, T2, and T3 with GDM and controls. According to the findings of the [28] study, GDM pregnancies produce more ROS than normal pregnancies. The XO is the major free radical producing enzyme in the body that generates ROS and consequently functions as an oxidative stress marker [29]. [30] theorized that the XO enzyme's enzymatic process, which oxidizes hypoxanthine-xanthine into uric acid, causes oxidative stress. When it is synthesized, ROS are generated. XO is associated to hyperuricemia and diabetic complications in the vascular endothelium. [31], [32] showed that XO activity has also been connected to the emergence of many metabolic diseases and oxidative stress. It was concluded that an increase in XO activity is due to the increase conversion of the other form (XDH) to XO led to the production of reactive oxygen species and so, OS increase [33], [34].

Early studies have supported the significance of advanced oxidation protein products (AOPP) as an oxidative stress biomarker in a variety of pathological conditions such as diabetes mellitus, coronary artery disease, atherosclerosis, and non-diabetic nephropathy. AOPP concentrations were associated with atherosclerotic lesions and vascular inflammation in diabetic patients [35], [36]. The stimulation of redox-sensitive inflammation, mitochondrial dysfunction, and oxidative stress by AOPP causes early diabetic nephropathy [37].

The AOPP values in GDM patients are significantly higher than of the healthy group during (T1, T2, and T3), which may indicate the presence of oxidative stress. According to [38], persons with T2DM had (1.7-2) times higher AOPP levels than healthy patients, due to the fact that DM produces more ROS than normal according to [39], [40]. [41] proposed that AOPP levels were an independent risk factor for endothelial dysfunction in persons with diabetes in the early stages, while, [42] proposed a link between AOPP levels and glycemic impairments (plasmatic glucose and HbA1c). Both diabetic patients and diabetic experimental models have increased plasma protein oxidation levels [43]. According to a study by [44], on T2DM patients, plasma AOPP levels were significantly greater in diabetics with poor glycemic control than they those with acceptable glycemic control. The results of [45], [46] also showed that AOPP levels were greater in GDM than in normal pregnancies.

Total protein and albumin levels decrease throughout pregnancy, and this decrease is negatively correlated with the length of the pregnancy. Significant changes in the serum concentrations of total protein, albumin, and globulin from one trimester to the next could be due to changes in how these substances are involved in the metabolic processes linked to each stage of pregnancy. It is common for blood albumin concentrations to slightly decrease during pregnancy, although preeclampsia, gestational hypertension, gestational edema, and renal failure with proteinuria can all cause lower serum albumin levels [47].

Diabetes lowers the amount of albumin in the blood, requiring insulin therapy to prevent hypoalbuminemia [48]. Early biochemical experiments have shown that insulin increases hepatic gene transcription, which in turn boosts the manufacture of albumin [49].

In this study, albumin levels revealed no significant difference in GDM, which is consistent with the findings of the [50] study, which discovered that albumin concentrations were not significantly different between the normal pregnant group and the GDM group. The same outcomes were also observed in a

research conducted on 215 pregnant women by [51], with non-significant alterations in total protein, albumin, and globulin.

5. Conclusions

The GDM patients tend to have a higher TOS level and decreased TAS which led to oxidative stress may enhance the pathogenesis or pathophysiology of GDM.

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