THE STUDY OF MALONDIALDEHYDE, URIC ACID, AND C-REACTIVE PROTEIN IN OBESE AND HEALTHY PREGNANT WOMEN IN DIFFERENT TRIMESTERS

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ABSTRACT

Pregnancy or gestation is a complex period of human growth and development. It is a physiological process associated with the development of maternal pathologies, such as metabolic disorders (i.e. maternal obesity and hypercholesterolemia), preeclampsia and gestational diabetes mellitus. Obesity is a worldwide epidemic, it is considered a most common medical condition in women of reproductive age, during pregnancy has short term and long term adverse consequences for both mother and child, it is caused insulin resistance. There area closes relationship between the obesity, OS, antioxidants and inflammation. The aim of this study was the assessment to oxidative stress factor changes, uric acid and CRP in obese pregnant women in Misan province. The study included (60) obese pregnant women, aged (25 - 35) years. The study conducted during November 2018 to February 2019. Diagnosed parameters done using enzyme-linked immunosorbent assay (ELISA) and mind ray (BS -230).

Our results reveled almost parameters increased during pregnancy, highest increase in the third trimesters, it is increased significantly (p ≤0.05) in comparison with the first and second trimesters.

Results of current study showed clearly the following conclusion in obese pregnant women all parameters in our study elevated during trimesters.

Keywords: GDM, oxidative stress, antioxidants, uric acid, CRP

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INTRODUCTION

Pregnancy is the period in which a fetus develops inside a woman's uterus or womb, it is usually lasts about 40 weeks, or just over 9 months, as measured from the last menstrual period to delivery\(^1\), or as from fertilization continued with implantation (nidasi)\(^2\). It’s divided in to three stages or segments of pregnancy, called trimesters:
First Trimester: 1-14 weeks.

- Second trimester: from week 15-28 weeks.

- Third trimester: from week 29 and until birth [3].

It is a critical and unique period in a woman’s life [4]. And unique metabolic condition because of the changes in maternal metabolism needed to provide for fetal growth and increased maternal energy requirements [5,6].

In this period many dynamic change for a mother need a lot of care and rapid changes in the hormones like progesterone and estradiol (E2) [7,8]. In addition to its function as a gonadal hormone, is involved in the regulation of metabolism through the modulation of body weight, food intake, glucose/insulin balance, body fat distribution, lipogenesis and lipolysis, and energy consumption [9].

Oxidative stress is important for normal physiological functions during gestation, it’s play important roles in embryo development, implantation, placental development and function, fetal development, and labor [10,11].

The gestation is a physiological process that can involve the development of maternal pathologies, such as gestational diabetes mellitus, and metabolic disorders (maternal obesity, supraphysiological gestational weight gain (spGWG)) [12].

Obesity:

It is a worldwide epidemic, the wide prevalence of obesity was higher among middle-aged and older adults than younger adults, and higher in women than in men [13].

WHO reported in (2017) that the number of obese and overweight people is greater than the number of those who are underweight and that every person with a body mass index (BMI) of 30 or more is generally considered obese, equal to or more than 25 is considered overweight. Thus, the obesity is a public health problem that is increasing in all populations, including pregnant women [14].

There are many definitions for obesity; it is defined as abnormal or excessive fat accumulation that presents a risk to health [15]. Moreover, obesity is a chronic, relapsing medical condition that results from an imbalance of energy expenditure and consumption, it is a leading cause of preventable illness, disability and premature death, and the causes of obesity are multifactorial include behavioral, socioeconomic, genetic, endocrinal, environmental and psychosocial factors [16].

Obesity is considered a most common medical condition in women of reproductive age, obesity during pregnancy has short term and long term adverse consequences for both mother and child, it causes insulin resistance in early pregnancy, early placental response to maternal insulin, glucose intolerance in late gestation and fetal overgrowth [6,17].
Furthermore, obesity is a major factor in the development of insulin resistance and metabolic complications such as type II diabetes\textsuperscript{[18]}. Besides that, the obesity is accompanying with many clinical and biochemical alterations reflecting the pathological condition of various body tissues, it is impacts in cardiovascular\textsuperscript{[19]}. 

This oxidative stress caused dysregulated production of adipocytokines (fat-derived hormones), enlarged adipose tissue leading to infiltration of macrophages, imbalance of pro-inflammatory and anti-inflammatory factor\textsuperscript{[20]}.

Many studies shed a new light about “developmental obesogen hypothesis “, which suggests that the chemical exposures may increase the risk of obesity by altering the differentiation of adipocytes and the development of neural circuits, this hypothesis regulate feeding behavior, or may have damage many of the body’s natural weight-control mechanisms\textsuperscript{[21-23]}.

**Oxidative stress (OS)**

Defined as a state characterized by an imbalance between pro-oxidant molecules, and antioxidant defenses, OS result of overproduction of reactive oxygen species (ROS) in relation to antioxidant defense levels, excessive ROS production and resulting OS may contribute to aging and several diseased states affecting female reproduction\textsuperscript{[24]}.

Furthermore it is considered as harmful because oxygen free radicals attack biological molecules such as lipids, proteins, and DNA, however, oxidative stress also has a useful role in physiologic adaptation and in the regulation of intracellular signal transduction, therefore, a more useful definition of oxidative stress may be “a state where oxidative forces exceed the antioxidant systems due to loss of the balance between them”\textsuperscript{[25]}.

OS prevalence increases among urban life and changes in antioxidant capacity\textsuperscript{[26]}, it is well known to be involved in the pathogenesis of lifestyle-related diseases, such as hypertension, and diabetes mellitus, in addition to, there are many daily habits are closely associated with oxidative stress, which is augmented by smoking, drinking, and an irregular diet\textsuperscript{[26]}.

In the other hand, OS increased during pregnancy due to some changes in such biomarkers (TC, TG, LDL and uric acid), these changes were demonstrated by a rise in lipid peroxidation\textsuperscript{[27]}.

Myatt (2006) showed that the metabolic activity of placental mitochondria (trophoblast, syncytiotrophoblast and placental vascular endothelium) leads to oxidative stress even in normal pregnancy which is exacerbated further in diabetic\textsuperscript{[28]}.

OS is a lipid peroxidation that will produce lipid peroxide, lipid peroxide will decomposes to produce a number of compounds or number of secondary products such as epoxides, hydrocarbons and aldehydes i.e., malondialdehyde (MDA)\textsuperscript{[29]} and 8-iso-prostaglandin F2α (8-iso-PGF\textsubscript{2α})\textsuperscript{[30]}.
Malondialdehyde (MDA) is the product of polyunsaturated fatty acid peroxidation, this aldehyde is a highly toxic molecule and should be considered as more than just a marker of lipid peroxidation, its interaction with DNA and proteins has often been referred to as potentially mutagenic and atherogenic [31].

**Uric acid (UA)**

It is the final product of purine metabolism; synthesized by the enzyme xanthine oxidase, in humans most circulating of uric acid is produced in the liver [32].

Its considered as a powerful scavenger of singlet oxygen, peroxyl radicals (RO. 2) and hydroxyl radicals (.OH), urate circulating in elevated concentrations was proposed to be one of the major antioxidants of the plasma that protects cells from oxidative damage, thereby contributing to an increase in life span and decreasing the risk for cancer [33].

UA is a powerful scavenger of carbon-centered and peroxyl radicals in the hydrophilic environment but loses an ability to scavengelipophilic radicals and cannot break the radical chain propagation within lipid membranes [34].

Despite the proposed beneficial role of uric acid, hyperuricemia patients have a higher rate of cardiovascular and stroke in comparison to subjects with normal levels of uric acid [35]. The highly levels of UA is strongly associated and in many cases predicts development of hypertension [36], visceral obesity, insulin resistance, dyslipidemia [37], T2D [38], kidney disease, and cardiovascular andcerebro-vascular events [39].

Moreover, uric acid can become a pro-oxidant by forming radicals in reactions with other oxidants, and these radicals seem to target predominantly lipids (LDL and membranes) rather than other cellular components, at the same time, the hydrophobic environment created by lipids is unfavorable for the antioxidant effects of uric acid [34; 33], and oxidized lipids can even convert uric acid into an oxidant [40].

Cianni and his colleagues (2003) showed in (non-pregnant population) a close relationship between the uric acid and the IR [41]. UA may induce IR and causes inflammation and OS in adipocytes, which is a contributor to the development of metabolic syndrome [42].

**C-reactive protein (CRP)**

It is a liver specific acute phase protein known to be a marker forcardiovascular risk, it is correlated with insulin resistance during obesity [43].

CRP is a protein produced in response to inflammation to control it via activating the complementary immune system [44], and primarily synthesized in hepatocytes in response to infection and tissue injury [45], therefore it’s considered as sensitive marker of chronic inflammation and a risk factor for diabetes and mortality [46-48].

The production of CRP is stimulated by the release of proinflammatory cytokines including interleukin-1, interleukin-6, and tumor necrosis factor-alpha, although sometimes referred to as an acute-
phase reactant, CRP accompanies both acute and chronic inflammatory disorders \[49\]. There is a strong association between CRP and elevated BMI, because CRP is produced predominantly by the liver which in clearly contrasts with the adipose tissue macrophages responsible for the production of obesity associated inflammatory cytokines \[50\].

Besides that, Clark and his colleagues (2016) showed a stronger positive association between CRP and BMI among females \[48\], that pointed the relationship between CRP and obesity depended on both age and sex \[51\].

In the other hand, Shahid (2018) showed the relationship between the inflammatory marker C-reactive protein (CRP) and insulin resistance, insulin resistance was elevated with high CRP levels in both men and women \[52\].

Yudkin and his colleagues (1999) reported that insulin resistance syndrome is associated with CRP, IL-6, TNF-a, and fibrinogen \[53\].

These elevation of CRP levels increases with gestational weeks during pregnancy from 5 to 20 weeks and from 28 to 32 weeks, and modest elevation in CRP later in pregnancy may be expected to occur and reflects the immune adaptations during pregnancy \[54\].

In addition, the maternal immune system is also altered during pregnancy creating a state of balance between enhanced immune response in the form of increased circulating levels of C-reactive protein (CRP) \[55\]. Haidari and his colleagues (2016) showed the glucose intolerance and weight gain during pregnancy affected on CRP levels \[56\].

**MATERIAL AND METHODS**

**Subjects**

The current study has been done at al-Sadr educational hospital, child and birth governmental hospital, golden medical clinic, altayf laboratory, from November 2018 to February 2019 in Misan province.

**Sample selection**

The study included 60 pregnant women, aged 25 -35 years; it is classified into two groups first one healthy pregnant woman, the second group obese pregnant women. Obese pregnant women are classified according to the following criteria:

- Normal weight when BMI ranges 18.5 - 24.9 Kg/m².
- Overweight when BMI ranges 25 -29.9 Kg/m².
- Obese weight when BMI than 30 Kg/m² \[31\].
Blood samples

Five milliliters of venous blood samples were drawn, and left at room temperature for 15 minutes for clotting, centrifuged 3000 rpm for 5 minutes, then serum was separated and transported for storage. MDA hormone diagnosed by mybiosourse(USA) ELISA human kit, uric acid and CRP diagnosed by mindray(BS-230).

Statistical analysis

Statistical analysis was performed by IBM SPSS statistics, version 23. It was performed by one-way Analysis Of Variance (ANOVA), followed by Least Significant Difference (LSD) at (p ≤ 0.05) significant level.

RESULTS

The concentration of malondialdehyde (MDA) in different trimesters within each group:

First group:

Result revealed that the MDA concentration in the second trimester (3.420 ± 0.608 ng/ml) no significant difference in comparison with first trimester (2.970 ± 0.565 ng/ml).

The MDA concentration in the third trimester (4.150 ± 0.696 ng/ml) increased significantly (p<0.05) in comparison with the first and second trimesters. (Table 1, Figure 1).

Second group:

The MDA concentration in the second trimester (5.000 ± 0.740 ng/ml) have no significant difference in comparison with the first trimester (4.840 ± 0.729 ng/ml).

The MDA concentration in the third trimester (5.470 ± 0.868 ng/ml) have no significant difference in comparison with the first and second trimesters. (Table 1, Figure 1).

The concentration of MDA hormone in similar trimesters within different groups:

First trimester:

Results revealed that the MDA concentration in the first trimester in second group (4.840 ± 0.729 ng/ml) increased significantly (p<0.05) in comparison with the first trimester in first group. (Table 1, Figure 1).

Second trimester:

The MDA concentration in the second trimester in second group (5.000 ± 0.740 ng/ml) increased significantly (p<0.05) in comparison with the second trimester in first group (Table 1, Figure 1).
Third trimester:

The MAD concentration in the third trimester in third group (5.470±0.868 ng/ml) increased significantly (p<0.05) in comparison with the third trimester in first group. (Table 1, Figure 1).

The levels of uric acid in different trimesters within each group:

First group:

Results revealed that the uric acid level in the second trimester (4.169±0.850 mg/dl) increased significantly (p<0.05) in comparison with the first trimester (3.260±0.721 mg/dl).

The uric acid level in the third trimester (4.460±0.793 mg/dl) increased significantly (p<0.05) in comparison with the first trimester, but no significant difference with the second trimester (Table 2, Figure 2).

Second group:

The uric acid level in the second trimester (4.613±0.604 mg/dl) increased significantly (p<0.05) in comparison with the first trimester (3.473±0.690 mg/dl).

The uric acid level in the third trimester (5.008±0.820 mg/dl) increased significantly (p<0.05) in comparison with the first and second trimesters. (Table 2, Figure 2).

The levels of uric acid in similar trimesters within different groups:

First trimester:

The uric acid level in the first trimester in third group (3.473±0.690 mg/dl) have no significant difference in comparison with the first trimester in first group. (Table 2, Figure 2).

Second trimester:

The uric acid level in the second trimester in second group (4.613±0.604 mg/dl) have no significant difference in comparison with the second trimester in first group. (Table 2, Figure 2).

Third trimester:

The uric acid level in the third trimester in second group (5.008±0.820 mg/dl) increased significantly (p<0.05) in comparison with the third trimester in first group. (Table 2, Figure 2).

The levels of C-reactive protein (CRP) in different trimesters within each group:

First group:
Result revealed that the CRP level in the second trimester (9.020±0.468 mg/l) increased significantly (p<0.05) in comparison with the first trimester (5.150±0.117 mg/l).

The CRP level in the third trimester (12.610±0.576 mg/l) increased significantly (p<0.05) in comparison with the first and second trimesters (Table 3, Figure 3).

Second group:

The CRP level in the second trimester (12.850±0.606 mg/l) increased significantly (p<0.05) in comparison with the first trimester (8.700±0.210 mg/l).

The CRP level in the third trimester (18.480±0.880 mg/l) increased significantly (p<0.05) in comparison with the first and second trimesters. (Table 3, Figure 3).

The levels of CRP in similar trimesters within different groups:

First trimester:

The CRP level in the first trimester in second group (8.700±0.210 mg/l) increased significantly (p<0.05) in comparison with the first trimester in first group, but no significant difference with the first trimester in second group. (Table 3, Figure 3).

Second trimester:

The CRP level in the second trimester in second group (12.850±0.606 mg/l) increased significantly (p<0.05) in comparison with the second trimester in first group, and the second trimester in second group. (Table 3, Figure 3).

Third trimester:

The CRP level in the third trimester in second group (18.480±0.880 mg/l) increased significantly (p<0.05) in comparison with the third trimester in first group. (Table 3, Figure 3).

Table 1: The concentration of serum malondialdehyde (MDA) (ng/ml) during different groups and trimesters in pregnant women.

<table>
<thead>
<tr>
<th>Trimester</th>
<th>Group (1)</th>
<th>Group (2)</th>
<th>Group (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>2.970±0.565</td>
<td>3.420±0.608</td>
<td>4.150±0.696</td>
</tr>
</tbody>
</table>

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Table 2: The levels of uric acid (mg/dl) during different groups and trimesters in pregnant women.

<table>
<thead>
<tr>
<th>Trimester</th>
<th>Group (1)</th>
<th>1st</th>
<th>2nd</th>
<th>3rd</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>a 3.260 ±0.721\textsuperscript{A}</td>
<td>a 4.169 ±0.850\textsuperscript{B}</td>
<td>a 4.460 ±0.793\textsuperscript{B}</td>
<td></td>
</tr>
<tr>
<td></td>
<td>a 3.473 ±0.690\textsuperscript{A}</td>
<td>a 4.613 ±0.604\textsuperscript{B}</td>
<td>b 5.008 ± 0.820\textsuperscript{C}</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: The levels of C-reactive protein (CRP) (mg/l) during different groups and trimesters in pregnant women.

<table>
<thead>
<tr>
<th>Trimester</th>
<th>Group (1)</th>
<th>1st</th>
<th>2nd</th>
<th>3rd</th>
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<tbody>
<tr>
<td></td>
<td>a 5.150 ±0.117\textsuperscript{A}</td>
<td>a 9.020 ± 0.468\textsuperscript{B}</td>
<td>a 12.610 ±0.532\textsuperscript{C}</td>
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<tr>
<td></td>
<td>b 8.700 ±0.210\textsuperscript{A}</td>
<td>b 12.850 ±0.532\textsuperscript{B}</td>
<td>b 18.480 ±0.880\textsuperscript{C}</td>
<td></td>
</tr>
</tbody>
</table>

The values represent the mean ± SD.

Similar capital letters represent no significant difference between trimesters.

Different capital letters represent a significant difference (p<0.05) between trimester.

Similar small letters represent no significant difference between groups.

Different small letters represent a significant difference (p<0.05) between groups.
Figure 1: The concentration of serum Malondialdehyde (MDA) (ng/ml) during different groups and trimesters in pregnant women.

Figure 2: The levels of uric acid (mg/dl) during different groups and trimesters in pregnant women.
DISCUSSION

Our results revealed the oxidative stress factor (MDA) increased (non-significantly) during gestation. Generally, many causes behind this increase such as: the elevation of maternal hormones, IR, adipose tissue and uric acid.

Cited by Yüksel and Yiğit (2015) the oxidative stress increases during pregnancy because of the increased oxygen requirements of the placenta, which contains a large number of mitochondria[^57].
Furukawa (2017) showed that the adipose tissues are major sources of reactive oxygen species (ROS), therefore oxidative stress is enhanced in adipose tissue.[58]

Yaseen and Hussein (2017) showed the uric acid levels improved fact, the antioxidant system was stronger than peroxidation during pregnancy, that’s confirm the antioxidant role for uric acid, which is consistent with our results.[59]

MDA concentration was physiologically raised but statically nonsignificant in several trimesters within groups that are in agreement with the study by Mohammad et al. (2018).[60] This increase in the first group occurred through placental lipid production increase with gestation progressive. In the 2nd group MDA non-significant difference between trimesters. Suresh et al. (2010) this study showed MDA did not vary with body mass index.[61]

However, obesity is an independent risk factor for plasma lipid peroxidation in humans, and poor glycemic control is an important factor in generation of protein oxidation, plasma MDA levels were reduced, indicating decreased lipid peroxidation, that’s agreement with many studies [62;63] UA levels increase significantly (p≤0.05) in all trimesters within 2nd groups. But no significant increase in 1st group. The hormonal changes of IR, oxidative stress behind these increase.

Fawzy et al. (2017) showed in 1st trimesters decreased in comparison with others this normal result, increased glomerular filtration rate and decreased re absorption of UA from the renal tubules.[64] Many studies showed that the placenta leads to overproduction of UA which serves as a marker of the disease hyperuricemia may predate proteinuria by several weeks.[65;66]

Jaya and his colleagues (2018) study showed these increase suggesting excessive free radical production evokes a response to combat oxidative stress because different role for uric acid an antioxidant property, our result in oxidative factors confirms that.[67] Johnson et al. (2013) showed obesity was associated with a further increase uric acid secretion and produced by adipose tissue, UA may also induce insulin resistance via effects on adipocytes.[68]

Besides that, Kim and his colleagues (2012), Oliveira and Burini (2012) revealed that the elevation of UA levels associated with fat accumulation, obese adipose tissue is characterized by active fatty acids synthesis, it is presumed that fatty acids synthesis is closely associated with purine synthesis and UA is the final product of purine metabolism, thus, accelerating uric acid production.[69;70] CRP levels increased in all trimesters within all groups. This increase synchronizes with hormones level, insulin resistance and adipose tissue.

Other studies showed that the CRP, is a sensitive marker of the inflammation and a classical acute phase reactant in numerous pathologic conditions, and elevated CRP levels have been associated with abnormal metabolic conditions.[71;72]

Khaleel and his colleagues (2016) showed that the strong association between CRP and elevated BMI, and elevation of insulin hormone and IR may be causes highly level of CRP, moreover, obesity is a shape of persistent low grade inflammation which causes elevated concentrations of CRP.[73]
Clark and his colleagues (2016) found a considerably stronger positive association between BMI class and CRP among females, the reasons for a stronger relationship between BMI and CRP in females are still unknown, but the review offered three possible biological reasons: 1) metabolic activity of adipose tissue may differ by sex; 2) females have higher levels of leptin; and 3) body fat is higher and distributed differently in females [48].

Adabimohazab and his colleagues (2016) showed, in obesity, low-grade systemic inflammation is considered an important step in the pathogenesis of insulin resistance (IR) [50].

In other hand our results revealed the second group increased significantly (p≤0.05) in comparison with the first group because the inflammatory mediators are secreted both from adipose tissue and placenta, therefore the results revealed the third group increased significantly (p≤0.05) in comparison with the second group that’s agreement with other studies [74;75].

CONCLUSION

The results of current study showed clearly that in obese pregnant women, all parameters in the study were elevated during trimesters.

ETHICAL CLEARANCE

The Research Ethical Committee at scientific research by ethical approval of both environmental and health and higher education and scientific research ministries in Iraq.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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REFERENCES


44. Al-ofi, E. A. Implications of inflammation and insulin resistance in obese pregnant women with gestational diabetes: A case study. *SAGE Open Medical Case Reports*, 2019, 7, 2050313X19843737.


47. Franceschi, C., & Campisi, J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences*, 2014, 69(Suppl_1), S4-S9.


52. Shahid, R. *Examination of the Cross-Sectional Association between Insulin Resistance (HOMAIR) and an Inflammatory Marker (CRP) in a Representative Canadian Non-Diabetic Population* (Doctoral dissertation, University of Saskatchewan), 2018.


57. YÜKSEL, S., & YİĞİT, A. A. Malondialdehyde and nitric oxide levels and catalase, superoxide dismutase, and glutathione peroxidase levels in maternal blood during different trimesters of pregnancy and in the cord blood of newborns. *Turkish journal of medical sciences*, 2015, 45(2), 454-459.


