ORIGINAL RESEARCH

DOI: 10.17944/interdiscip.1344660
Interdisciplinary Medical Journal 2023;14(48):164-168.

The effect of obesity on oxidative stress parameters in pregnant women

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Abstract

Objective: In recent years, there has been a growing public concern about obesity, since it is known to reduce fertility in women and increase the duration of conception. Maternal obesity is also related to adverse pregnancy outcomes affected by placental malfunction. Therefore, in this study, we aimed to compare levels of oxidative stress between obese women and women of normal weight in the second trimester.

Method: We assessed lipid peroxidation by measuring the thiobarbituric acid reactive species (TBARS), as well as the antioxidant defense system by measuring the activity of superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (CAT) enzymes in 50 obese women (body mass index, BMI:36.60±4.95) and 51 women of normal weight (BMI:24.51±3.47).

Results: Increased lipid peroxidation and SOD enzyme activity were determined in obese pregnant women when compared to women of normal weight. Also, we found a significantly positive correlation (r:0.286, p:0.0435) between BMI and TBARS level as well as a significantly negative correlation (r: -0.421, p:0.002) between TBARS level and SOD enzyme activity. No significant difference was observed between the two groups in CAT and GPx enzymes activities.

Conclusion: Although increased SOD enzyme activity indicates that the antioxidant defense system is activated to deal with increased production of reactive oxygen species, maternal obesity is induced by oxidative stress via increased lipid peroxidation. Hence, maternal-obesity-induced oxidative stress in the second trimester should be followed up by clinicians since it may cause oxidative damage in the placenta during pregnancy.

Keywords: Antioxidant Defense System, Lipid Peroxidation, Maternal Obesity, Oxidative Stress

INTRODUCTION

Obesity is a serious health concern and is accepted as the fourth most common risk factor for noncommunicable diseases worldwide, after hypertension, dietary risks, and tobacco. According to the World Health Organization Obesity Report (1), nearly 60% of the adult population is either overweight or obese. Unfortunately, the numbers have also shown that the levels of both overweight and obesity in women of childbearing age are also at alarming levels. For instance, almost 70% of women of childbearing age are overweight and 40% are obese in Turkey. Also, a similar tendency has been reported in women of childbearing age in EU countries, including Hungary, Ireland, Portugal, Spain and UK (1). Our knowledge from previous studies is that maternal obesity not only affects mother health but also negatively affects health of the newborn. For instance, it enhances the risk of miscarriage, preeclampsia, gestational diabetes, excessive weight gain, and postpartum hemorrhage

Cite this article: Kocamaz D, Demiray GA, Yildiz SM, Arlier S, Guvenc B. The effect of obesity on oxidative stress parameters in pregnant women. Interdiscip Med J. 2023;14(50):164-168. https://doi.org/10.17944/interdiscip.1344660

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Received: September 7, 2022
Accepted: May 30, 2023

(2,3). Also, it is responsible for an increased risk of neural tube defects, fetal cardiac malformation, and congenital malformation (4-6).

Obesity is related to disturbances in metabolic balance, including lipid metabolism, inflammatory and hormonal processes. However, the etiology of obesity is a highly complex process including genetic, physiologic, psychological, and environmental factors (7). The latest studies have focused on the role of oxidative stress as a key mechanism that may increase the adverse conditions mentioned (8,9). Oxidative stress can be defined as an imbalance between oxidants like reactive oxygen species (ROS) and antioxidants. Reactive oxygen species include superoxide anion, hydroxyl radical, hydrogen peroxide etc. Oxygen-containing metabolites can be generated during normal cellular metabolism, but they are highly reactive and can oxidize macromolecules like lipids, proteins, and DNA (10,11). During pregnancy, mothers face several anatomical, physiological, and metabolic changes in their organisms. For fetal growth and maternal placental tissues, supplemental energy is required. For instance, it has been calculated that a mother needs 80.000 kcal of additional energy for 9 months (12). Therefore, it's known that the susceptibility to oxidative stress increases during pregnancy since the mother's body supports ROS production, especially in the second trimester, due to an increasing basic metabolism and oxygen consumption, as well as the use of fatty acids as a primary energy source for placental tissues (13). However, the placental antioxidant defense system has the ability to reduce the harmful effects of ROS for a healthy pregnancy (12). Bioindicators have become critical due to early diagnosis of several diseases in recent years. Thiobarbituric acid reactive substances (TBARS) are known as lipid peroxidation byproducts, and they are commonly used as one of the indicators of oxidative stress (14). Antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) provide primer protection against ROS, and they are also mostly used as biomarkers to determine the body`s antioxidant status. Superoxide dismutase (SOD) catalyzes superoxide anion dismutation to hydrogen peroxide. Catalase (CAT) and glutathione peroxidase (GPx) catalyze the reduction of hydrogen peroxide to water (15). A few studies have revealed that total antioxidant levels are reduced in obese people, and as a result, oxidative stress is induced (16). It is also reported that excessive ROS production has adverse effects, including miscarriages, premature births, and malformations during pregnancy (13). On the other hand, some studies have shown that total antioxidant status is increased in the second trimester of pregnancy (12).

In light of these facts, it's important to use oxidative stress parameters as a routine laboratory test to reduce or take precautions against unexpected situations such as preeclampsia and miscarriage. The effect of obesity on oxidative stress is not fully elucidated during pregnancy; thus, in this study, we investigated the relationship between lipid peroxidation, antioxidant enzymes and body mass index to understand the role of overweight on oxidative stress during pregnancy.

METHOD

After the approval Local Ethics Committee (2018-82), women of normal weight (n:51) as a control group and obese women (n:50) who were in the second trimester of pregnancy were included in this study (Table 1). To find out whether obesity on its own is an independent risk factor for oxidative stress, subjects with a history of smoking, regular drug use, previous miscarriage and other diseases such as diabetes and hypertension were excluded. The body mass index (BMI) for each subject was calculated as weight divided by height squared and was used to assess obesity. Women whose BMI was higher than 30 kg/m^2 BMI were evaluated as obese. Venus blood samples (3 mL) from women were collected into EDTA tubes. Erythrocytes were washed with NaCl after centrifugation. Then, hemolysates, which are added with tris/HCl (20 mM, pH 8.0) were stored at -80 ^{0}C until analysis.

Table 1. Characteristics of the study population

	Control	Obese
Number	51	50
Age (years)	27.059±4.483	29.680±3.381
Gestation weeks	23.275±1.898	22.840±1.730
BMI	24.510±3.477	36.60±4.955*

BMI: Body mass index (kg/m^2). Asterisks indicate a significant difference between the control and obese groups ($p \leq 0.05$).

Biochemical Analysis

Lipid peroxidation (TBARS) analysis was determined by the method of Wills and Wilkinson (17), which measures thiobarbituric acid reagents and thiobarbituric acid (TBA) in aerobic conditions at 100 ^{0}C to give a pink-colored complex at 535 nm. Superoxide dismutase enzyme activity was analyzed indirectly by the method of McCord and Fridovich (18), which contained the inhibition of cytochrome c reduction at 550 nm. Firstly, 1.87 mU/mL xanthine oxidase was added to the medium containing 50 mM phosphate buffer, 0.1 mM EDTA, 10 mM cytochrome c, 0.05 mM hypoxanthine and the supernatant. Catalase enzyme activity was measured by the method of Aebi (19), which observes the reduction of absorbance due to hydrogen peroxide (H_2O_2) consumption at 240 nm for 1 min. The reaction was started after adding 20 µL of supernatant into the medium, including 75 mM phosphate buffer /pH 7.4) and 25 mM H_2O_2. Glutathione peroxidase enzyme activity was analyzed according to nicotinamide adenine dinucleotide phosphate (NADPH) reduction at 340

nm (ε = 6.22 µmol/cm2) for 1 min (20).

Statistical Analysis

The Kolmogorov-Smirnov test was conducted to determine the data normality, and Levene`s test was performed to control variance homogeneity among groups. Unpaired T test was performed to determine differences between groups (p≤0.05 considered significant). Pearson correlation analysis was conducted to calculate the correlation between biochemical analysis and BMI. All statistical analyses were performed using GraphPad Prism 9.0 software. All data were represented as the mean value ± standard deviation (SD). For estimating the sample power (1-β err prob) of the analyses, we first calculated the effect size (Cohen's d) for the respective T-test. Then, a power analysis was performed with Cohen's d and the sample size of each group using G*Power 3.1.7.

RESULTS

TBARS level was found to be significantly higher in the obese group than the control group (p≤0.001; 1-β err prob=0.912), (Figure 1). Also, SOD activity was found to be higher in the obese group when compared to the control (p≤0.0001; 1-β err prob=1.00), (Figure 2). However, no significant difference was detected for CAT and GPx activities between the control and obese groups (p≤0.05; 1-β err prob=0.798 for CAT; 0.697 for GPx). A Pearson correlation analysis in the obese group revealed a positive correlation between BMI and TBARS level (r: 0.286; p:0.0435) as well as a strong negative correlation between TBARS level and SOD activity (r: -0.421; p: 0.002), (Table 2).

Table 2. Correlation analysis between BMI and biochemical parameters in obese group

	BMI	TBARS	SOD	CAT	GPx
TBARS	r:0.2867 p:0.0435*	1	r: -0.4215 p: 0.0023*	r: 0.05249 p:0.717	r: 0.06187 p:0.821
SOD	r:0.0875 p:0.545	r: -0.4215 p: 0.0023*	1	r: 0.01665 p:0.9086	r: 0.02201 p: 0.8013
CAT	r: 0.01025 p: 0.9437	r: 0.05249 p:0.717	r: 0.01665 p:0.9086	1	r: 0.04309 p:0.638
GPx	r:0.01221 p:0.8752	r: 0.06187 p:0.821	r: 0.02201 p: 0.8013	r: 0.04309 p:0.638	1

BMI: Body mass index (kg/m²), TBARS: Thiobarbituric acid reactive substances (nmol/mg protein) SOD: Superoxide dismutase (U/mg protein) CAT: Catalase (µmol H_2O_2/mg protein/minute), GPx: Glutathione peroxidase (µmol/mg protein/minute) (p≤0.05). Asterisks indicate a significant difference between BMI and biochemical parameters (p≤0.05).

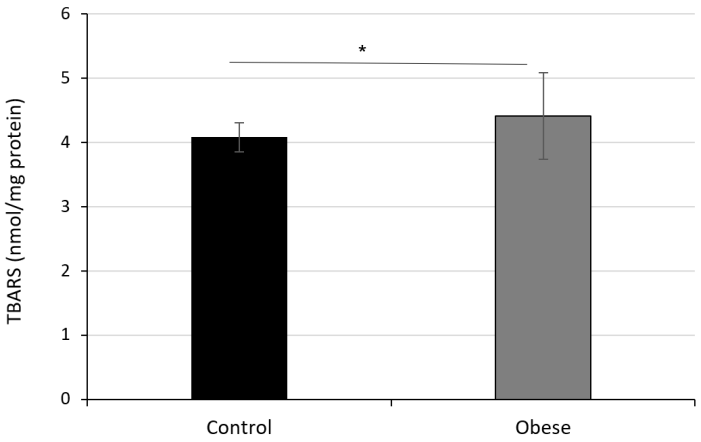

Figure 1: TBARS levels (nmol/mg protein) in the control and obese groups. Asterisks indicate a significant difference between the control and obese groups (p≤0.05).

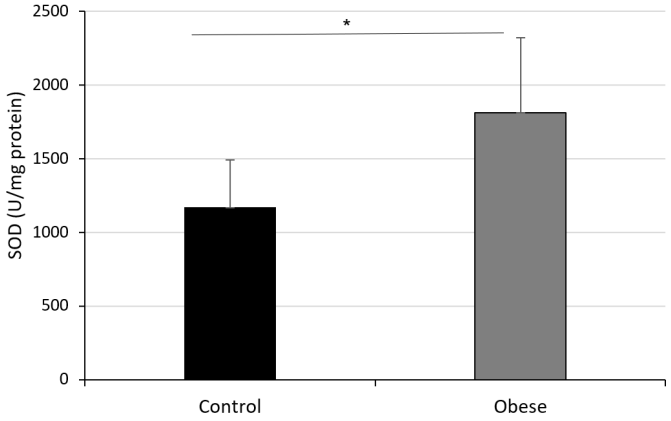

Figure 2: SOD activity (U/mg protein) in the control and obese groups. Asterisks indicate a significant difference between the control and obese groups (p≤0.05)

DISCUSSION

As we mentioned in the Introduction, the susceptibility to oxidative stress increases during pregnancy due to increased metabolic activity of the placenta and decreased antioxidant capacity, which are related to placental dysfunction. Dividing placental cells causes an increase in the production of ROS such as superoxide anion, which is a byproduct of aerobic respiration by the mitochondrial electron transport chain (21). Therefore, it is accepted by researchers that normal pregnancy is also a state close to the limit at which oxidative stress may alter to pathology (22). On the other hand, our knowledge from previous studies is that oxidative stress markers such as lipid peroxidation are increased in obese, non-pregnant women (23,24). However, the relationship between maternal obesity and placental oxidative stress is not fully clear. Adipose tissue in obesity has been recognized as a key underlying factor in several metabolic diseases (25). Previous studies have declared that the antioxidant defense

system is activated via upregulation of antioxidant enzymes to prevent oxidative damage in tissues in the early stages of obesity, but as fat accumulation increases, the antioxidant defense system is suppressed, and oxidative stress occurs (9). In normal conditions, there is a common belief that placental oxidative stress happens after 10 weeks of gestation due to high intervillous oxygen tension and contact between the fetal circulation and uterine spiral arteries (26). Thus, we have selected the second trimester of pregnancy to compare oxidative stress parameters in obese and pregnant women of normal weight. We found that TBARS levels, a byproduct of lipid peroxidation, are increased in obese pregnant women when compared to women of normal weight. Similar results were also reported in previous studies (27,28). For instance, Alanis et al. (22) have shown that maternal oxidative stress was found to be 31% higher in the obese group compared to the control group. In this study, we also determined a significantly positive correlation between BMI and TBARS levels in obese women, which is also in accordance with previous findings (28). The data of this experiment support the hypothesis that obesity promotes the induction of lipid peroxidation and suggest that increased lipid peroxidation can induce the production of ROS and oxidative stress.

On the other hand, in this study, antioxidant SOD enzyme activity in obese group was found to be significantly higher than in the control group. Similar findings were reported in the animal studies. For instance, SOD enzyme activity was increased in rats with diet-induced obesity (29). Also, we determined a significantly negative correlation between TBARS and SOD levels in obese women. However, no significant difference was observed for CAT and GPx activities in both groups. Amirkhizi et al. (30) have shown an inverse relationship between BMI and SOD activity in obese pregnant women. They mentioned that maternal obesity did not induce CAT enzyme activity. According to our results, despite the elevated SOD activity, increased TBARS levels in obese pregnant women suggest that elevated SOD enzyme activity alone is not adequate to protect placental lipids against oxidation.

Limitations of the Study

The study includes various limitations, such as a lack of results from other trimesters in comparison with the second trimester, as well as a lack of understanding of how maternal obesity affects oxidative stress parameters in newborns. Despite all these limitations, we believe that this study will help clinicians to take precautions to protect the health of obese pregnant women and their newborns.

CONCLUSION

In conclusion, results showed that maternal obesity is related to oxidative stress. This may be due to 1) the failure of the upregulation of antioxidant defense system, which may be affected by the duration of obesity, or 2) an increased availability of polyunsaturated lipids in the placenta, which triggers oxidative damage via lipid peroxidation. Therefore, maternal obesity-induced oxidative stress in the second trimester should be followed up by clinicians since it may cause oxidative damage in the placenta during pregnancy and affect newborns.

ACKNOWLEDGEMENT

Peer-Review

Both externally and internally peer reviewed.

Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article.

Financical Support

This study was funded by Cukurova University with the project number 2019/11291.

Ethical Declaration

Ethical permission was obtained from the Cukurova University, Medical Faculty Clinical / Human Research Ethics Committee for this study with date 2018 and number 82, and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: DK, SMY, Design: DK, SA, GAD, Supervising: DK, BG, SMY, Financing and equipment: DK, SA, GAD, SMY, Data collection and entry: DK, GAD, SMY, SA, Analysis and interpretation: DK, BG, SMY, GAD, Literature search: SA, GAD, Writing: DK, SMY, BG, Critical review: BG, SMY

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