Online ISSN: 2588-3526

Journal of Wildlife and Biodiversity

Volume 7 (Special Issue): 403-414 (2023) (http://www.wildlife-biodiversity.com/)

Research Article

Study of the level of C-reactive protein and some oxidative stress markers in pregnant and aborted women in the first trimester of pregnancy

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Received: 20 August 2023 / Revised: 26 September 2023 / Accepted: 29 October 2023/ Published online: 28 November 2023.

How to cite: Al–Dulymi, H.J., Oubeid, W., Ali, I. (2023). Study of the level of C-reactive protein and some oxidative stress markers in pregnant and aborted women in the first trimester of pregnancy, Journal of Wildlife and Biodiversity, 7 (Special Issue), 403-414**. DOI**: https://doi.org/10.5281/zenodo.10246400

Abstract

Miscarriage is a term that refers to the loss of a pregnancy before twenty weeks of the fetus's lifespan. This leads to complications and psychological disorders for the aborted woman. Studies are continuing to find out the reasons that lead to miscarriage. To identify the effect of the levels of (CRP), (SOD), (GSH), and (MDA) on pregnancy and miscarriage in the first trimester of pregnancy, the study was conducted in the gynaecology department and maternity hall at Salah al-Din General Hospital / Tikrit City / Salah al-Din Governorate for the period between: "October 2022 to March 2023". The study included 90 samples, 20 samples for the control group the same for the pregnancy group and 50 samples for the abortion group, half is for the one-time miscarriage group and the other half for the recurrent miscarriage group. In this study, we explored the biochemical markers of oxidative stress in various pregnancy-related conditions. Our research focused on assessing the concentrations of C-reactive protein (CRP), Superoxide Dismutase (SOD), Glutathione (GSH), and Malondialdehyde (MDA) in different groups: pregnant women, women with a history of one miscarriage, and women with repeated miscarriages, comparing these to a control group. Our findings revealed that CRP levels showed a notable escalation in groups with pregnancy, one-time miscarriage, and repeated miscarriages, indicating a highly significant difference ($P \leq 0.05$) in each case. This pattern suggests a progressive increase in CRP concentration across these groups. Conversely, SOD concentrations did not display significant differences across the groups studied, including the control group, at the $P \leq 0.05$ level. This indicates that SOD levels remained relatively stable across different pregnancy conditions. In terms of GSH levels, we observed a highly significant variation ($P \leq 0.05$). The pregnant group

showed a non-significant increase in GSH compared to the control group. However, both the one-time miscarriage and repeated miscarriage groups exhibited a significant decrease in GSH levels when compared to the control group. Lastly, the analysis of MDA concentrations revealed significant differences ($P \leq 0.05$) across the groups. Each of the pregnancy, one-time miscarriage, and repeated miscarriage groups registered a notable decrease in MDA levels in comparison to the control group. This study thus contributes important insights into the oxidative stress markers in various pregnancy-related conditions, highlighting the role and variation of CRP, SOD, GSH, and MDA in these scenarios.

Keywords: C-reactive protein, superoxide dismutase, glutathione, malonedi aldehyde, abortion

Introduction

Miscarriage is defined as the loss of a fetus before it becomes able to live and grow independently outside the uterine (Quenby et al., 2021). Nearly 80% of miscarriages occur before 12 weeks of pregnancy, which is considered a spontaneous miscarriage. Recently, miscarriage has become one of the most serious adverse pregnancy outcomes as it occurs early (Gynecologists, 2018). The uterine lining secretes a large number of cytokines and a group of regulatory factors for growth and differentiation. It has been found that cytokines have an effect not only on the cells of the lining and their preparation for the implantation process but also on the trophoblast cells surrounding the embryo (Lessey & Young, 2019).

Oxidants, key players in the process of oxidative stress, exert their effects through two primary mechanisms. Firstly, they can generate reactive oxygen species (ROS), a group of free radicals including hydrogen peroxide, hydroxyl radical, hydroxyl ion, peroxide, singlet oxygen, and superoxide anion. These ROS are often produced as by-products of various biological processes, according to a study by (Sotler et al., 2019). Secondly, oxidants can induce oxidative stress by inhibiting antioxidants, which are crucial for neutralizing free radicals and protecting cells from damage. The presence and activity of reactive oxygen species have far-reaching implications for cellular health and function. ROS can catalyze the oxidation of proteins and lipids, as mentioned in the research by (Memar et al., 2018). This oxidative modification can alter the structure and function of these vital biomolecules, potentially leading to various pathological conditions. Furthermore, as highlighted in the study by (Yang et al., 2021), ROS can also inflict damage on nucleic acids. This damage to DNA and RNA is particularly concerning, as it can lead to mutations and genomic instability, contributing to the development of diseases, including cancer.

Thus, understanding the dual role of oxidants in generating ROS and inhibiting antioxidants provides critical insight into the mechanisms underlying oxidative stress and its impact on biological systems. Lipid peroxidation represents a crucial process in cellular damage and is intimately linked with the activity of reactive oxygen species (ROS). As elucidated in the study by (Su et al., 2019), lipid peroxides are compounds formed when ROS react with lipids in cell membranes. This reaction is not merely a passive occurrence; lipid peroxides have the ability to self-propagate the oxidative process, leading to extensive cell membrane damage and, ultimately, cell death. This mechanism underscores the deleterious effects of oxidative stress at a cellular level, particularly in the context of various diseases and pathological conditions.

Turning to C-reactive protein (CRP), it is a pentameric protein synthesized primarily in the liver. Its levels in the bloodstream rise in response to inflammation, serving as a biomarker for inflammatory conditions. This relationship between CRP levels and inflammation is well-established in numerous studies. Furthermore, there is a noted correlation between obesity, particularly central obesity, and inflammation. Central obesity, as defined in the research by (Asgari et al., 2023), refers to the excessive accumulation of fat in the abdominal area and its surroundings. This specific distribution of body fat is particularly concerning due to its association with various metabolic and cardiovascular disorders. The underlying cause of central obesity is an imbalance between energy intake and expenditure. This form of obesity is not just a matter of excess body weight but is intricately linked with systemic inflammation, thereby potentially influencing CRP levels and contributing to the risk of related health issues.

These insights into lipid peroxidation and the role of CRP in inflammation, especially in the context of obesity, highlight the interconnected nature of metabolic processes, oxidative stress, and inflammation in human health. Superoxide Dismutase (SOD) holds a vital position in the cellular defense system against oxidative stress. As the primary detoxification enzyme, SOD stands out as one of the most potent antioxidants within the cell. Its fundamental role, as highlighted in the study by (Jefferies et al., 2003), is to act as a critical component of the cell's first line of defense against reactive oxygen species (ROS). SOD achieves this by catalyzing the dismutation of two molecules of the superoxide anion into hydrogen peroxide (H2O2) and molecular oxygen (O2). This reaction is crucial as it transforms the superoxide anion, a potentially harmful ROS, into less dangerous substances. Through this mechanism, SOD plays a significant role in mitigating oxidative damage and maintaining cellular health. In parallel, glutathione, a tripeptide of low molecular weight, is another key player in the cellular defense against oxidative

stress. Present in both plants and animals, glutathione is of immense physiological importance. Its primary function lies in its ability to act as a major antioxidant, directly neutralizing free radicals and reactive molecules, thereby preventing their harmful effects on cellular components. The presence and activity of glutathione in various organisms underscore its universal significance in maintaining redox balance and protecting cells from oxidative damage.

Both SOD and glutathione exemplify the complex and efficient antioxidant systems that have evolved in living organisms to counteract the deleterious effects of ROS. Their roles in detoxifying harmful reactive species and maintaining cellular integrity are fundamental to understanding the broader context of oxidative stress and its implications for health and disease. The status and concentration of glutathione in the body is an essential biomarker and therapeutic target for many chronic and age-related diseases. It has been suggested that glutathione levels in humans can be improved by consuming fruits and vegetables that contain glutathione or amino acids that aid in glutathione synthesis (Minich & Brown, 2019). Malondialdehyde (MDA) is widely recognized as a critical biomarker in the field of oxidative stress research. As (Grune & Berger, 2007; Nawrocka-Rutkowska et al., 2022) have noted, MDA is the end product of the oxidative degradation of polyunsaturated fatty acids, making it a frequent measure in studies assessing oxidative stress. This degradation is a result of radical-initiated reactions, particularly within the context of chronic oxidative stress. The significance of MDA extends beyond being a mere by-product of lipid peroxidation. It is also indicative of broader cellular damage. Studies, including those by (Marrocco et al., 2017; Mohammadi, 2019), have emphasized the utility of MDA and other oxidative stress biomarkers in evaluating the risk of various diseases. These biomarkers can provide insights into the extent of oxidation and its pathological implications. Moreover, recent research, such as the work of (Enechukwu et al., 2019), has shed light on the role of MDA in reflecting damage to cell membranes and DNA. MDA is one of the products released during lipid peroxidation involving unsaturated fatty acids and is influenced by the action of hydroxyl radicals. The increase in MDA levels, particularly in the blood, is indicative of heightened lipid peroxidation and consequent damage to cellular structures, including cell membranes and genetic material. Given these properties, MDA serves as a valuable tool in assessing the effectiveness of antioxidant treatments. As (Nawrocka-Rutkowska et al., 2022) suggest, the measurement of MDA levels can be instrumental in evaluating the efficacy of interventions aimed at mitigating oxidative damage. This makes MDA not only a marker of oxidative stress but also a potential indicator of the success of antioxidant therapies in reducing cellular damage and improving health outcomes.

Materials and Methods

The current study was conducted for women attending in the gynecology department and the maternity ward at Salah al-Din General Hospital in the city of Tikrit / Salah al-Din Governorate, where samples collection lasted from 10/15/2022 and continued until 3/15/2023, as it included collecting a Blood sample from each patient of the studied groups, in addition to the information obtained according to the questionnaire. As for the women's groups, they were distributed into four groups and within a specific age group between (25-38) years, as follows:

1. Control group: 20 married women, not pregnant, and in the ovulation phase of the menstrual cycle, in addition to being free of diseases such as (diabetes and high blood pressure).
2. Pregnant group: 20 women who are characterized as being pregnant with their first child within the first trimester of pregnancy and who do not have a history of previous miscarriage, in addition to being free of diseases such as (diabetes and high blood pressure).
3. One-time abortion group: 25 women characterized by having had a miscarriage during the first trimester of pregnancy, in addition to being free of diseases such as (diabetes and high blood pressure).
4. Recurrent miscarriage group: Recurrent miscarriage group 25 women characterized by having suffered recurrent miscarriage two or more times during the first trimester of pregnancy, in addition to being free of diseases such as (diabetes and high blood pressure).

C-Reactive Protein (CRP) concentration:

The concentration of C-Reactive Protein was estimated using an analysis kit "ELISA kit used the sandwich system – ELISA" produced by the Chinese company Sun long, according to its steps and working principle.

Superoxide dismutase (SOD)

The concentration of (SOD) enzyme activity was estimated using the modified method, the photochemical Nitroblue Tetrazolum (NBT). This method included the use of sodium cyanide as an inhibitor of the peroxidase enzyme. This method relies on estimating the activity of the (SOD) enzyme indirectly through the appearance of a change in the optical density of the formalin formed. From the O2 reduction of (NBT) dye, which in turn is generated from irradiation of blood serum (Brown & Goldstein, 1983), as a decrease in the optical density of formalin is an indication of an increase in the activity of the (SOD) enzyme (Zhang et al., 2016).

Glutathione (GSH) estemation

The principle: The level of glutathione in blood serum was measured using the Ell man reagent method.

Malondialdehyde estimation

The estimation technique for Malondialdehyde, a critical endpoint in the lipid peroxidation chain, employs the revised version of the Thiobarbituric Acid (TBA) reaction, a methodology referenced by (Guidet & Shah, 1989). This particular approach is centered around the measurement of MDA, a key indicator of lipid peroxidation. The fundamental aspect of this method lies in the specific interaction that occurs between lipid peroxides, predominantly malondialdehyde, and TBA, within an environment characterized by acidic pH levels. The process hinges on the chemical reaction between these components, crucially influenced by the acidic conditions.

Statistical analysis

The statistical evaluation of our findings was conducted under the framework of a Completely Randomized Design (CRD). This approach was essential to ascertain the presence of any statistically significant variations among the different groups concerning the parameters under investigation. We employed the Analysis of Variance (ANOVA) test for the statistical analysis of the gathered data. This analysis was carried out using the SAS software, version 2010, specifically utilizing its Data Analysis feature. In instances where significant differences were identified, we further compared the means using the Least Significant Difference (LSD) test. This comparison was made at a probability threshold of $P \leq 0.05$ to establish the significance of the observed differences.

Results and Discussion

The current study showed that the concentration of (CRP) gave a high significant effect at the level ($P \leq 0.05$), In the study, it was observed that both the pregnancy group and the group with a history of one-time abortion exhibited increases in certain parameters; however, these increases were not statistically significant when compared to the control group. On the other hand, the group with repeated miscarriages showed a statistically significant increase in these parameters compared to the control group. Furthermore, among all the groups, the recurrent miscarriage group demonstrated the most pronounced increase, significantly surpassing not only the control group but also the other groups under study (Table 1).

Table 1. The effect of the levels of (CRP), (SOD), (GSH), and (MDA) on pregnancy and miscarriage in the first trimester of pregnancy.

Groups	M±SD MDA µMOL/ L	GSH µMOL / L M±SD	SOD Per ml M±SD	CRP ng/ ml M±SD
Control(20)	55.438±1.598 [a]	10.479 ± 0.110 [a]	5.379 ± 0.202 [a]	9.827±0.457 [b]
Pregnant (20)	30.120±5.573 [b]	10.501± 0.044 [a]	5.149 ± 0.283 [a]	10.956±0.425 [b]
Abortion for one time (25)	27.756±1.125 [b]	9.499 ± 0.442 [b]	5.253 ± 0.327 [a]	11.940±0.452 [b]
Recurrent abortion(25)	24.102±3.383 [b]	9.745 ± 0.081 [b]	4.844 ± 0.293 [a]	14.737±1.640 [a]
P-Valu	0.0293	0.0040	0.5762	0.0021

When groups are marked with identical letters, it indicates a lack of significant variance between them. On the other hand, if the groups are denoted with distinct letters, this signifies that the differences between them are statistically significant, particularly at a level where the probability value is equal to or less than 0.05.

The study presented by (Nikbakht et al., 2020) indicated the presence of CRP at the beginning of pregnancy and that the inflammatory process may be present from the beginning of pregnancy, which leads to the occurrence of pregnancy complications. This study was consistent with the current study through the results it presented, but it was contrary to the opinion of the study presented by (Bakalis et al., 2012) that the level of CRP at the beginning of pregnancy has no relationship to pregnancy complications. The study presented by (Komsa-Penkova et al., 2022). The level of (CRP) in the one-time abortion group was similar to its level in the control group, which is not in agreement with the current study. (Ahmed et al., 2015) indicated that cases of recurrent miscarriage are linked to high levels of (CRP) in the mother's- blood, and thus this study is consistent with the results of the current study regarding the recurrent miscarriage group. C-reactive protein (CRP) is a protein with a phase Acute is made in liver cells and other tissue cells such as Trophoblasts and is considered an indicator of a state of systemic inflammation.

The increase in its levels is explained by the fact that it is associated with an inflammatory condition that occurs in the body, such as cancer, asthma, type 2 diabetes, sickle cell anemia, cardiovascular diseases, and also in cases of adverse pregnancy. This explains the results stated in the current study, and that the successful implantation that occurs in the fertilized egg is an indicator of a high level of (CRP), and perhaps also one of the reasons for its rise at the beginning of pregnancy due to (IL-6) produced by activated macrophages and monocytes, as these

macrophages are in addition to Natural killer cells, which are mainly composed of the interaction between the trophoblast and the mother's immune system Which is an important source of (IL-6) and high levels of (CRP), as exposure to chemicals such as Bisphenol and parabens, which have various effects on disrupting the functioning of the endocrine glands, and these substances are related to an increase in the level of pro-inflammatory biomarkers such as (CRP) (IL-6) which leads to pregnancy complications such as miscarriage (Ahmed et al., 2015).

In this study, the impact of SOD (Superoxide Dismutase) concentration did not show a statistically significant difference at the $P \leq 0.05$ level. Both the pregnancy group and the group with a single-time abortion exhibited a minor, yet statistically insignificant, reduction in SOD levels compared to the control group. Similarly, the group with repeated miscarriages showed a decrease in SOD levels, but this too was not statistically significant when compared with the control group. This contrasts with findings from a 2019 study by (Khan et al., 2019), which noted a significant decrease in SOD levels in the pregnancy group relative to their control group. While both studies observed a decline in SOD levels, the difference lies in the statistical significance of this decrease.

(Hameed, 2012) found that the group with a single-time abortion exhibited a reduction in their measurements compared to the control group, aligning with the findings of the current study. In contrast, the study by (M Saleem & A SALIH, 2017) reported that the group with recurrent miscarriages showed a significant decrease in SOD (Superoxide Dismutase) concentration when compared to the control group's results.

Thus, it is somewhat consistent with the results stated in the current study In terms of decline, but it differs in significance, (SOD) is an antioxidant that defends the body against the superoxide anion that destroys the tissues of the living body. It is capable of disrupting free radicals in the body, whose activity leads to an imbalance in the physiological state of the body and the emergence of many complications, especially during pregnancy, including high blood pressure and preeclampsia. The decrease in (SOD) leads to an increase in the rates of conversion of enzymes that inhibit free radicals in order to remove the oxidative stress that results from the increase in fat peroxides in pregnant women and thus reduce the resulting damage (Zych et al., 2022).

The current study suggests that the absence of increased lipid peroxides and thus the lack of oxidative stress, particularly in the groups in the first trimester of pregnancy and miscarriage, might be due to the absence of heightened fetal metabolic processes that typically lead to oxidative stress. It also revealed that the GSH (Glutathione) levels exhibited highly significant differences at the $P \leq 0.05$ level. The pregnancy group showed a minor, non-significant rise in GSH levels

compared to the control group. Both the groups with a single-time miscarriage and repeated miscarriages recorded a significant decline in GSH levels compared to the control group.

This finding contrasts with the results from the 2016 study by (Ramiro-Cortijo et al., 2016), which observed a significant decrease in antioxidants, including GSH, in the pregnant group. They linked this decrease in early pregnancy to potential subsequent pregnancy complications, differing from the current study's findings. Similarly, the (Hameed, 2012) reported an increase in GSH levels for the single-time abortion group compared to the control group, which also does not align with the current study.

Zachara et al., (2001) study mirrored the results reported by (Hameed, 2012), observing an increase in GSH levels in the single-time abortion group compared to the control group, again differing from the current study's findings. In contrast, the study by (AL-Hamdani & Al-Helaly, 2023) noted a significant decrease in GSH levels in the recurrent miscarriage group when compared to the control group, which is in agreement with the results of the current study.

Glutathione, a significant non-protein substance in mammal cells, plays a crucial role in detoxifying and providing antioxidant defense against both external and internal substances, thereby helping to regulate cellular oxidation levels. It's found in sulfur-rich foods like cauliflower, cabbage, garlic, onions, and whey, and is a vital antioxidant that safeguards cells against oxidative damage. Moreover, it's essential in keeping the redox state in balance and aids in repairing fats, proteins, and nucleic acids during peroxidation. According to (Ra et al., 2023), a notable observation was the impact of MDA concentration, showing a marked decrease in groups with single or recurrent miscarriages compared to the control group, at a statistically significant level ($P \leq 0.05$).

Contrastingly, previous studies by (Ghneim & Alshebly, 2016; Ilhan et al., 2002; Mushouh et al., 2023), showed a rise in MDA levels in pregnant women, contradicting the current study's findings. (Torkzahrani et al., 2019) research also reported an increased MDA concentration in women who had a single miscarriage, which doesn't align with the recent findings. (Ghneim & Alshebly, 2016) found similar results in the recurrent miscarriage group. MDA, an indicator of lipid peroxidation, reflects the oxidative stress levels in the body, which are crucial in female fertility and related physiological disturbances in pregnancy and childbirth. MDA is a more prominent marker of oxidative stress due to lipid peroxidation, linked to pregnancy, where expectant mothers experience oxidative stress from accumulated lipid peroxides. This stress is particularly evident during the initial phase of pregnancy when the placenta, connecting mother and fetus, has a

reduced oxygen environment. As pregnancy progresses, especially after the first trimester, the placenta's metabolic activities and the need for antioxidant enzymes increase to support fetal development, as noted by (Holland et al., 2017).

Conclusion

It has been concluded that the presence of (CRP) is linked to the presence of inflammation in the body, where the greater the inflammatory state, the higher the percentage of (CRP) in the blood, which leads to pregnancy complication the most dangerous of which is abortion. When the levels of (GSH) and (SOD) decrease in the blood, it leads to a state of oxidative stress, which is linked to many female reproductive diseases that lead to pregnancy complications such as miscarriage. As for the levels of (MDA), it is a sign of the presence of lipid peroxidation as well as an indicator of the effectiveness of treatment with antioxidants, and both cases are linked to pregnancy complications and miscarriage.

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