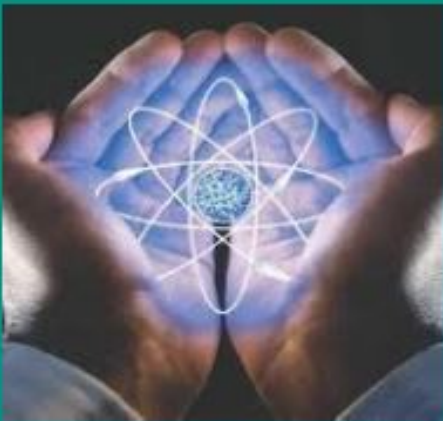


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## **Evaluation of Oxytocin Level and Its Relationship With Oxidant-Antioxidant Status in Women With Polycystic Ovarian Syndrome**

*Evaluasi Tingkat Oksitosin dan Hubungannya dengan Status Oksidan-Antioksidan pada Wanita dengan Sindrom Ovarium Polikistik (SOPK)*

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### **Abstract**

Polycystic Ovarian Syndrome (PCOS) is a prevalent endocrine disorder associated with infertility in a substantial number of women globally. This study aimed to investigate the potential role of oxytocin (OXT) in PCOS pathogenesis and its implications for oxidative stress. A cohort of 120 females, comprising 60 PCOS patients and 60 healthy controls, aged between 25 and 31, was examined. Serum concentrations of OXT, superoxide dismutase (SOD), and myeloperoxidase (MPO) were measured. The results revealed significantly decreased OXT levels in PCOS patients compared to controls ( $p < 0.001$ ). Additionally, PCOS patients exhibited elevated MPO levels and reduced SOD levels, suggesting increased oxidative stress. Furthermore, a positive correlation between OXT and SOD and a negative correlation between OXT and MPO were observed within the PCOS group. These findings highlight the potential of OXT as a diagnostic tool and predictor of ovarian response and treatment success in PCOS, emphasizing the need to target oxytocin for mitigating oxidative stress in this complex endocrine disorder.

#### **Highlights:**

- **Oxytocin Deficiency:** This study identifies significantly reduced oxytocin levels in PCOS patients, shedding light on its potential role in the disorder's pathogenesis.
- **Oxidative Stress Imbalance:** PCOS patients displayed an imbalance in oxidative

stress markers, with elevated myeloperoxidase and reduced superoxide dismutase levels, indicating increased oxidative stress.

- **Diagnostic and Therapeutic Implications:** Oxytocin emerges as a promising diagnostic tool and predictor of ovarian response and treatment success in PCOS, emphasizing its potential as a therapeutic target to mitigate oxidative stress in this complex endocrine disorder.

**Keywords:** PCOS,Oxytocin,Oxidative Stress,Infertility,Diagnostic Tool

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## Introduction

Hyperandrogenism, polycystic ovary morphology, and irregular menstrual periods are the main features of the disorder known as polycystic ovarian syndrome (PCOS). Women who are of childbearing age experience it frequently [1]. Between 5% and 21% of people worldwide have this condition [2]. Despite the fact that the Pathological causes are unknown, disturbance of oxidant processes and an increase in inflammatory mediators are believed to be the cause [1,3,4].

After a number of changes and the exclusion of other endocrinopathies, the Rotterdam criteria, which contain two of the three following characteristics—oligomenorrhea, hyperandrogenism (clinical or biochemical), and polycystic ovary on ultrasound—were decided upon [5]. Atypical follicular growth is a characteristic of PCOS, which is frequently present along with insulin resistance (IR), compensatory hyperinsulinemia, hyperandrogenism, and low-grade inflammation [6].

The activation, survival, development, and selection of follicles can be adversely affected in PCOS patients by alterations in the hormonal signals in the follicles, insulin resistance, increased blood sugar, and androgen elevation. These effects cause the development of polycystic construction, the accumulation of small follicles near the ovary, damage to the development of follicles, and the lack of anovulation. The majority of PCOS patients are overweight, have abdominal obesity, or are obese. Obesity can lead to an increase in the number of PCOS-related problems, including anovulatory issues, hyperandrogenism, insulin resistance, and inflammation [7, 8]. As such, With the increase in the severity of the imbalances aforementioned, the amount of lipogenesis increases, and lipid catabolism decreases. PCOS is closely associated with obesity, hyperinsulinemia, and peripheral insulin resistance [9,10,11].

Increased secretion of LH, which is released from the anterior pituitary, is most likely the cause of anovulation and increased testosterone levels in these individuals [12,13]. These cells facilitate the production of androgens like testosterone and androstenedione. There would be a lower amount of follicular stimulation, which is associated with LH, this would prevent the ovarian granulosa cells from converting androgens to estrogens. The volume of estrogen and the number of eggs would decrease as a consequence [13,14].

Oxytocin (OT) is a nanopeptide that is produced in the Paraventricular Nuclei of the Hypothalamus and is transported to the posterior pituitary by the axons of the cells. It functions as a neurotransmitter and neuromodulator as well as a hormone. In obstetrics, the OT is primarily employed to hasten or initiate labor, because it is a powerful uterine contraction inducer [15,49]. Other cells that contain oxytocin have been observed, these include the corpus luteum, placenta, and Leydig cells in the testis [8]. These cells are all associated with the reproductive system. Because it decreases the desire to eat and decreases the fear, anxiety, and despair associated with it, oxytocin has been considered a potential treatment for diseases of the psychiatric nature of autism and borderline personality disorders [16]. Other than its traditional duties, OT participates in multiple metabolic pathways as a means of anti-inflammatory, anti-apoptotic, anti-stress, and antioxidant [17,18, 49]. Other research demonstrated that the oxytocin nasal spray increased the metabolism of triglycerides, decreased the weight of the person, and improved the profile of glucose and insulin. Additionally, it reduces body weight [19].

Creating and cleaning up Reactive oxygen/ nitrogen species (ROS/RNS) excessively, which results in stress-induced oxidative stress (OS) [20]. Cells [24, 25], proteins [22, 23], and lipids [21] can all be adversely affected by a buildup of ROS in the body that is too large. The radical hydroxyl (OH), as well as the singlet oxygen ( $1/2 O_2$ ), are both part of the oxygenated compounds in ROS that are free radicals and non-free radicals. Other components of OS include iron, copper, sulfur, and reactive nitrogen [26, 27]. Unpaired electrons are present in the external orbit of free radicals, these radicals are considered to be autonomous entities [27, 28]. It's possible to categorize substances employed to assess the oxidative status according to the chemical components affected by reactive oxygen in general. Transcription factors, chemical compounds that inhibit the generation of ROS and enzymes that consume the radical are all part of the same system that controls the production of ROS.

It's difficult to adequately describe the OS state with the same biomarkers in multiple diseases, however, because of the distinct roles that OS typically plays in different diseases and the way it activates different pathways in different diseases, this is possible [23, 29-32]. As a result, there are few biomarkers that can be used to assess the degree of OS in a particular setting.

It is not possible to distinguish between OS and inflammation because they usually coexist [29]. A large number of studies have shown the close relationship between OS and androgen levels, and this explains why patients with PCOS suffer from hyperandrogenism. [34, 35].

antioxidant, which is a term for compounds, that are usually involved in defending against oxidative stress. They include non-enzymatic compounds such as GSH, thioredoxin, thiols, vitamin C, vitamin A, and vitamin E, as well as enzymatic compounds like catalase peroxidase, and paraoxonase [36]. SOD, on the other hand, is responsible for converting oxygen into  $H_2O_2$  [33].

Chronic inflammation has been associated with PCOS, a condition that specifically affects women. Studies indicate



that women with PCOS exhibit increased levels of inflammatory markers, indicating potential involvement of inflammation in the onset of the condition. The development of PCOS-associated inflammation is believed to be influenced by various factors, such as obesity, insulin resistance, and elevated androgen hormone levels. Patients with PCOS [39-41] may experience inflammation, which can contribute to the development of other conditions like diabetes, heart disease, and hypertension [37, 38]. This inflammation is not unique to PCOS but is instead a contributing factor.

MPO is more prevalent in individuals with obesity than in controls [30]. In patients with PCOS and insulin resistance, the levels of MPO are even higher [42]. This means that regardless of their hormonal levels, BMI, and other factors that make them susceptible, individuals with PCOS are likely to experience inflammation associated with the condition [43].

In multiple studies, it has been consistently noted that women with PCOS frequently experience oxidative stress (OS). These studies have found that indicators of substances that are capable of causing oxidation are significantly higher in PCOS patients compared to those who are healthy. It is believed that this may be a potential cause of PCOS [24]. The SOD family of metalloenzymes plays a role in mitigating the harmful effects of superoxide radicals, reducing their toxicity. By dismutating the O<sub>2</sub>-ion, these antioxidant enzymes generate O<sub>2</sub> and H<sub>2</sub>O<sub>2</sub> [44]. When the antioxidant enzymes are unable to shield against oxidative damage, the destruction of lipids is initiated by oxygen free radicals in the cell and organelle membranes [45-47]. In order to assess the serum levels of oxytocin, this investigation examined infertile women with PCOS and non-PCOS. Additionally, they studied the correlation between oxytocin levels and chemical mediators associated with oxidant-antioxidant balance.

## Method

Individuals with neoplasms or thyroid issues, or who had recently used insulin sensitizers, oral contraceptives, antiandrogens, corticosteroids, or other hormones, were not included in the investigation. The investigation also excluded those with elevated prolactin or congenital adrenal overgrowth. To begin, the levels of hormone (OXT) and indicators of oxidative stress - MPO and SOD - were measured in the serum. Blood samples were taken from each participant and evaluated for hormonal content and blood properties before being centrifuged at 3,000 revolutions for 10 minutes. The collected serum was then stored at -20 degrees Celsius until it was needed.

Using the Competitive ELISA technology, the kits were utilized to determine the serum OXT activity of all groups.

Using the MPO ELISA kit from Bioassay Technology in China, the quantification of serum MPO activity was performed using the ELISA method.

The immunosorbent used for quantifying the serum SOD activity was the SOD ELISA kit (Bioassay Technology, China) using the ELISA method.

### Statistical evaluation

Data were analyzed using Microsoft Excel 2010 and software version 23.0 for Windows. The findings were presented with mean  $\pm$  SD, and the probability was expressed with a one-way ANOVA. P values less than 0.05 were considered significant for comparing the parameters of the different study groups. The strength between two variables can be determined by utilizing the Pearson correlation coefficient (r), which takes on values of +1 or -1. The relationship between each patient's various parameters was assessed using the person's correlation coefficient (r)..

## Result and Discussion

### Result

In the current investigation, 120 women are involved, which are split into two groups according to the methodology.

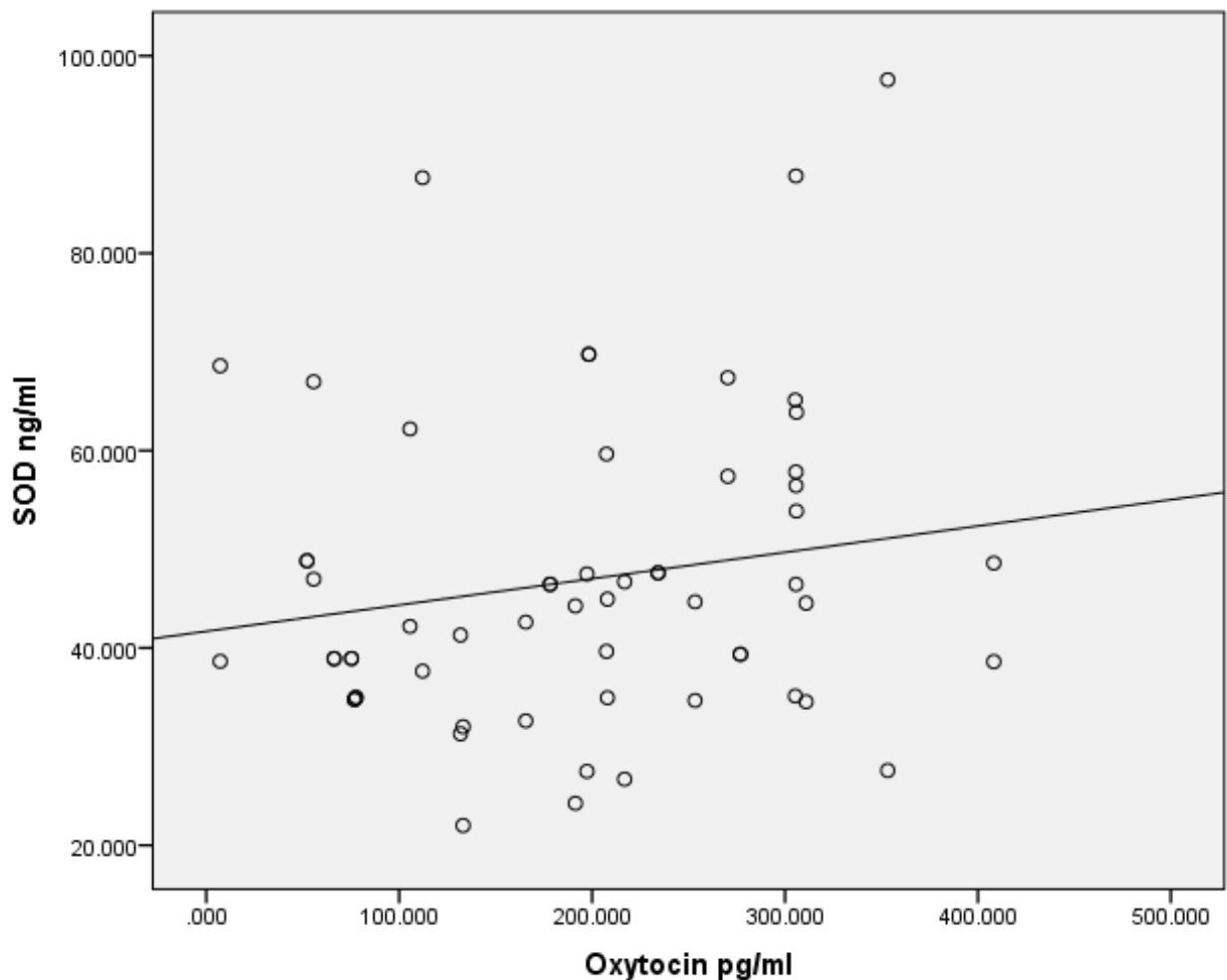
		N	Mean	Std. Deviation	Sig.
BMI (kg/m <sup>2</sup> )	PCOS	60	25.162	3.304	0.00140
	Control	60	22.682	4.855	
	Total	120	23.922	4.318	
Age(years)	PCOS	60	26.367	3.231	0.27837
	Control	60	27.150	4.539	
	Total	120	26.758	3.943	
Gravidity	PCOS	60	0.583	0.720	0.00032

	Control	60	2.050	1.692	
	Total	120	1.317	1.489	
Duration of infertility (years)	PCOS	60	2.917	1.369	0.00092
	Control	60	0.000	0.000	
	Total	120	1.458	1.753	

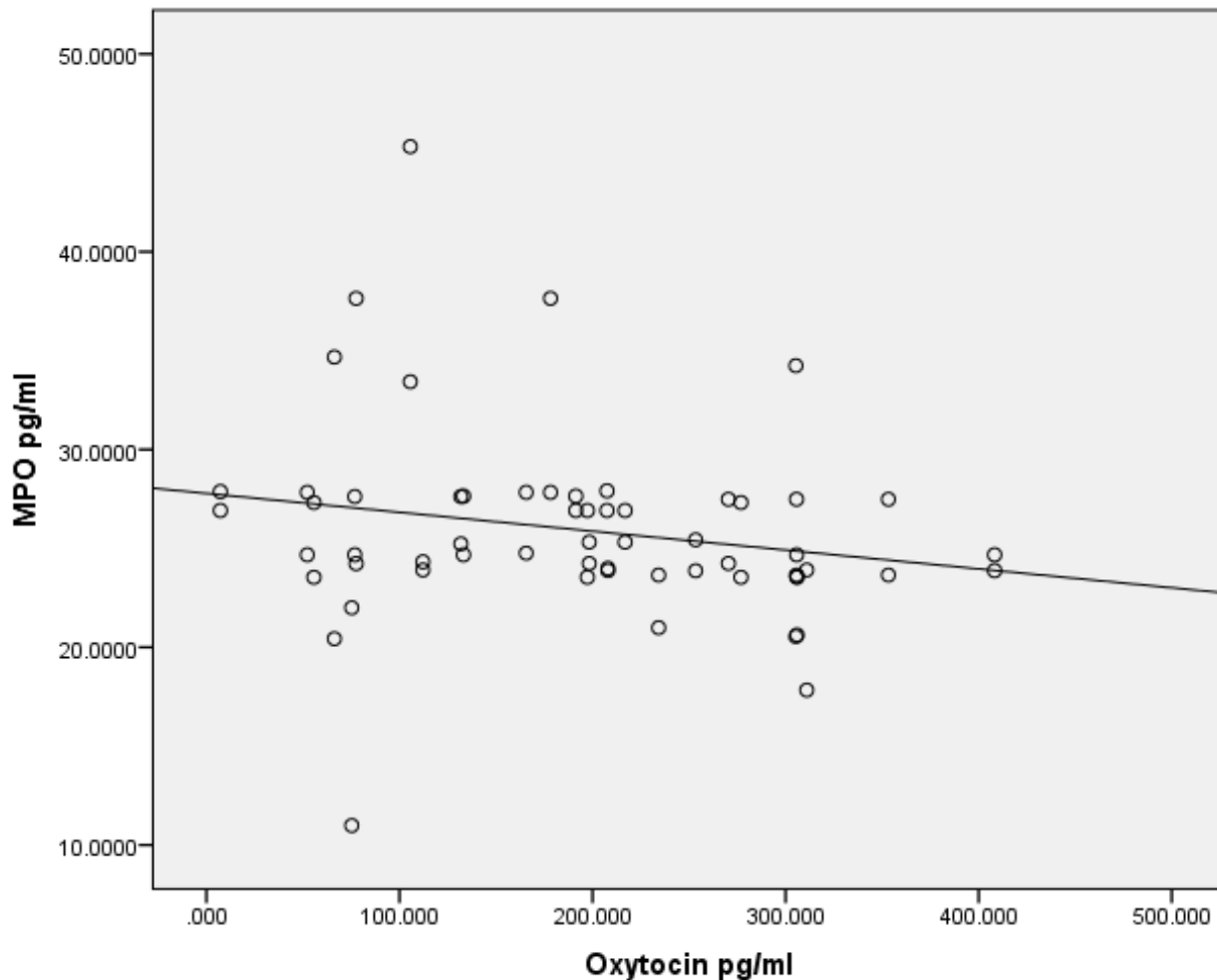
**Table 1.** Describes The Singular Attributes of Every Collective

	G	N	Mean	Std. Deviation	P.V
Oxytocin pg /ml	PCOS	60	194.88	42.26	0.000
	Control	60	324.51	60.47	
SOD ng/ml	PCOS	60	65.82	11.17	0.000
	Control	60	47.00	12.80	
MPO pg /ml	PCOS	60	23.60	8.89	0.000
	Control	60	2.35	0.97	

**Table 2.** Levels of OXT, MPO & SOD For Two Study Groups



**Figure 1.** Serum OXT in PCOS patients was positively correlated with SOD, and the correlation coefficient was ( $r=0.17$ )



**Figure 2.** There was a negative correlation between serum OXT and MPO in the PCOS patient group, and the correlation coefficient was ( $r = -0.20$ )

Table1: Demographic characteristics such as age, BMI, pregnancy, parity, and duration of infertility are displayed for all groups. The mean age ( $\pm$ SD) of the PCOS group was ( $26.367 \pm 3.231$  years), while that of the control group was ( $27.150 \pm 4.539$  years). The age difference between the PCOS group and the control group was not significant. The mean BMI ( $\pm$ SD) of the PCOS group was ( $25.162 \pm 3.304$ ), while that of the control group was ( $22.682 \pm 4.855$ ). Pregnancy values were significantly lower in women with PCOS compared to controls.

Table 2: Means ( $\pm$  SD) of plasma levels of oxytocin, MPO, and SOD in the two groups are shown. The average OXT value of the PCOS group was ( $194.88 \pm 42.26$ pg/ml), and the average OXT value of the control group was ( $324.51 \pm 60.47$ pg/ml). Compared with the PCOS group, the plasma OXT level was reduced in the control group, which was very significant. The mean MPO value of the PCOS group ( $23.60 \pm 8.89$  ng/ml) was the same as that of the control group ( $2.35 \pm 0.97$  ng/ml). The mean SOD value of PCOS group and control group was ( $65.82 \pm 11.17$ ng/ml) and control group ( $47.00 \pm 12.80$ ng/ml).

**Discussion**

Commonly, the main cause of anovulation is PCOS, a condition that presents with diverse symptoms. The complex pathophysiology and various factors can be attributed to this. A significant reduction in oxytocin levels was discovered in this study. Oxytocin, a neuropeptide, is produced by the supraoptic and paraventricular nuclei of the hypothalamus. It is released through the electrical activity of hypothalamic cells [50]. A clinical pregnancy can potentially be achieved with the increase in follicle growth due to the concentration of oxytocin in the brain being 1000 times higher than in the surrounding tissues. Interestingly, following the treatment of individuals, a small number of studies have shown this [48,49].

Our findings, which corroborate those of research by Jahromi et al. [31], revealed that PCOS women had considerably lower mean oxytocin levels. PCOS patients are classified as type 2 normogonadotropics by the World Health Organization for prolonged anovulation [51]. They have a dysfunctional hypothalamic-pituitary-ovarian

(HPO) axis, which results in hormonal abnormalities. The reduced amounts of oxytocin found in PCOS are likely related to this issue. Therefore, it's probable that chronic anovulation's pathophysiology also involves reduced oxytocin synthesis from the posterior hypophysis.

A deviation from the hypothalamus-pituitary-gonadal system and other influencing mechanisms results in a change in oxytocin concentration. It has been observed in separate studies that stimuli like fear, stress, and various psychological and social pressures can cause an increase in hormone levels in both the central and peripheral nervous systems [52].

The timely detection and prevention of PCOS could be aided by the early identification of oxidative stress levels. Therefore, this study aimed to assess any correlations between the characteristics of PCOS and the diagnostic potential of MPO and SOD levels in serum, thus understanding the unknown processes surrounding oxidative stress mechanisms in this condition.

Oxidative stress (OS) is caused by the uneven (production/Removal) of reactive oxygen and nitrogen species (ROS and RNS), creating an imbalance [53]. Excessive ROS can have a negative impact on cells [24, 25], proteins, and lipids [54]. A mixture of oxygenated molecules, including the radical hydroxyl ( $\bullet\text{OH}$ ), the singlet oxygen ( $1/2 \text{O}_2$ ), the superoxide ( $\text{O}_2\bullet^-$ ), and the hydrogen peroxide ( $\text{H}_2\text{O}_2$ ), make up the ROS group, some being free radicals and others not. Exist on their own, and possess unpaired electrons in the outer orbital are free radicals [27, 28]. Additional elements found in the OS include nitrogen, iron, copper, and sulfur [26, 27].

The study focused on MPO, a key enzyme associated with oxidative stress in leukocytes, and its association with PCOS. In our latest study, we made an interesting observation that MPO levels were increased in the leukocytes of PCOS patients compared to controls. These results are consistent with the work of Ribeiro et al. They also found elevated levels of MPO in PCOS patients [43]. MPO is produced by activated leukocyte granules as a defense mechanism against infection by generating ROS [56]. Interestingly, endothelial injury seems likely to occur [55].

In addition, vessel walls may experience oxidative stress from the oxidation of MPO released by activated leukocytes. These leukocytes continuously produce ROS and can even adhere and remain on the vessel wall for a long time [57]. This leads to increased endothelial damage.

In the examined research, a significant distinction was discovered in the average serum SOD activity comparing the PCOS group to the control group ( $p < 0.001$ ). The findings coincided with the study conducted by Zhang et al. [58]. The decline in SOD activity overall is likely due to the consumption of SOD as a response to the heightened generation of ROS prompted by hyperglycemia and excessive levels of free fatty acids. Additionally, PCOS-related OS has been linked to the rise of the pro-inflammatory state, ultimately increasing the likelihood of various comorbidities. These include abdominal obesity, endothelial dysfunction, dyslipidemia, hyperandrogenism, higher insulin levels, and insulin resistance [59, 60].

Various methods have been evolved by the human body to hinder the accumulation of detrimental molecules that are caused by oxidative damage. In this process, antioxidants have a vital function as they safeguard organisms from oxidative stress. An important role is also played by the SOD enzyme in counteracting the harmful outcomes of ROS. It is the first step in the defense against ROS and works by transforming the superoxide anion into hydrogen peroxide. (61-63).

## Conclusion

Overall, the study demonstrated that PCOS patients had lower levels of oxytocin in their blood, higher rates of oxygen production due to the elevated serum level of MPO, and lower concentrations of SOD. Ultimately, we advise accurately evaluating the function of oxytocin as a PCOS diagnosis tool as well as a predictor of ovarian response and treatment success.

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