Mediterranean Journal of Pharmacy & Pharmaceutical Sciences
ISSN: 2789-1895 online
www.medjpps.com
doi: 10.5281/zenodo.00000000
ISSN: 2958-3101 print

ORIGINAL RESEARCH article

Estradiol hormone and oxidative stress markers in women with polycystic ovary syndrome

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Received: 03-05-2026, **Accepted**: 27-07-2026, **Published online:** 00-00-2026

HOW TO CITE THIS

AL-Hamdani AH. Estradiol hormone and oxidative stress markers in women with polycystic ovary syndrome. Mediterr J Pharm Pharm Sci. 2026; 6(3): 16-21. [Article number: 257]. https://doi.org/10.5281/zenodo.0000000

Keywords: Estradiol, glutathione, malondialdehyde, peroxynitrite, polycystic ovary syndrome, oxidative stress

Abstract: Polycystic ovary syndrome (PCOS) is a multifaceted metabolic and endocrine disorder affecting the female reproductive stage, characterized by infertility, anovulation, polycystic ovaries, insulin resistance, and obesity. Neuroendocrine alterations, genetics, lifestyle, and environmental pollutants are among the danger issues that contribute to PCOS in women. Hence, this study aimed to evaluate estradiol hormone (E2 and explore the grade of oxidative stress status in PCOS patients by measuring oxidant/antioxidant markers (Malondialdehyde MDA, peroxynitrite $ONOO^-$, and Glutathione GSH) in their sera. The current study included 96 women consists of 40 healthy volunteers, fertile women without PCOS, as the control group, and 56 PCOS patients who were divided into subcategories according to their BMI and age. In this study, a significant elevation of estradiol E2 and oxidant markers MDA and ONOO-) was observed among PCOS patients in contrast with non-PCOS, whereas the antioxidant marker GSH was decreased in PCOS patients. The effect of BMI within PCOS patients showed a significant elevation of E2 and oxidant biomarkers in obese PCOS, while GSH showed a significant decline as compared to non-obese PCOS. The outcomes show that the levels of E2, MDA, and ONOO- are significantly elevated with increasing age; however, GSH significantly drops.

Introduction

Polycystic ovary syndrome (PCOS) is a predominant fertility complaint [1, 2] affecting about 10.0% of middle-aged females internationally [3]. Meanwhile its first reported by Stein and Leventhal in 1935, and PCOS was identified as Stein-Leventhal syndrome [4]. Diagnosis is directed according to the Rotterdam standards: hyperandrogenism, oligoanovulation, and polycystic ovaries [5, 6]. Symptoms may be metabolic (i.e., obesity, type 2 diabetes, cardiovascular illness, dyslipidemia, hypertension, and sleep apnea), reproductive (irregular menstrual cycles, infertility, endometrial cancer, and gravidity problems), psychological (anxiety, depression, eating disorders, and poor quality of life), and dermatological (hirsutism and acne) [6-8]. Cumulative evidence proposes that oxidative stress (OS) contributes to its reproductive and metabolic complications [9].

Estradiol-E2 is a gender steroid hormone that plays an important role in male and female fertility and fitness. It is mainly formed by the female's ovary; however, minor quantities are similarly manufactured in the adrenal glands and, throughout pregnancy, via the placenta. In males, estradiol is made in lesser amounts by the testes

and adrenal glands [10]. There are four different types of estrogen: estrone (E1), estradiol (E2), estriol (E3), and estetrol (E4). Estradiol (E2) is the most powerful and abundant estrogen throughout a woman's fertile years [11]. They play a dominant part in many biological developments, mainly in the female fertility system [12]. It is vital for modifying the menstrual cycle, promoting fertility system improvement, and supporting cardiovascular and bone health [13].

Imbalance between oxidants and antioxidants is related to the production of extreme quantities of reactive oxygen species (ROS) and the ability of antioxidants in the body to protect against the harmful effects of ROS [14]. Too much ROS causes harm to DNA, lipids, and proteins, contributing to loss of cellular functions [15]. This may lead to abnormal conditions in the reproductive system, including endometriosis, preeclampsia, infertility, and recurrent abortion [16, 17]. OS plays an essential part in the pathogenesis of long-lasting illnesses such as cancer, cardiovascular diseases, diabetes, and neurodegenerative illnesses. Long exposure to high concentrations of pro-oxidant factors may lead to organizational abnormality at a mitochondrial DNA level, in addition to functional modification of numerous cellular structures and enzymes, leading to anomalies in gene expression [18, 19]. OS and Inflammation have been connected to the pathological disorder of PCOS [1].

Materials and methods

This study involves 96 women of reproductive age (21 - 40 years). 56 women with PCOS and forty same ages non PCOS, as the control group, with normal ovulating cycles (no history of infertility or hormone disorders), contributed to this work. Females with additional fertility complaints affecting productivity, like Cushing's syndrome, diabetes mellitus, hyperprolactinemia, and thyroid disease, in addition to pregnant women, were excluded from this study. PCOS female separated according to body mass index (BMI): obese PCOS females had a BMI $\geq$ 25 kg/m^2, and non-obese PCOS females had a BMI < 25 kg/m^2. BMI is calculated by the formula [20]. Furthermore, PCOS patients were grouped by age into two main age categories (younger fertility age = 21 - 30 years, and older fertility age = 31 - 40 years). Disposable syringes and needles were used for collection approximately five millimeters of venous blood from all women in early follicular phase from menstrual cycle (two or three days from the onset menstruation), immediately transferred into a non-heparinized gel separator tube, then incubated at 37 °C for ten minutes to form a coagulation in the sample before being centrifuged for 15 min at 3000 rpm to ensure separation of blood serum. The separated blood sera were used for assessments of estradiol hormone and oxidative stress markers (MDA, $ONOO^-$, and GSH). Estradiol-E_2 level was assessed using ELFA (enzyme-linked fluorescence assay). The level of malondialdehyde was estimated by an improved method described by Muslih and others [21], using the thiobarbituric acid (TBA) method to quantify malondialdehyde (MDA). Vanuffelene et al. [23] established an altered method for assessing $ONOO^-$ concentration [22]. Finally, GSH concentration levels in sera were checked using the dithiobisnitrobenzoic acid (DTNB) method.

Ethical approval: The reference code for the approval is PREC-26-1-52. Date: 6, 2026. The ethical committee of the University of Mosul, College of Pharmacy, Mosul, Iraq (pharmacy.ethics@uomosul.edu.iq**)**.

Statistical analysis: A statistical t-test was used for analysis the data in this study. The results were expressed as means with standard deviations (SD). A significance level of $p \leq 0.05$ [24].

Results

In this study, the compares of the mean values of estradiol and oxidative stress markers between women with and without PCOS as presented in **Table 1**, the outcomes revealed that a significantly elevation of sera E2, MDA, and $ONOO^-$ levels associated with PCOS (60.09 ±0 8.77), (7.11 ± 1.43) and (69.7 ± 14.1) respectively compared to

women without PCOS (54.90 ± 10.2), (6.42 ± 0.974) and (60.9 ± 19.0) respectively. Conversely, a significant reduction of GSH in PCOS women (5.815 ± 0.985) in contrast to non-PCOS (6.41 ± 1.24) was observed.

According to the effect of BMI on estradiol and oxidative stress markers within PCOS group; as exposed in **Table 2**; the E2 and MDA, $ONOO^-$ levels showed a significant higher in obese PCOS (62.68 ± 8.03), (7.53 ± 1.18), and (73.8 ± 11.6) respectively than those of non-obese PCOS (56.64 ± 8.67), (6.56 ± 1.57), and (64.3 ± 15.3) respectively whereas GSH showed a significant reduction (5.528 ± 0.957) in comparable with non-obese PCOS (6.199 ± 0.904). **Table 3** established the effect of age on estradiol and oxidative stress status within PCOS women. The results showed that the levels of E2, MDA, and $ONOO^-$ are significantly elevated with increasing age; however, the antioxidant GSH decreased significantly.

Table 1: Estradiol and oxidative stress markers in PCOS and control groups

Parameters	Mean ± S.D.		t-value	P value
	Control group (n = 40)	PCOS group (n = 56)		
Estradiol (pg/ml)	54.90 ± 10.2	60.09 ± 8.77	- 2.67	0.0089
MDA (µmol/L)	6.42 ± 0.974	7.11 ± 1.43	- 2.65	0.0093
$ONOO^-$ (µmol/L)	60.9 ± 19.0	69.7 ± 14.1	- 2.62	0.01
GSH (µmol/L)	6.41 ± 1.24	5.815 ± 0.985	2.62	0.01

Table 2: Effect of BMI on estradiol and oxidative stress markers in the PCOS group

Parameters	Mean ± S.D.		t-value	P value
	Obese PCOS (n = 32)	Non PCOS (n = 24)		
Estradiol (pg/ml)	62.68 ± 8.03	56.64 ± 8.67	2.69	0.0095
MDA (µmol/L)	7.53 ± 1.18	6.56 ± 1.57	2.66	0.01
$ONOO^-$ (µmol/L)	73.8 ± 11.6	64.3 ± 15.3	2.66	0.01
GSH (µmol/L)	5.528 ± 0.957	6.199 ± 0.904	- 2.66	0.01

Table 3: Effect of age on estradiol and oxidative stress markers in the PCOS group

Parameters	Mean ± S.D.		t-value	P value
	Younger PCOS (n = 27)	Elderly PCOS (n = 29)		
Estradiol (pg/ml)	57.07 ± 9.04	62.91 ± 7.61	- 2.62	0.011
MDA (µmol/L)	6.62 ± 1.50	7.57 ± 1.22	- 2.59	0.012
$ONOO^-$ (µmol/L)	65.0 ± 14.6	74.1 ± 12.2	- 2.52	0.015
GSH (µmol/L)	6.159 ± 0.964	5.495 ± 0.908	2.66	0.010

Discussion

The present work focused on assessing blood serum estradiol (E2 and oxidative stress markers in female have and without PCOS, which revealed a significant elevation of E2, MDA, and ONOO- in PCOS women, while GSH showed a significant decline. MDA is a biomarker of OS, an end product of lipid peroxidation. It is a highly reactive product formed by the oxidation of polyunsaturated fatty acids (PUFAs) [25]. Peroxynitrite (ONOO-) is one of the most powerful biological nitrosative causes and has been implicated in various pathologies; it is formed when nitric oxide and superoxide combine [26]. OS state is mainly triggered by both internal metabolic processes and external lifestyle, environmental, and toxic metals exposures [27, 28]. Mitochondrial dysfunction, enzymatic

oxidative systems, and inflammatory cell engagement are the key biological causes of ROS in PCOS, and they all contribute to the growth of oxidative injury in numerous tissue compartments [29]. These findings are consistent with Sabuncu et al. [30], Almasoodi [31], and Callard and others [32], which prove that E2 is a key that encourages the growth of the endometrium and prepares it for the embedding of the embryo. If E2 levels are elevated in females with PCOS, these levels may be unbalanced, leading to irregular growth of the endometrium and an increased risk of endometrial hyperplasia, which is consistent with our results that showed raised E2 levels in PCOS women. PCOS is characterized by hyperandrogenism, and visceral and hepatic adipose tissue are the sites of additional gonadal aromatization of sex hormones caused by the activity of aromatase. This enzyme catalyzes the conversion of androgens to estrogens [33]. One of the chief mechanisms producing OS in PCOS is mitochondrial dysfunction and decreased ATP synthesis [34]. Likewise, a high androgen concentration boosts the manufacture of ROS, which deteriorates mitochondrial damage and additional oxidative injury [35, 36]. In PCOS, estrogens, particularly estradiol, have antioxidant and anti-inflammatory properties [37]. E2, which owns a phenolic hydroxyl group, has real antioxidant activity and prevents lipid peroxidation in model membranes. Antioxidant properties of E2 have been proposed for the prevention of oxidation of LDL, an important phase in atherogenesis [38-41]. Furthermore, GSH is a non-enzymatic antioxidant that acts to detoxify H2O2 in human cells by giving an electron and is changed to the oxidized form (GSSG) [42]. The effect of BMI and age in women with PCOS highlights a significant elevation of serum estradiol, MDA, and ONOO- in obese women with PCOS compared to non-obese women with PCOS, while GSH was decreased. Similar results were observed in elderly PCOS women compared with younger PCOS women. These findings are in agreement with Uçkan et al. [43] and Fatima et al. [44].

Conclusion: Oxidative stress has detrimentally influence on human health, which is widely recognized as a central player in the pathophysiology of PCOS. It creates a state of imbalance between harmful ROS creation and the body's ability to counteract them, which directly disrupts ovarian function. Moreover, BMI and age play a crucial role in oxidative stress status and contribute to it within PCOS.

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Acknowledgments: The author would like to thank the University of Mosul, College of Pharmacy, for the great assistance in completing this study.
Conflict of interest: The author declares the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
Ethical issues: The author completely observed ethical issues, including plagiarism, informed consent, data fabrication or falsification, and double publication or submission.
Data availability statement: The raw data that support the findings of this article are available from the corresponding author upon reasonable request.
Author declarations: The author confirms that they have followed all relevant ethical guidelines and obtained any necessary IRB and/or ethics committee approvals.
Generative AI disclosure: No Generative AI was used in the preparation of this manuscript.