HAYATI
Journal of Biosciences

Vol. 32 No. 6, November 2025 1447-1452
DOI:10.4308/hjb.32.6.1447-1452
ISSN: 1978-3019
EISSN: 2086-4094

Research Article

Check for updates

OPEN ACCESS

The Potential Role of The Nuclear Factor Erythroid 2–Related Factor 2 Depletion on Gonadotropin-Releasing Hormone Imbalance in Polycystic Ovarian Syndrome Iraqi Patients

Zaman N. Hameed[1*], Rashied M. Rashied[1], Sawsan M. Kareem[2]

[1]*Department of Biology, University of Anbar, Al-Anbar, Iraq*
[2]*Department of Biology, Mustansiriyah University, Baghdad, Iraq*

ARTICLE INFO

Article history:
Received February 13, 2025
Received in revised form March 21, 2025
Accepted July 7, 2025
Available Online July 29, 2025

KEYWORDS:
GnRh imbalance,
Nrf2 depletion,
PCOS

Copyright (c) 2025@ author(s).

ABSTRACT

The nuclear factor erythroid 2-related factor 2 (Nrf2) is a master regulator of most cytoprotective genes that respond to oxidative stresses. Thus, Nrf2 depletion is usually associated with excessive oxidative stress (OS). We sought to assess Nrf2 concentration as an indicator of elevated OS in women with PCOS. Likewise, study the effects associated with this depletion on the balance of gonadotropin-releasing hormone (GnRH). The case-control study comprised ninety women of reproductive age. Our results revealed that women with PCOS had significantly higher blood Nrf2 depletion compared with the non-PCOS group (P = 0.000). So, there was a significant increase in both Luteinizing hormone (LH) concentration and LH\FSH ratio (P = 0.000 and P = 0.007, respectively. In the PCOS group, Nrf2 depletion was adversely correlated with elevated LH level (-0.551) at (P = 0.012), and elevated LH\FSH ratio (-0.628) at (P = 0.003), infertility (-0.460) at (p = 0.041) and menstrual irregularity (-0.575) at (P = 0.008). Meantime, according to the odds ratio analysis, Nrf2 depletion had a high relative risk in the etiology of syndrome 0.967 (0.932–0.945) at (P = 0.048). In conclusion, Nrf2 depletion had a role in the GnRH imbalance in PCOS through several mechanisms. Thus, we can suggest that enhancing the Nrf2 pathway can be a possible therapeutic approach for PCOS treatment.

1. Introduction

Nrf2 is a master transcriptional regulator that controls the production of antioxidant proteins to fend against oxidative stress (OS) damage. The excessive production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) which known as OS can oxidize specific cysteine residues in Keap1, changing the protein's structure leading to Nrf2 releasing, which finally translocation to the cell nucleus, through the activation of the antioxidant response element ARE in the nucleus (Chełchowska *et al.* 2023). It participates in the transcriptional regulation of many antioxidant genes, including superoxide dismutase, catalase, and heme oxygenase-1 (Lőrincz *et al.* 2024).

Polycystic ovarian syndrome (PCOS) is one of the metabolic diseases related to the endocrine glands. It is characterized by the presence of multiple cysts on the ovaries, irregular or absent menstrual periods, and high levels of male hormones (androgens) (Witchel *et al.* 2019). Other symptoms may include weight gain, acne, and excess hair growth on the face and body (hairsutism) (Goodman *et al.* 2015). Nrf2 depletion usually accompanies elevated OS in the body (Zeber-Lubecka *et al.* 2023).

Many different mechanisms explain PCOS etiology caused by GnRH imbalance, one of which is the presence of a defect in the hypothalamic-pituitary axis, leading to increased imbalance impulses of secretion of luteinizing hormone LH (Laven *et al.* 2002).

The excessive secretion of the luteinizing hormone LH from the anterior pituitary gland can cause increased

* Corresponding Author
E-mail Address: zam21s1016@uoanbar.edu.iq

ovarian sensitization to this stimulation, which may reduce the level of sex hormones associated with globulin, which leads to an increase in androgens (Strauss 2003).

Abnormalities in the neuroendocrine system, such as increased pulse frequency of GnRH, which stimulates the pituitary to produce excessive luteinizing hormone rather than follicle-stimulating hormone, are observed in women with PCOS (Dong & Rees 2023). Excess LH concentration enhances ovarian androgen production, whereas a deficiency in FSH hinders follicular growth. The imbalance in LH: FSH induces proliferation of ovarian theca cells, resulting in increased steroidogenesis and, eventually, hyperandrogenism in PCOS women (Ashraf *et al.* 2019).

Recently studies revealed that elevated oxidative stress had been detected in PCOS (Rudnicka *et al.* 2022). These studies suggest that an imbalance of antioxidants and ROS in follicular fluid may impact ovum quality (Hameed *et al.* 2025), leading to irregular ovulation and infertility in PCOS patients (Uçkan *et al.* 2022). So, elevated oxidative stress may cause GnRH imbalance which contributes in some way to infertility disorders (Agarwal *et al.* 2012) including polycystic ovaries (Zeber-Lubecka *et al.* 2023).

2. Materials and Methods

2.1. Samples Characterization

Women of reproductive age who had been documented as PCOS patients according to the 2003 Rotterdam Criteria (Fauser *et al.* 2004), were chosen for a case-control study that took place between December 2023 and May 2024. Samples were collected from Ramadi Women's and Children's Teaching Hospital. The criteria mentioned that women with hyperandrogenism, ovulatory dysfunction, and/or polycystic ovaries had to have two of the three conditions. This research did not include women with Cushing's syndrome, adrenal hyperplasias, hormone imbalances, thyroid abnormalities, or other endocrine conditions.

Women who were taking medications to treat PCOS or any other condition were excluded. Participants were divided into two groups: Group I consisted of 30 healthy women without PCOS, who were considered the control group, while Group II comprised 60 women with PCOS syndrome.

During their clinical interview, according to a specific Questionnaire, the anthropometric and demographic data of each participant, including age, height, Weight, family history, menstruation regularity, and fertility, were collected.

2.2. Laboratory Assessment

Following an overnight fast, blood samples were obtained from each participant in the early morning on the second or third day of menstruation. Biochemical estimation of LH and FSH hormones was analyzed using the enzyme-linked immunosorbent assay (ELISA) (DRG, Germany). Meanwhile, Nrf2 was analyzed using the enzyme-linked immunosorbent assay (ELISA) (Sunlong, China).

Body mass index (BMI) was calculated using the formula: BMI = Weight (kg) / HeighHeight²ers² (Pray & Riskin 2023).

2.3. Statistical Analysis

Statistical analyses were performed using SPSS version 26. The Kolmogorov-Smirnov test was used to evaluate the normal distribution of continuous variables in the study. Clinical characteristics of PCOS patients and control subjects were presented as (mean ± SD), and a P value <0.05 was considered statistically significant.

Comparisons between the two study groups were performed using an independent samples t-test. Pearson's correlation was used to correlate scale variables. At the same time, point-biserial correlation was used to correlate nominal scale variables. The multiple logistic regression analyses were used to estimate the risk of PCOS according to Nrf2 depletion and GnRH imbalance.

3. Results

3.1. Comparison of Parameters between the Two Study Groups

The comparison of demographic and biochemical criteria in the current study is presented in Table 1. Compared with the healthy group, women with PCOS showed a significant increase in BMI, LH hormone concentration, and LH/FSH ratio. While there was a substantial increase in Nrf2.

3.2. The Relative Risk of Nrf2 Depletion and Hormonal Imbalance in PCOS Development

The risk of PCOS, based on blood Nrf2 depletion and GnRH imbalance, is shown in Table 2, which was determined using multiple logistic regression. Nrf2 depletion was substantially related to an increased risk of developing PCOS. So, hormonal imbalance

Table 1. Comparison of hormones and biochemical parameters between the two study groups

	Mean ± S.D		P value
	PCOS (N = 60)	Healthy (N = 30)	
Age	27.5±5.6	26.04±5.1	
BMI (kg/m^2)	28.32±6.3	20.26±2.33	0.01*
LH hormone (mIU/mL)	17.18±5.53	8.72±5.67	0.000**
FSH hormone (mIU/mL)	11.29±6.34	9.19±4.71	0.12
LH\FSH ratio	2.005±0.14	1.045±0.19	0.007**
Nrf2 (pg/mL)	9.92±4.02	16.42±4.66	0.000**

Table 2. Odds ratios and 95% CIs for Nrf2 and hormonal imbalance in the PCOS group

Parameters	Odds ratio (95% CI)	P value
Nrf2	0.967 (0.932–0.945)	0.048*
LH	1.045 (1.008–1.083)	0.017*
FSH	1.030 (0.990–1.072)	0.143
LH\FSH ratio	1.509 (1.165–1.956)	0.002*

appeared to have a significant effect in increasing the risk of PCOS development.

3.3. The Correlation between Nrf2 Depletion and Hormonal Imbalance

The Pearson correlation was used to assess the impact of Nrf2 depletion on GnRH imbalance. In contrast, point biserial correlation was used to estimate the effects of Nrf2 depletion on fertility and menstruation regularity in the two study groups.

As shown in Table 3, in PCOS patients, the Nrf2 concentration was significantly negatively correlated with LH hormone concentration and the LH/FSH ratio. Meanwhile, blood Nrf2 depletion was negatively correlated with both infertility and menstruation irregularity in the two study groups.

3.4. The Correlation between GnRH Imbalance and Women's Infertility

As shown in Table 4, PCOS patients undergo GhRH imbalance, presented as an elevated LH/FSH ratio, which was positively associated with infertility and menstrual irregularities.

4. Discussion

The ovulation process is a key component of the menstrual cycle. It begins with the rupture and release of the dominant follicle from the ovary to the fallopian tube, where fertilization can occur (Zeber-Lubecka *et al.* 2023). The pituitary gland releases gonadotropic

Table 3. Correlation between Nrf2 and parameters in study groups

Blood Nrf2 concentration depletion				
	PCOS		Control	
Parameters	R	P value	R	P value
LH[a]	-0.551	0.012*	0.022	0.925
FSH[a]	- 0.081	0.733	-0.400	0.080
LH\FSH[a]	- 0.628	0.003**	-0.211	0.317
Infertility[b]	- 0.460	0.041*	0.208	0.378
Irregularity[b]	- 0.575	0.008**	-0.281	0.340

[a]Pearson correlation, [b]point biserial correlation

Table 4. Correlation between the LH/FSH ratio and parameters in the study groups

Elevated LH\FSH ratio				
	PCOS		Control	
Parameters	R	P value	R	P value
LH[a]	0.780	0.000**	0.375	0.104
FSH[a]	- 0.117	0.625	0.126	0.596
Infertility[b]	0.650	0..002**	-0.241	0.307
Irregularity[b]	0.494	0.027*	0.181	0.601

[a]Pearson correlation, [b]point biserial correlation

hormones, including FSH and LH, which impact ovulation control (Awonuga *et al.* 2023).

The current study revealed GnRH imbalance associated with PCOS in the study groups. There was a non-significant increase in the FSH hormone level between patients with PCOS and the healthy women group; these results were in agreement with the results of other studies that found that there was an elevation in FSH hormone in PCOS patients (Kafhage *et al.* 2023) (Catteau *et al.* 2019). While there was a significant increase in the LH hormone level and LH/FSH ratio in patients with the PCOS group compared with the healthy group, the results agreed with those of other studies, which found an increase in LH hormone associated with PCOS (Patel *et al.* 2003; Kafhage *et al.* 2023).

There are a lot of reasons that can cause GnRH imbalance in PCOS patients. Patients with PCOS typically have an imbalance in the hypothalamic-pituitary-ovarian axis. Where an increased GnRH pulse frequency can lead to incorrect regulation of FSH secretion, ultimately resulting in high FSH levels (Liao *et al.* 2021). So, the central dysregulation of gonadotropin production is the leading cause of elevated LH hormone levels in PCOS, where an enhanced pituitary sensitivity to gonadotropin-releasing hormone (GnRH) as a result of prolonged unopposed estrogen exposure accounts for the increased amplitude of LH pulses in PCOS (Dong & Rees 2023). Furthermore, the decrease in

progesterone levels, a common feature of PCOS, may be caused by elevated levels of luteinizing hormone. The progesterone inhibits the release of LH from the pituitary gland through a feedback mechanism that regulates the rate of GnRH secretion, leading to GnRH imbalance (Rojas *et al.* 2014). Moreover, recent studies have found that high oxidative stress in PCOS patients affects the hormonal balance of the GnRH hormone, causing hormonal balance disruption, and has a close relation to the development of PCOS (Li *et al.* 2022).

Our study revealed a highly significant decrease in blood Nrf2 concentration in the PCOS group compared with the control group, which is an indicator of high oxidative stress in PCOS patients caused by the close relation between elevated OS and blood Nrf2 depletion (Ngo & Duennwald 2022).

The Keap/NRF2 pathway is one probable pathway that has been associated with the development of PCOS. According to studies, women with PCOS experience more oxidative stress than those without the disease. This result suggests that by reducing the body's capacity to resist oxidative stress, disruption of the Keap/NRF2 pathway may contribute to the development of PCOS (Wang *et al.* 2021) .

Nrf2 depletion can also be associated with hormonal imbalance in PCOS caused by elevated OS, In study conducted by Rashidi and her colleagues in 2019 found that there was an association between reduced Nrf2 cell content and hyperandrogenism, insulin resistance, and obesity in patients with PCOS (Rashidi *et al.* 2019).

Numerous other studies discussed the role of elevated OS in the ovulation process (Hameed *et al.* 2025), elevated LH secretion before to ovulation triggers the production of inflammatory chemicals inside the ovary leading to an overproduction of ROS (Bhattacharya *et al.* 2024).

ROS levels influence various aspects of ovulation, such as cumulus expansion, progesterone production, pre-ovulatory gene expression, and ovulatory signaling (Zeber-Lubecka *et al.* 2023).

The interaction between ROS and SOD in the corpus luteum is crucial for regulating the duration and efficacy of progesterone synthesis. Increased SOD activity protects against ROS-induced damage, whereas decreased SOD activity causes ROS-triggered apoptosis and corpus luteum regression. SOD antioxidant enzyme transcription is activated by Nrf2 (Lőrincz *et al.* 2024). Therefore, Nrf2 depletion can be the primary cause of SOD deficiency, leading to irregularity in ovarian physiology and reproductive health problems (Li *et al.* 2022).

Moreover, studies have demonstrated that in animal models of PCOS, activation of the Keap/NRF2 pathway can enhance insulin sensitivity, lower inflammation, and control hormone levels. This result suggests that targeting the Keap/NRF2 pathway may be a potential therapeutic approach for PCOS treatment (Chełchowska *et al.* 2023).

Wang and his colleagues in 2020 focused on the effect of oxidative stress in patients with polycystic ovary syndrome on the level of Nrf2. It was suggested that attempts to persist in the purposeful elimination of reactive oxygen species were responsible for the rise in Nrf2 accumulation observed during the early phases of oxidative stress in PCOS. Nevertheless, sustained oxidative stress causes antioxidant dysfunction, eventually reducing Nrf2 expression (Wang *et al.* 2021).

Likewise, another Iranian study conducted on human granulosa cells of PCOS patients found that enhancing the Nrf2 pathway can improve the outcomes of assisted reproduction cycles. It verified that the treatment of granulosa cells with Sulforaphane a natural free radical scavenger, can lessen oxidative stress via modulating the signaling pathway of the Nrf2 antioxidant response element (Nrf2\ARE), leading to increase the antioxidant enzyme concentrations, improve granulosa cells apoptosis, and assisted reproduction cycles by improving the quality of granulosa cells and the embedded oocyte, especially in PCOS patients (Esfandyari *et al.* 2021).

In another study, an attempt to explain the decrease in Nrf2 levels in patients with PCOS suggests that the reason for this decrease is the local effect of Nrf2 in mitochondrial membranes, as an attempt to protect them from oxidative stress damage. Strom conducted a study with his group in 2015, suggesting that Nrf2 protects against mitochondrial decay by oxidative stress. They revealed that Nrf2 plays a crucial role in protecting mitochondria in cardiomyocytes. Knocking out Nrf2 increases susceptibility to mitochondrial swelling, whereas overexpression prevents changes such as disruption of networks and loss of membrane potential. Nrf2 localization to the outer membrane of mitochondria suggests a direct interaction with mitochondrial components (Strom *et al.* 2016). Nrf2 signaling may interact with mitochondria-related reactive oxygen species (ROS) production and changes in membrane permeability. Nrf2 protects mitochondria by activating

the HO-1 and NAD(P)H quinone oxidoreductase one genes, which regulate mitochondrial fatty acid oxidation and ROS generation. In cells lacking Nrf2, mitochondrial membrane potential drops, whereas activation improves it (Piantadosi *et al.* 2008).

Recently, some studies suggest that enhancing the Nrf2 signaling pathway can show therapeutic behavior for PCOS patients, where they have found that the use of some naturally compound as Genistein and Osthole as enhance of Nrf2 signaling pathway can exerts therapeutic strategy for PCOS treatment (Wang & Li 2023; Valipour *et al.* 2024).

In conclusion, high oxidative stress has a vital role in the emergence and development of PCOS.

The current study found that Nrf2 depletion, caused by high oxidative stress, plays a role in the GnRH imbalance in PCOS through several mechanisms. Our study confirmed an association between Nrf2 depletion and elevated LH/FSH ratio. So, Nrf2 depletion was correlated with infertility and menstrual irregularity caused by the role of Nrf2 depletion and GnRH imbalance. Thus, we can suggest that enhancing the Nrf2 pathway can be a possible therapeutic approach for PCOS treatment.

Acknowledgements

The authors would like to thank the University of Anbar Al-Anbar, Iraq for its support to complete this work. So, The authors would like to express their thanks to the Mustansiriyah University / Baghdad, Iraq for its support to complete this work.

References

Agarwal, A., Aponte-Mellado, A., Premkumar, B.J., Shaman, A., Gupta, S., 2012. The effects of oxidative stress on female reproduction: a review. *Reproductive Biology and Endocrinology*. 10, 1. https://doi.org/10.1186/1477-7827-10-49

Ashraf, S., Nabi, M., Rasool, S. ul A., Rashid, F., Amin, S., 2019. Hyperandrogenism in polycystic ovarian syndrome and role of CYP gene variants: a review. *Egyptian Journal of Medical Human Genetics*. 20, 25. https://doi.org/10.1186/s43042-019-0031-4

Awonuga, A.O., Camp, O.G., Abu-Soud, H.M., 2023. A review of nitric oxide and oxidative stress in typical ovulatory women and in the pathogenesis of ovulatory dysfunction in PCOS. *Reproductive Biology and Endocrinology*. 21, 1–15. https://doi.org/10.1186/s12958-023-01159-6

Bhattacharya, K., Dey, R., Sen, D., Paul, N., Basak, A.K., Purkait, M.P., Shukla, N., Chaudhuri, G.R., Bhattacharya, A., Maiti, R., Adhikary, K., Chatterjee, P., Karak, P., Syamal, A.K., 2024. Polycystic ovary syndrome and its management: In view of oxidative stress. *Biomolecular Concepts*. 15, 20220038. https://doi.org/10.1515/bmc-2022-0038

Catteau, A., Bach-Ngohou, K., Blin, J., Barrière, P., Fréour, T., Masson, D., 2019. Abnormally elevated follicle-stimulating hormone (FSH) level in an infertile woman. *Case Reports in Endocrinology*. 2019, 1-5. https://doi.org/10.1155/2019/3071649

Chełchowska, M., Jurczewska, J., Gajewska, J., Mazur, J., Szostak-Węgierek, D., Rudnicka, E., Ambroszkiewicz, J., 2023. Antioxidant defense expressed as glutathione status and keap1-Nrf2 system action in relation to anthropometric parameters and body composition in young women with polycystic ovary syndrome. *Antioxidants*. 12, 730. https://doi.org/10.3390/antiox12030730

Dong, J., Rees, D.A., 2023. Polycystic ovary syndrome: pathophysiology and therapeutic opportunities. *BMJ Medicine*. 2, e000548. https://doi.org/10.1136/bmjmed-2023-000548

Esfandyari, S., Aleyasin, A., Noroozi, Z., Taheri, M., Khodarahmian, M., Eslami, M., Rashidi, Z., Amidi, F., 2021. The protective effect of Sulforaphane against oxidative stress through activation of NRF2/ARE pathway in human granulosa cells. *Cell Journal.* 23, 692–700. https://doi.org/10.22074/cellj.2021.7393

Fauser, B.C.J.M., Tarlatzis, Fauser, Chang, Aziz, Legro, Dewailly, Franks, Balen, Bouchard, Dahlgren, Devoto, Diamanti, Dunaif, Filicori, Homburg, Ibanez, Laven, Magoffin, … Lobo, 2004. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Human Reproduction*. 19, 41–47. https://doi.org/10.1093/humrep/deh098

Goodman, N.F., Cobin, R.H., Futterweit, W., Glueck, J.S., Legro, R.S., Carmina, E., 2015. American association of clinical endocrinologists, American college of endocrinology, and androgen excess and pcos society disease state clinical review: guide to the best practices in the evaluation and treatment of polycystic ovary syndrome - part 1. *Endocrine Practice*. 21, 1291–1300. https://doi.org/10.4158/EP15748.DSC

Hameed, Z.N., Rashied, R.M., Kareem, S.M., 2025. The relative copy number of mitochondrial DNA in peripheral blood as a prognostic marker for the development of polycystic ovarian syndrome in west Iraqi women. *Human Gene.* 45, 201442. https://doi.org/10.1016/j.humgen.2025.201442

Kafhage, F.Al.A.L., Abbas, A.N., Al-Masaoodi, R.A., Hassan, S., Al-Shemery, M.K., 2023. The relationship between hormonal levels and hematological parameters in cystic ovarian syndrome. *Journal of Medicine and Life*. 16, 937–940. https://doi.org/10.25122/jml-2022-0315

Laven, J.S.E., Imani, B., Eijkemans, M.J.C., Fauser, B.C.J.M., 2002. New approach to polycystic ovary syndrome and other forms of anovulatory infertility. *Obstetrical and Gynecological Survey*. 57, 755–767. https://doi.org/10.1097/00006254-200211000-00022

Li, W., Liu, C., Yang, Q., Zhou, Y., Liu, M., Shan, H., 2022. Oxidative stress and antioxidant imbalance in ovulation disorder in patients with polycystic ovary syndrome. *Frontiers in Nutrition*. 9, 1–10. https://doi.org/10.3389/fnut.2022.1018674

Liao, B., Qiao, J., Pang, Y., 2021. Central regulation of PCOS: abnormal neuronal-reproductive-metabolic circuits in PCOS pathophysiology. *Frontiers in Endocrinology*. 12, 1–11. https://doi.org/10.3389/fendo.2021.667422

Lőrincz, C.E., Börzsei, D., Hoffmann, A., Varga, C., Szabó, R., 2024. Mechanisms and target parameters in relation to polycystic ovary syndrome and physical exercise: focus on the master triad of hormonal changes, oxidative stress, and inflammation. *Biomedicines*. 12, 560. https://doi.org/10.3390/biomedicines12030560

Ngo, V., Duennwald, M.L., 2022. Nrf2 and oxidative stress: a general overview of mechanisms and implications in human disease. *Antioxidants*. 11, 2345. https://doi.org/10.3390/antiox11122345

Patel, K., Coffler, M.S., Dahan, M.H., Yoo, R.Y., Lawson, M.A., Malcom, P.J., Chang, R.J., 2003. Increased luteinizing hormone secretion in women with polycystic ovary syndrome is unaltered by prolonged insulin infusion. *Journal of Clinical Endocrinology and Metabolism*. 88, 5456–5461. https://doi.org/10.1210/jc.2003-030816

Piantadosi, C.A., Carraway, M.S., Babiker, A., Suliman, H.B., 2008. Heme oxygenase-1 regulates cardiac mitochondrial biogenesis via nrf2-mediated transcriptional control of nuclear respiratory factor-1. *Circulation Research*. 103, 1232–1240. https://doi.org/10.1161/01.RES.0000338597.71702.ad

Pray, R., Riskin, S., 2023. The history and faults of the body mass index and where to look next: a literature review. *Cureus*. 15, e48230. https://doi.org/10.7759/cureus.48230

Rashidi, Z., Aleyasin, A., Eslami, M., Nekoonam, S., Zendedel, A., Bahramrezaie, M., Amidi, F., 2019. Quercetin protects human granulosa cells against oxidative stress via thioredoxin system. *Reproductive Biology.* 19, 245–254. https://doi.org/10.1016/j.repbio.2019.07.002

Rojas, J., Chávez, M., Olivar, L., Rojas, M., Morillo, J., Mejías, J., Calvo, M., Bermúdez, V., 2014. Polycystic ovary syndrome, insulin resistance, and obesity: navigating the pathophysiologic labyrinth. *International Journal of Reproductive Medicine*. 2014, 1–17. https://doi.org/10.1155/2014/719050

Rudnicka, E., Duszewska, A.M., Kucharski, M., Tyczyński, P., Smolarczyk, R., 2022. Oxidative stress and reproductive function, oxidative stress in polycystic ovary syndrome. *Reproduction.* 164, 145–154. https://doi.org/10.1530/REP-22-0152

Strauss, J.F., 2003. Some new thoughts on the pathophysiology and genetics of polycystic ovary syndrome. *Annals of the New York Academy of Sciences*. 997, 42–48. https://doi.org/10.1196/annals.1290.005

Strom, J., Xu, B., Tian, X., Chen, Q.M., 2016. Nrf2 protects mitochondrial decay by oxidative stress. *FASEB Journal*. 30, 66–80. https://doi.org/10.1096/fj.14-268904

Uçkan, K., Demir, H., Turan, K., Sarıkaya, E., Demir, C., 2022. Role of oxidative stress in obese and nonobese PCOS patients. *International Journal of Clinical Practice*. 2022, 4579831. https://doi.org/10.1155/2022/4579831

Valipour, J., Taghizadeh, F., Esfahani, R., Ramesh, M., Rastegar, T., 2024. Role of nuclear factor erythroid 2-related factor 2 (Nrf2) in female and male fertility. *Heliyon*. 10, e29752. https://doi.org/10.1016/j.heliyon.2024.e29752

Wang, K., Li, Y., 2023. Signaling pathways and targeted therapeutic strategies for polycystic ovary syndrome. *Frontiers in Endocrinology*. 14, 1–28. https://doi.org/10.3389/fendo.2023.1191759

Wang, Y., Li, N., Zeng, Z., Tang, L., Zhao, S., Zhou, F., Zhou, L., Xia, W., Zhu, C., Rao, M., 2021. Humanin regulates oxidative stress in the ovaries of polycystic ovary syndrome patients via the Keap1/Nrf2 pathway. *Molecular Human Reproduction*. 27, 1-14. https://doi.org/10.1093/molehr/gaaa081

Witchel, S.F., Oberfield, S.E., Peña, A.S., 2019. Polycystic ovary syndrome: pathophysiology, presentation, and treatment with emphasis on adolescent girls. *Journal of the Endocrine Society*. 3, 1545–1573. https://doi.org/10.1210/js.2019-00078

Zeber-Lubecka, N., Ciebiera, M., Hennig, E.E., 2023. Polycystic ovary syndrome and oxidative stress-from bench to bedside. *International Journal of Molecular Sciences*. 24, 14126. https://doi.org/10.3390/ijms241814126