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Integral assessment of lipoperoxidation processes in women with ovarian hyperandrogenism

Kolesnikova L.I., Krusko O.V., Belenkaya L.V., Sholokhov L.F., Grebenkina L.A., Kurashova N.A., Kolesnikov S.I.

Scientific Centre for Family Health and Human Reproduction Problems
16, Timiryazeva Str., Irkutsk, 664003, Russian Federation

ABSTRACT

Aim. To assess the state of the 'lipid peroxidation – antioxidant defense' system using an integrated indicator (coefficient of oxidative stress) in women with ovarian hyperandrogenism in various periods of reproductive age.

Materials and methods. During an annual preventive medical examination at the Scientific Centre for Family Health and Human Reproduction Problems, 92 women of reproductive age (18–45 years old) were divided into two groups: a group of women with polycystic ovary syndrome (PCOS) ($n = 47$) and a control group of healthy women ($n = 45$). The group of women with PCOS was further divided into subgroups according to age characteristics: the 1st subgroup consisted of women with PCOS of early reproductive age (18–35 years old), and the 2nd group included women with PCOS of late reproductive age (35–45 years old). Practically healthy women of the corresponding ages made up the 3rd and 4th control subgroups. Standard methods were used to study the LPO–antioxidant defense system. The oxidative stress severity was assessed by an integrated indicator: the coefficient of oxidative stress.

Results. An increase in the serum levels of ketodienes and coupled trienes, a decrease in the concentrations of reduced glutathione, α-tocopherol and retinol levels, and an increase in superoxide dismutase (SOD) activity in PCOS women of reproductive age (18–45 years old) were detected, as opposed to the control group. Early reproductive age PCOS women also demonstrated an increase in oxidized glutathione and a decrease in retinol concentrations. In the late reproductive age group of PCOS women, an increased SOD activity was registered. The integrated indicator of oxidative stress in the main group of women with PCOS was 2.5, which shows the enhancement of oxidative processes and imbalance in the LPO–antioxidant defense system. This indicator was the most pronounced (2.8) in women of early reproductive age. In women of late reproductive age, this indicator was equal to 1.9.

Conclusion. The obtained data indicate the development of oxidative stress in women with ovarian hyperandrogenism, which is more pronounced in the group of late reproductive age.

Key words: hyperandrogenism, ovarian dysfunction, polycystic ovary syndrome, reproductive age, pro-oxidants, antioxidants, oxidative stress.

Conflict of interest. The authors declare the absence of obvious or potential conflict of interest related to the publication of this article.

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Conformity with the principles of ethics. All patients signed an informed consent to participate in the study. The study was approved by the Committee on Biomedical Ethics at Scientific Centre for Family Health and Human Reproduction Problems (Protocol No. 2.1 of 24.02.2016).

✉ *Krusko Olga V.,* e-mail: panarinaolya08@mail.ru.

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Интегральная оценка процессов липопероксидации у женщин с овариальной формой гиперандрогении

Колесникова Л.И., Круско О.В., Беленькая Л.В., Шолохов Л.Ф., Гребенкина Л.А., Курашова Н.А., Колесников С.И.

Научный центр проблем здоровья семьи и репродукции человека (НЦ ПЗСРЧ)
Россия, 664003, г. Иркутск, ул. Тимирязева, 16

РЕЗЮМЕ

Цель. Оценить состояние системы «перекисное окисление липидов – антиоксидантная защита» (ПОЛ–АОЗ) с использованием интегрального показателя (коэффициента окислительного стресса) у женщин с овариальной формой гиперандрогении в различные периоды репродуктивного возраста.

Материалы и методы. В ходе ежегодного профилактического медицинского осмотра 92 женщины репродуктивного возраста (18–45 лет) были разделены на группу женщин с синдромом поликистозных яичников (СПКЯ) (n = 47) и контрольную группу практически здоровых женщин (n = 45). Далее группа СПКЯ была разделена на подгруппы в соответствии с возрастными характеристиками: 1-я подгруппа – женщины с СПКЯ раннего репродуктивного возраста (18–35 лет), 2-я группа – позднего репродуктивного возраста (35–45 лет). Практически здоровые женщины соответствующих возрастов составили 3-ю и 4-ю контрольные подгруппы. В работе использованы общепринятые методы исследования системы ПОЛ–АОЗ. Выраженность окислительного стресса оценивали по интегральному показателю – коэффициенту окислительного стресса.

Результаты. Отмечено повышение в сыворотке крови уровней кетодиенов и сопряженных триенов, снижение восстановленного глутатиона, α-токоферола и ретинола, увеличение активности супероксиддисмутазы у женщин раннего репродуктивного возраста с овариальной формой гиперандрогении по сравнению с группой контроля. Также показано повышение содержания окисленного глутатиона и снижение концентрации ретинола. В группе женщин с гиперандрогенией позднего репродуктивного возраста отмечается увеличение активности супероксиддисмутазы. Интегральный показатель оценки окислительного стресса в общей группе женщин с СПКЯ составил 2,5, что свидетельствует об усилении окислительных процессов, дисбалансе в системе ПОЛ–АОЗ. Наиболее выражен данный показатель у женщин в раннем репродуктивном возрасте (2,8). У женщин в позднем репродуктивном возрасте значение показателя равно 1,9.

Заключение. Полученные данные свидетельствуют о развитии окислительного стресса у женщин с гиперандрогенией овариального генеза.

Ключевые слова: гиперандрогения, дисфункция яичников, синдром поликистозных яичников, репродуктивный возраст, прооксиданты, антиоксиданты, окислительный стресс.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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Соответствие принципам этики. Все пациенты подписали информированное согласие на участие в исследовании. Исследование одобрено комитетом по биомедицинской этике при ФГБНУ НЦ ПЗСРЧ (протокол № 2.1 от 24.02.2016).

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INTRODUCTION

Despite being natural for homeostasis, free radical processes sometimes contribute to the development of oxidative stress (OS), which is found in numerous pathological conditions and triggers the aging process. OS is a state when the balance between oxidative and antioxidant systems of cells and tissues has been lost. Enhanced generation of free radicals due to overproduction of reactive oxygen species (ROS) along with weakening of antioxidant defense mechanisms, leads to oxidation of biomolecules with the subsequent loss of their biological functions and / or homeostatic imbalance, potential oxidative damage to cells and tissues, and even their death. Excessive ROS generation can damage such cell components as proteins, lipids, and nucleic acids, which leads to cellular dysfunction [2].

Possible reasons for the decreased antioxidant activity and OS development may include various endocrine disorders (hyperprolactinemia, hyperandrogenism, defective luteal phase etc.). Hyperandrogenism, ovarian dysfunction, which is one of the main manifestations of polycystic ovary syndrome (PCOS), is particularly interesting here [3, 4]. The issue is relevant, as hyperandrogenism is common among women of reproductive age and can be distinguished by high frequency of associated complications and its leading manifestation, which is infertility [5]. Depending on the diagnostic criteria used and the characteristics of the population sample, this complex heterogeneous condition of unknown etiology affects 5–20% of fertile age women [6, 7].

Despite a long history of study, there is still no complete pathogenesis scheme of this disease [8], hence we consider it important to study such pathogenetic factors of many reproductive diseases as an imbalance in the 'lipid peroxidation – antioxidant defense' (LPO–AOD) system. OS development features due to androgen overproduction in ovaries in different periods of reproductive age have not been studied well yet. In our opinion, they need to be investigated thoroughly for further development of antioxidant therapy [9].

According to the existing views, when assessing whether LPO–AOD processes are balanced or not, comparison of individual indicators is not sufficiently informative. In this regard, integrated indicators may be more promising and sensitive. The coefficient of oxidative stress (COS) is often used as an integrated indicator to assess an imbalance between oxidative processes and the antioxidant defense system. This coefficient shows the accumulation of primary, intermediate, and end products of LPO and the activity of various AOD components (enzymes, glutathione, fatsoluble vitamins). The prooxidants / antioxidants ratio can reflect the stage of pathological conditions in the body. Using COS, it is possible to simultaneously assess both LPO and AOD states, as well as to timely assess the degree of imbalance in the LPO–AOD system at any stage of lipoperoxidation [10].

Considering everything mentioned above, the aim of the study was to assess the state of the LPO–AOD system using the coefficient of oxidative stress in women with ovarian hyperandrogenism at different periods of reproductive age.

MATERIALS AND METHODS

We conducted a single-center, cross-sectional, observational study, which included women of reproductive age (18–45 years old), who underwent an annual preventive medical examination (in the period from 2017 to 2019) at the Scientific Centre for Family Health and Human Reproduction Problems. All women were examined during the follicular phase of their menstrual cycle (from day 1 to day 12). The main group comprised 47 women with verified PCOS. PCOS was verified according to ESHRE / ASRM criteria (Rotterdam, 2003) [11]. The control group included 45 gynecologically and somatically healthy women. We further divided the groups into subgroups according to age characteristics: the 1st subgroup consisted of women with PCOS of early reproductive age (18–35 years old), the 2nd group included women with PCOS of late reproductive age (35–45 years old). The 3rd and 4th groups were control subgroups of the corresponding ages.

According to ESHRE / ASRM criteria (Rotterdam criteria), women of reproductive age (18–45 years old) who had two out of three criteria for PCOS (oligo- or anovulation, clinical and/or biochemical hyperandrogenism, polycystic ovarian morphology on the ultrasound) were included in the group with PCOS. Exclusion criteria for the group of women with PCOS were hyperprolactinemia, thyroid disor-

ders, current pregnancy or lactation, removal of the uterus and / or appendages on both sides, endometrial ablation and / or uterine artery embolization, and taking hormonal medications. Inclusion criteria for the control groups were the reproductive age (18–45 years old), regular menstrual periods, and follicular phase of the menstrual cycle. Exclusion criteria for the control groups were current pregnancy or lactation, removal of the uterus and / or appendages on both sides, endometrial ablation and / or uterine artery embolization, taking hormonal medications, and a chronic disease in the medical history.

All women underwent standard clinical and laboratory examinations. Blood was collected in accordance with the standard requirements from the ulnar vein in the morning, on an empty stomach. Plasma and hemolysate of red blood cells were the materials for the study. Standard methods were used to determine the products of LPO and components of AOD: conjugated dienes (CDs), ketodienes and coupled trienes (KD and CT), double bonds (DB), thiobarbituric acid (TBA) reactive substances (TBARS), superoxide dismutase (SOD) activity, reduced (GSH) and oxidized (GSSG) glutathiones and their ratio (GSH/GSSG), α-tocopherol and retinol, total antioxidant activity (TAA).

Measurements were carried out with the help of spectrophotofluorometer BTS-350 (Spain) and Fluorat 02 ABFF-T (Russia). To assess oxidative stress in women with PCOS, the formula for COS calculation was used [12]. To calculate the COS, the following indicators of the LPO–AOD system were used: DB (UL), CDs (umol / l), KD and CT (UL), TBARS (umol / l), SOD (UL), GSH (mmol / l), GSSG (mmol / l), α-tocopherol (umol / l), retinol (umol / l).

$$\mathrm{COS} = \frac{(\mathrm{DB}_i/\mathrm{DB}_n) \cdot (\mathrm{CDs}_i/\mathrm{CDs}_n) \cdot (\mathrm{KD\ and\ CT}_i/\mathrm{KD\ and\ CT}_n) \cdot (\mathrm{TBARS}_i/\mathrm{TBARS}_n)}{(\mathrm{SOD}_i/\mathrm{SOD}_n) \cdot (\mathrm{GSH_i}/\mathrm{GSH_n}) \cdot (\mathrm{A}_i/\mathrm{A}_n) \cdot (\mathrm{E}_i/\mathrm{E}_n)}$$

Where *i* – implies indicators of the examined patient, *n* – indicators of the control group.

The ratio of indicators of the LPO–AOD system of women with PCOS to the average indicators in the control groups was calculated. The value of COS > 1 was considered an increase in the degree of OS, that is, the higher the obtained value of COS, the higher the intensity of lipoperoxidation and the less effective the antioxidant protection.

Statistica 6.1 (Stat-Soft Inc., USA) was used to carry out statistical processing of data. To determine the proximity to the normal law of data distribution, the Shapiro − Wilk test was applied. *Me* (Q_1–Q_3) was used as descriptive statistics for variables with quantitative data. The nonparametric Mann – Whitney test was used in the analysis of intergroup differences for independent samples with non-normal distribution. The differences were considered statistically significant at $p < 0.05$.

RESULTS

The research results showed that ovarian hyperandrogenism is followed by the activation of lipoperoxidation and a decrease in antioxidant protection. A change in the concentration of secondary LPO products (KD and CT), which increased by 43% ($p = 0.0001$) compared to the control value, indicated activation of LPO in the experimental group of women of reproductive age (18–45 years old) with PCOS. During the study of primary (KD) and end (TBARS) products of LPO, no significant differences from the control group were found.

In the same group of women, a decrease in the TAA by 15% ($p = 0.0312$) indicated that the AOD system is under strain. a 9% ($p = 0.0323$) increase in the key SOD anti- oxidant enzyme was registered. At the same time, a 11% ($p = 0.0001$) decrease in GSH and a slight increase in GSSG were detected. This influenced the GSH / GSSG ratio, which was 16% lower in the group of women with PCOS ($p = 0.0065$). However, the content of α-tocopherol and retinol decreased by 12% ($p = 0.0001$) and 22% ($p = 0.0315$), respectively, compared to the control group.

The group of PCOS women of early reproductive age (18–35 years old) did not show statistically significant differences in the content of primary, secondary, and end lipoperoxidation products compared to the control group of the same age. However, the antioxidant defense mechanism changed: a

decrease in the level of TAA by 25% (p = 0.0005) and an increase in the oxidized glutathione concentration by 14% (p = 0.0001) were detected, but the reduced glutathione level remained unchanged. The GSH / GSSG ratio was 13% lower (p = 0.0323) than in the control group. Increased consumption of retinol was observed, which was a consequence of a decrease in its concentration by 26% (p = 0.0012). No significant differences in α-tocopherol levels were found.

In the subgroup of women of late reproductive age (35–45 years old) with hyperandrogenism, only a statistically significant increase in SOD by 9% (p = 0.0004) was found in comparison with the control group of the same reproductive period. When analyzing the peroxidation indicators and the AOD system in the control groups of early and late reproductive age, no statistically significant differences were found. Comparison of early and late reproductive age groups of women with PCOS revealed a statistically significant decrease in the GSSG level by 15% (p = 0.0032) and an increase in the GSH / GSSG ratio by 22% (p = 0.0001) in the late reproductive age subgroup.

Further, to assess the oxidative stress level in women with ovarian hyperandrogenism, the COS formula was used. The obtained COS values of more than 1.0 in the groups of women with PCOS indicated an increase in the OS degree.

The subgroup of women of early reproductive age with PCOS demonstrated more pronounced oxidative stress. COS values confirming dysregulation in the LPO–AOD system in PCOS women are shown in Figure.

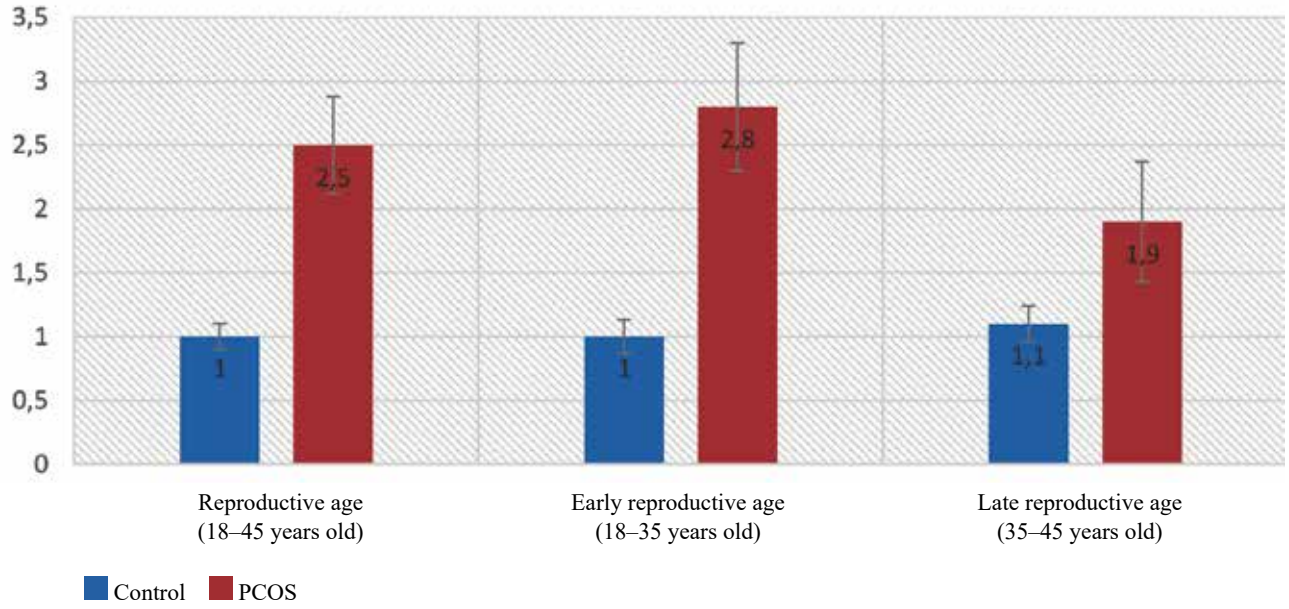

Figure. COS values in women with PCOS and in the control group

DISCUSSION

It is well known that women with ovarian hyperandrogenism have metabolic disorders, and the socalled "mitochondrial" dysfunction, which is closely connected with OS, plays an essential role in their pathogenesis. The pathogenetic role of OS in the development of reproductive disorders and decline of female reproductive function is also well-known [14, 15].

The main group of PCOS women showed activation of lipoperoxidation processes, which is manifested in an increase in the content of secondary LPO products–KD and CT. Increased production of LPO products at intermediate stages of lipid peroxidation, process, in particular, KD and CT, is proved to lead to toxic compound formation and accumulation and provoke extended damage to biopolymers, cytoplasmic membranes, and subcellular structures [16].

Though the most important indicator reflecting increased oxidative degradation of lipids is TBARS products, our study did not show statistically significant differences in this parameter. TBARS are end

products of oxidation indicating a serious damaging effect.

However, according to the existing concepts, free radical oxidation processes do not cause damage if the antioxidant defense mechanism keeps oxidative reactions at the balanced level. The components of the AOD system inactivate reactive oxygen species and inhibit the development free radical chain mechanisms of organic compound oxidation. The balance of the prooxidant and antioxidant components determines the intensity of metabolism and the adaptive potential of the body [17].

The results of the study of the AOD system components in the experimental group of women with PCOS showed increased activity of the main enzyme – superoxide dismutase, as well as a decrease in the blood total antioxidant activity (TAA). The changes in these indicators may reflect tension in the AOD system and a decrease in adaptive and compensatory capabilities in women with ovarian dysfunction [18]. Suppression of LPO processes in the cells at different stages is carried out by both enzymatic and nonenzymatic systems. In PCOS, there is a decrease in the concentration of molecular antioxidants, such as α-tocopherol and retinol. Decreased concentration of α-tocopherol, the most important regulator of oxidative balance, can affect the reproductive function and may contribute to the development of PCOS [9].

Lowering the level of retinol, a component of antioxidant protection, is associated with its increased consumption, since, in addition to fighting free radicals, it also increases the antioxidant effect of α-tocopherol [19]. A simultaneous decrease in the reduced glutathione concentration and a slight increase in the oxidized glutathione level, may be associated with the decreased activity of glutathione reductase and / or increased activity of glutathione peroxidase. Such changes lead to a decline in the total glutathione pool, which indicates a decrease in the contribution of this tripeptide to the anti-radical protection of the body [20, 21].

The study found that in different periods of reproductive age, LPO processes in women with ovarian hyperandrogenism are inactivated by various components of the AOD system. In early reproductive age, the main antioxidant protection is provided by the redox system of glutathione, and in late reproductive age, the processes of lipoperoxidation are mainly regulated by SOD.

The results of our study indicate the development of pronounced OS in women with ovarian hyperandrogenism, as evidenced by COS values. The COS value in the experimental group of women with PCOS equals to 2.5, in women of early reproductive period with PCOS, it is 2.8, and in late reproductive period subgroup it equals to 1.9. This coefficient value indicates a significant imbalance in the LPO–AOD system, highlighting the intensification of LPO processes, especially in early reproductive age women with PCOS.

CONCLUSION

Thus, the presence of hyperandrogenism in women of reproductive age is followed by the activation of adaptive and compensatory mechanisms for preserving the LPO–AOD system homeostasis and preventing LPO end product formation.

In this regard, COS, as an integrated indicator, helps to more objectively describe changes in the LPO–AOD system disorders and is a more sensitive indicator than separate individual components of this system, since it comprises both the products of lipid peroxidation at different stages and the activity of various components of antioxidant protection. COS shows the nature of peroxide processes in peroxide damage in the body and helps to choose rational antioxidant correction strategies. The oxidative stress coefficient can also be used for personalized evaluation of the effectiveness of antioxidant therapy and its correction in different pathological conditions.

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Authors contribution

Kolesnikova L.I., Sholokhov L.F., Grebenkina L. A., Kurashova N.A. – conception and design of the study. Krusko O.V. – implementation of the practical part of the study, analysis and interpretation of data. Belenkaya L.V. – collection of clinical material. Kolesnikov S.I. – critical revision for important intellectual content, final approval of the manuscript for publication.

Authors information

Kolesnikova Lyubov I., Dr. Sci. (Med.), Professor, Academician of RAS, Scientific Director, Scientific Centre for Family Health and Human Reproduction Problems, Irkutsk, Russian Federation. ORCID 0000-0003-3354-2992.

Krusko Olga V., Post-Graduate Student, Junior Researcher, Laboratory of Physiology and Pathology of the Endocrine System, Scientific Centre for Family Health and Human Reproduction Problems, Irkutsk, Russian Federation. ORCID 0000-0001-9111-7914.

Belenkaya Liliya V., Cand. Sci. (Med.), Senior Researcher, Laboratory of Physiology and Pathology of the Endocrine System, Scientific Centre for Family Health and Human Reproduction Problems, Irkutsk, Russian Federation. ORCID 0000-0003-4904-3709.

Sholokhov Leonid F., Dr. Sci. (Med.), Professor, Head of the Laboratory of Physiology and Pathology of the Endocrine System, Scientific Centre for Family Health and Human Reproduction Problems, Irkutsk, Russian Federation. ORCID 0000-0003-3588-6545.

Grebenkina Lyudmila A., Dr. Sci. (Biology), Head of the Laboratory of Pathophysiology, Scientific Centre for Family Health and Human Reproduction Problems, Irkutsk, Russian Federation. ORCID 0000-0002-1263-5527.

Kurashova Nadezhda A., Dr. Sci. (Biology), Leading Researcher, Laboratory of Pathophysiology, Scientific Centre for Family Health and Human Reproduction Problems, Irkutsk, Russian Federation. ORCID 0000-0001-8591-8619.

Kolesnikov Sergey I., Dr. Sci. (Med.), Professor, Leading Researcher, Academician of RAS, Scientific Centre for Family Health and Human Reproduction Problems, Irkutsk, Russian Federation. ORCID 0000-0003-2124-6328.

(✉) **Krusko Olga V.,** e-mail: panarinaolya08@mail.ru.

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