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Impact of Age on some Oxidant and Antioxidants Marker During Menstrual Cycles

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ABSTRACT

This study aims to investigate the effect of age on some oxidant and antioxidant markers during menstrual cycles. The sample included thirty healthy women (aged 20-45 years), divided into two groups (15 women /group) according to their ages, the first group: 20-25 years, the second group: 40-45 years, blood was drawn in the eighth, sixteenth and twenty-fourth days of the menstrual cycle. Results revealed: Hydrogen peroxide (H_2O_2) levels increased not statistically on the 16^{th} day compared with the 8^{th} day and statistically ($p\leq0.05$) in the 24^{th} day of both groups. In addition, H_2O_2 increased statistically ($p\leq0.05$) in the second group compared with the first group for the similar days. Catalase (CAT) levels increased not statistically on the 8^{th} day compared with the 16^{th} day and statistically ($p\leq0.05$) in the 24^{th} day. In addition, CAT increased statistically ($p\leq0.05$) in the second group in compared with the first group for similar days. Lecithin-cholesterol acyltransferase LCAT levels increased not statistically on the 8^{th} day compared with the 16^{th} day and statistically ($p\leq0.05$) with the 24^{th} day. In addition, LCAT increased not statistically in the second group in compared with the first group for the similar days. The physiological impact of these results be discussed according to the effects of the menstrual cycle phases and progressive age, leading to these oxidants and antioxidant markers during the cycle and to decrease ovarian efficiency.

Keywords: Hydrogen peroxide (H_2O_2), Catalase (CAT), Lecithin-cholesterol acyltransferase (LCAT)

INTRODUCTION

The primary risk factors for heart disease, atherosclerosis, myocardial infarction, stroke hypertension are associated with different hormonal, pro inflammatory and oxidative stress markers changes in advancing age. (Lakatta and Levy, 2003; North and Sinclair, 2012; Al-Nadji and Khalifa, 2021; Debbarh *et al*., 2021; Hasan and Khalifa, 2023). In addition to supporting healthy cellular homeostasis, oxidativestress (OS) and reactive oxygen species (ROS) have important direct and indirect functions in a wide variety of physiological activities. (Hardy *et al*., 2021). Whereas, the reproductive system is an illustration of how ROS have expanded into physiological and regulatory roles for folliculogensis, oocyte maturation, luteal regression, and fertilization. (Agarwal *et al*., 2012).

Moreover, maximum defense against ROS and their byproducts may be achieved by the coordinated activity of antioxidant enzymes and non-enzymatic antioxidants. (Carbone *et al*., 2003).

Additionally, one of the main reasons for cellular and molecular damage brought on by aging is OS, whereas, SOD and CAT are two antioxidants that have a negative correlation with advancing age (Debbarh *et al*., 2021). Reproductive aging was accompanied by a shift in the antioxidant enzymatic pathway in follicular fluid that reduced ROS scavenging effectiveness (Debbarh *et al*., 2021). Moreover, a gradual rise in follicularROS levels during ovarian aging, which is followed by follicular depletion and a decline in oocyte quality, may result from either an increase in ROS synthesis or a reduction in ROS breakdown by antioxidants (Tatone *et al*., 2006; Elizur *et al*., 2014), there is a collection of antioxidants that act to suppress or prevent the formation of ROS in cells (Ighodaro and Akinloye, 2018).

The ratio of ROS to endogenous antioxidants may have an impact on oocyte development, ovulation, luteal maintenance, and fertility, ROS can induce pathological conditions when chronically elevated, whereas, a group of oocytes start to develop and mature in the ovary each month, but only the dominant oocyte resumes meiosis I; this process is aimed at by an increase in ROS and is thwarted by antioxidants(Agarwal *et al*., 2012). In contrast, the progression of meiosis II is promoted by antioxidants (Behrman *et al*., 2001), demonstrating that there is a complex relation between ROS and ovarian antioxidants, steroid production increase of the growing follicle causes an increase in cytochrome P (P450), resulting in ROS formation, whereas, ROS produced by the pre-ovulatory follicle are considered important inducers for ovulation (Ruder *et al*., 2009).

Furthermore, Karowicz-Bilinska and his colleagues 2008 found that when compared to the luteal phase,the H_2O_2 levels are higher during the follicular phase, especially in its final days. Since hormonal balance changes during the menstrual cycle affect these oxidative stress markers, the phase of the cyclemay contribute to the variability of oxidative stress markers measured in females.

Furthermore, Gupta and his colleagues 2011 showed that CAT activity is highest in follicular fluid of small follicles, whereas, H_2O_2 levels were lowest in large compared.

In view of the above, this study is an attempt to shed some light about the role of the progressive age on the oxidant (H_2O_2) and antioxidants (CAT and LCAT) in different phases of menstruated women.

MATERIALS AND METHODS

The present study was carried out during 2022- 2023 on 30 healthy women divided (according to their ages) into two groups (15 women/group) as first (20-25 y) and second (40-45 y) groups. Blood samples were drawn in eighth, sixteenth and twenty fourth days of the cycle in menstruated women, to compare studied parameters between these days for eachgroup and also to compare these parameters between similar days for the first and second groups. The sample's individuals have been diagnostic healthy women whom have a regular menstrual cycle and checked medically by specialist's physician. Serum H_2O_2, CAT and LCAT assayed using enzyme-linked-immunosorbent-assay (ELISA) system kits. The statistical analysis performed by one-way Analysis of Variance (ANOVA), followed by Duncan's test and by t-test at (p-value ≤ 0.05) for both groups.

RESULTS AND DISCUSSION

Hydrogen Peroxide

First group:

Results revealed that H_2O_2 increased not significantly in the 16th day (5.712 ± 0.843 pg/ml) in comparison with the 8th day (5.613 ± 0.873 pg/ml) and significantly ($p \leq 0.05$) with the 24th day (4.048 ±0.729 pg/ml). H_2O_2 increased significantly ($p \leq 0.05$) in the 8th day in comparison with the 24th day. Fig. (1).

Second group:

Results revealed that H_2O_2 increased not significantly in the 16th day (6.293 ± 0.437 pg/ml) in compared with the 8th day (6.149 ± 0.527 pg/ml) and significantly ($p \leq 0.05$) with the 24th day (4.567 ± 0.481 pg/ml). H_2O_2 increased significantly ($p \leq 0.05$) in the 8th day in compared with the 24th day. Fig. (1).

Ovulation is an inflammatory process that Is characterized by high levels of ROS (such as present H_2O_2), high levels of cytokines and high levels of WBCs, thereby, H_2O_2 is increased during the ovulation period, in addition, H_2O_2 mimics the effects of LH via series of steps to ensure successful ovulation and corpusluteum development.

The results are in agreement with many studies. Ovulation has several similarities with inflammation and is closely connected to the activity of leukocytes and inflammatory cytokines, moreover, ROS are massively generated during the inflammatory process and could be involved in the signaling cascade, leading to ovulation, in addition, the effect of LH in follicle rupture, mimicked by H_2O_2, whereas, through the numerous signaling pathways, including protein kinase A (PKA), protein kinase C (PKC), phosphatidylinositol 3-kinase (PI3K) and p38MAPK, ending by release of the oocyte activated by LH (Yanagi *et al*., 2002; Fujii *et al*., 2005; Shkolnik *et al*., 2011; Ciani *et al*., 2015; Duffy *et al*., 2019).

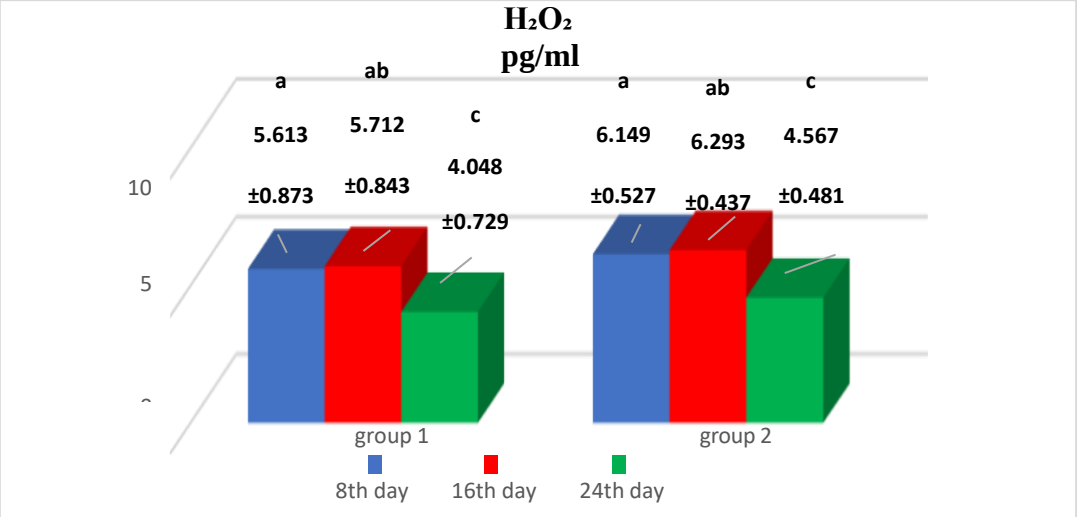

Fig. 1: The levels of H_2O_2 during different menstrual cycle's phases in both groups.

- The values represent mean ± SD.
- Different letters and similar letters represent significant ($P \leq 0.05$) and not significantdifferences, receptively, among different days of the groups.

Between groups:

Results revealed that H_2O_2 increased statistically ($p \leq 0.05$) for all days of the second group in comparison with the first group for the similar days. Fig. (2).

This increase may be attributed to the ovarian aging related with advancing age, that considered as low-grade inflammation characterized by high levels of pro-inflammatory cytokines, ROS (present H_2O_2) and WBC. In addition, the low estradiol (second group) may by caused H_2O_2 increase, due to its low anti-oxidant effect.

Oocyte aging may occur as a result of oxidative stress, which as reflected a gradual decline in oocyte quantity and quality and may be the "initiator" of oocyte aging due to the breakdown of the equilibriumbetween ROS and antioxidants (Miyamoto *et al*., 2010; Wang *et al*., 2022).

Moreover, low-grade inflammation, also known as "inflammaging", is frequently associated with aging and is characterized by an increase in the generation of ROS (such as H_2O_2) and pro-inflammatory cytokines. (Korolchuk *et al*., 2017; Gorgoulis *et al*., 2019; Saavedra *et al*., 2023).

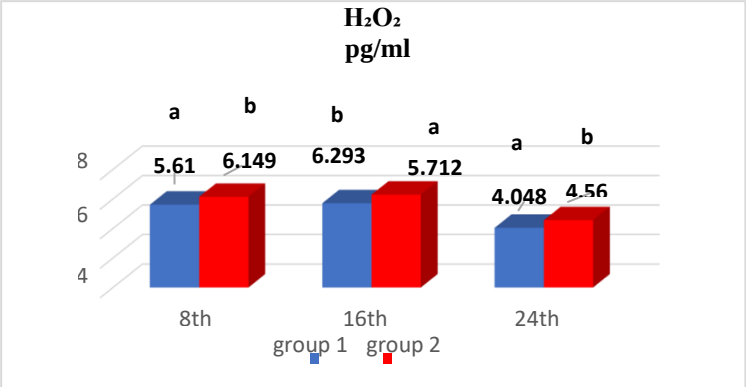

Fig. 2: The levels of H_2O_2 for similar days during different menstrual cycle's phases in bothgroups.

- The values represent mean ± SD.
- Different letters and similar letters represent significant ($P \leq 0.05$) and not significantdifferences, receptively, among similar days of the groups.
- n=15

Catalase

First group:

Results revealed that CAT increased not significantly in the 8th day (51.280 ± 6.369 KU/L) in comparison with the 16th day (48.038±6.223 KU/L) and significantly ($p \leq 0.05$) with the 24th day (38.582 ± 7.360 KU/L). CAT increased not significantly in the 16th day in comparison with the 24th day. Fig. (3).

Second group:

Results revealed that CAT increased not significantly on the 8th day (43.033 ± 4.538 KU/L) in compared with the 16th day (42.740 ± 4.161 KU/L) and significantly ($p \leq 0.05$) with the 24th day (33.340 ± 3.334 KU/L). CAT increased significantly ($p \leq 0.05$) in the 16th day compared with the 24th day. Fig. (3).

This CAT increases during follicular phase may be attributed to maintenance and protection of the developing follicles against oxidative stress attack resulting by increase ROS levels need high levels of CAT. Oocytes are protected from oxidative stress by the increased CAT activity that occurs during follicle growth and the absence of a rise in ROS levels in follicular fluid (Basini *et al*., 2008; Gupta *et al*., 2011; Paine *et al*., 2013; Wang *et al*., 2017; Akhigbe *et al*., 2022).

The antioxidant enzyme CAT and estradiol activity of ovarian follicular cells fluctuated with FSH, concurrent increases in CAT and estradiol in response to FSH are indicative of their functions in follicular selection, folliculogensis, and apoptosis prevention, whereas, CAT acts as a protective factorto neutralize H_2O_2, to maintain ROS balance and prevention of apoptosis (Behl and Pandey, 2002; Paine *et al*., 2013; Wang *et al*., 2017)

On the same time, the effects of the oxidative and antioxidant continuing during the luteal phase, whereas, at the end of the reproductive cycle, uncontrolled ROS generation brought on by an imbalance between the ROS and antioxidant systems is detrimental for the death of the corpus luteum, whereas the regulation of physiological luteal ROS concentrations by antioxidant enzymes is a crucial component of corpus luteum progesterone production (Al-Gubory *et al*., 2012; Wang *et al*., 2017).

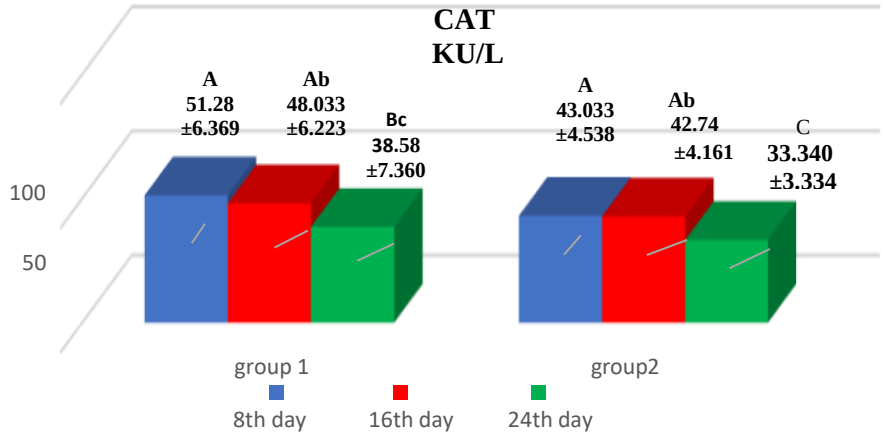

Fig. 3: The levels of CAT during different menstrual cycle's phases in both groups.

- The values represent mean ± SD.
- Different letters and similar letters represent significant ($P \leq 0.05$) and not significantdifferences, receptively, among different days of the groups.
- n=15

Between groups:

Results revealed that CAT decreased significantly ($p \leq 0.05$) in all days in second group in comparison with first group. Fig. (4).

This CAT decrease may be attributed to the ovarian aging related with advancing age (considered as low- grade inflammation) characterized by low levels of antioxidants (CAT and high oxidative stress).The reproductive aging was accompanied by a change in the antioxidant enzymatic pattern (such as CAT) in follicular fluid that impaired ROS scavenging efficiency, therefore, CAT and age have a negative relation (Carbone *et al*., 2003; Wang and Sun, 2006; Debbarh *et al*., 2021).

Follicular ROS levels (H_2O_2) gradually rise with ovarian age, which may be due to either an increase in ROS synthesis or a decrease in ROS breakdown by antioxidants such CAT, which are present as theprimary antioxidant defense (Elizur *et al*., 2014; IgIghodaro and Akinloye, 2018).

Advancing age characterized by reduced reproductive function, accompanied by decreased levels of estrogen (an established antioxidant in the body), thus leads to oxidative stress due to production of ROS (H_2O_2) (Randolph *et al*., 2011; Doshi and Agarwal, 2013; Wu *et al*., 2016; Chon *et al*., 2021).

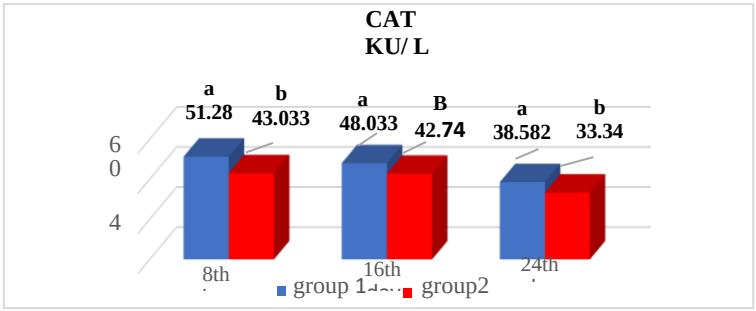

Fig. 4: The levels of CAT for similar days during different menstrual cycle's phases in bothgroups.

- The values represent mean ± SD.
- Different letters and similar letters represent significant ($P \leq 0.05$) and not significantdifferences, receptively, among similar days of the groups.
- n=15

Lecithin-Cholesterol Acyltransferase

First group:

Results revealed that LCAT increased not significantly in the 8th day (98.026 ± 6.424 U/L) in comparison with the 16th day (91.586 ± 5.807 U/L) and significantly (p≤0.05) with the 24th day (86.746 ± 5.676 U/L). LCAT increased not significantly in the 16th in comparison with the 24th day Fig. (5).

Second group:

Results revealed that LCAT increased not significantly in the 8th day (84.674 ± 5.434 U/L) in comparison with the16th day (79.835 ± 5.434 U/L) and significantly (p≤0.05) with the 24th day (68.194± 4.326 U/L). LCAT increased significantly (p≤0.05) on the 16th day in comparison with the 24th day. Fig. (5).

The steroidogenesis process (follicular phase) requires sufficient amounts of cholesterol provided by LCAT that considered as a maturation factor for HDL to complete a successful of ovulation, later, in addition, LCAT associated with the FSH and estradiol levels to facilitate folliculogensis. Furthermore, LCATmay play a role during this phase as an antioxidant agent to reduces oxidative stress and to ensure an intact oocyte.

The present findings and ideas about the role of LCAT are in agreements with many studies. During the follicular phase there was an increase in total cholesterol (required for steroidogenesis), which represent the precursor substrate molecule for all steroid hormones (Oria *et al*., 2020; Bassi *et al.*, 2022; Sharm *et al*., 2022).

LCAT has an important role in reverse cholesterol transport and follicular synthesis of estrogen, high LCAT activity was positively associated with antioxidant accumulation and lower LCAT activity was associated with their consumption, antioxidants are accumulated in the mature follicles to protect LCAT from oxidative damage and promote steroidogenesis (Cigliano *et al*., 2002; Ruder *et al*., 2008; Kunnenand Van, 2012; Cruz *et al*., 2014; Onaolapo *et al*., 2022).

Follicular fluid LCAT activated by apolipoprotein A1 (APOA1) (the major protein of HDL) by gonadotropin-dependent upregulation, thereby, expression of HDL receptors in the ovary cells increase, whereas, HDL are the main lipoproteins present in human follicular fluid and are important in fertilization and human reproduction (Balestrieri *et al*., 2001; Adhikari, 2011; Chang *et al*., 2017; Huang *et al*., 2019).

Many studies mentioned that LCAT increases the rate of fertilization, catalyzes lipid transfer, and reduces oxidative stress, all of which are necessary for the maintenance and repair of oocytes (Pfrieger andUngerer, 2011; Buschiazzo *et al*., 2013; Wu *et al*., 2016).

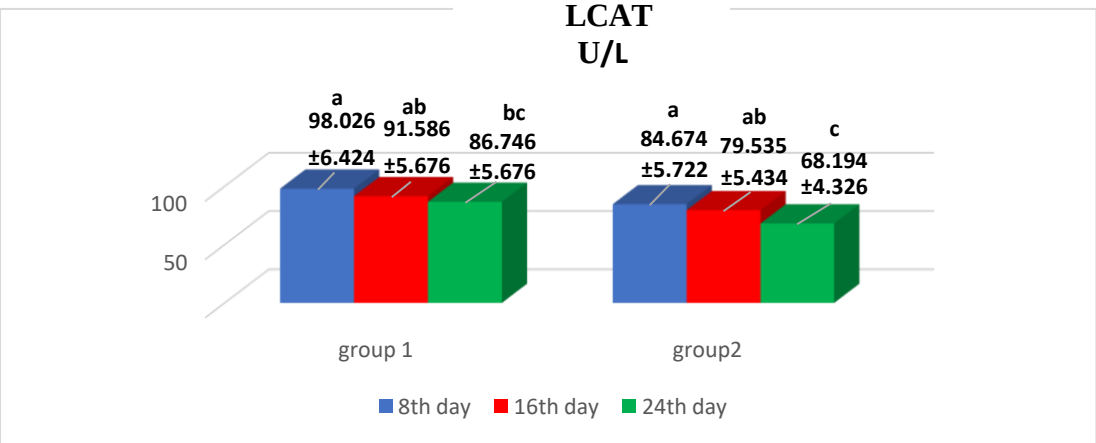

Fig. 5: The levels LCAT during different menstrual cycle's phases in both groups

- The values represent mean ± SD.
- Different letters and similar letters represent significant (P ≤ 0.05) and not significantdifferences, receptively, among different days of the groups.
- n=15

Between groups:

Results revealed that LCAT decreased not significantly in all days of the second group in comparison with the first group. Fig. (6). This LCAT decrease may be attributed to the ovarian aging related with advancing age and to the low levels of estradiol. These results are in agreement with many studies. LCAT concentrations decrease with advancing age, whereas, advancing age characterized by reduced reproductive function, accompanied by decreased levels of estrogen (an established antioxidant), thus leads to oxidative stress due to the release of ROS (Swapnali *et al*., 2011; Randolph *et al*., 2011; Doshi and Agarwal, 2013; Chon *et al*., 2021).

Decreased APOA1 levels, HDL and LCAT concentrations due to estrogen deficiency with advancing age, whereas, LCAT (catalyses the esterification of cholesterol) activates by APOA1, thereby, APOA1interact with HDL receptor and facilitate to remove cholesterol from the peripheral cells to transport itback to liver (Balestrieri *et al.*, 2001; Swapnali *et al*., 2011; Hirashio *et al*., 2014; Wu *et al.*, 2016; Dobiasova, 2017; Ko *et al*., 2020).

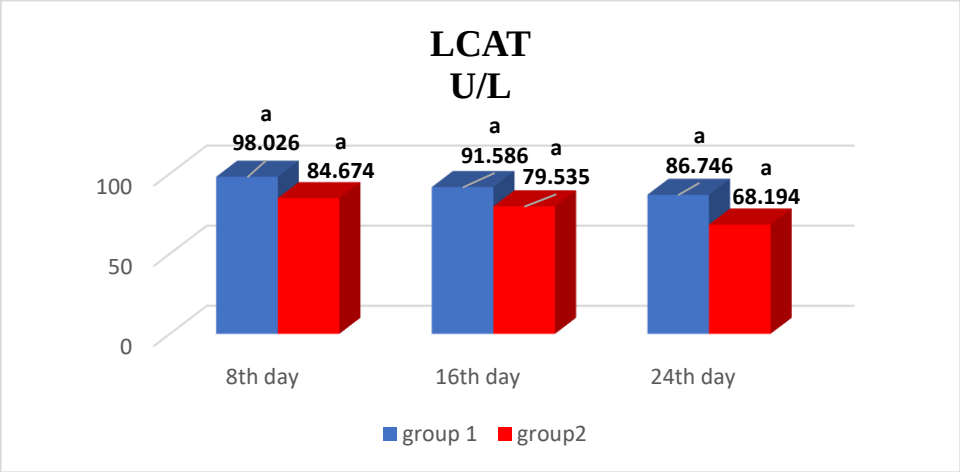

Fig. 6: The levels of LCAT for similar days during different menstrual cycle's phases in bothgroups.

- The values represent mean ± SD.
- Different letters and similar letters represent significant ($P \leq 0.05$) and not significantdifferences, receptively, among similar days of the groups.
- n=15

CONCLUSIONS

The high levels of CAT and LCAT associated with the follicular phase (8^{th} day) reflect the preparation role of these anti-oxidants in such of reproductive process…ie, folliculogensis and steroidogenesis that facilitate the ovulatory process together with the high levels of H_2O_2 which mimics LH activation to ensure good quality of oocyte leading to successful ovulation. Similarity, changes in oxidants and antioxidants in young women also reflect some favorable effects to complete the menstrual cycle and their requirements and phases beside other process like folliclogenesis, steroidogenesis, ovulation and the formation and maintenance of corpus luteum, in contrarily the detrimental effects that associated with elderly women caused by inflammaging, ovarian aging and high oxidative stress with low antioxidants in old women. On the other hand, the high levels of oxidative stress (H_2O_2 in second group) pointed out by this present finding (H_2O_2 in second group) a low grad inflammation in these women s' age which might be characterized a favorable hormonal and biochemical parameters associated commonly with their menstrual cycle.

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Conflicts of interest

There are no conflicts of interest.

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تأثير التقدم بالعمر على بعض علامات الاكسدة ومضاداتها خلال الدورة الشهرية

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الملخص

هدفت الدراسة إلى معرفة بعض علامات الأكسدة ومضادات الأكسدة في أعمار مختلفة للدورات الشهرية للنساء. اشتملت العينة على ثلاثين امرأة سليمة (أعمارها 20–45 سنة)، قسمت إلى مجموعتين (15 امرأة/ مجموعة) حسب أعمارهم، المجموعة الأولى: 20–25 سنة، المجموعة الثانية: 40–45 سنة، تم سحب الدم في الأيام الثامن، السادس عشر والرابع والعشرين من الدورة الشهرية.

النتائج: ارتفاع مستويات بيروكسيد الهيدروجين (H_2O_2) في اليوم السادس عشر بشكل غير معنوي مقارنة باليوم الثامن وبشكل معنوي ($p<0.05$) مع اليوم الرابع والعشرين لكلا المجموعتين، إضافة إلى ذلك ارتفع مستوى H_2O_2 معنويا ($p<0.05$) في المجموعة الثانية مقارنة مع المجموعة الأولى وللأيام المتماثلة. ارتفعت مستويات الكاتالايز (CAT) في اليوم الثامن بشكل غير معنوي مقارنة باليوم السادس عشر وبشكل معنوي ($p<0.05$) في اليوم الرابع والعشرين، بالإضافة إلى ذلك ارتفاع مستويات (CAT) معنويا ($p<0.05$) في المجموعة الثانية مقارنة بالمجموعة الأولى وللأيام المتماثلة. ارتفعت مستويات الليسيثين–الكوليسترول أسيل ترانسفيراز (LCAT) في اليوم الثامن بشكل غير معنوي مقارنة باليوم السادس عشر وبشكل معنوي ($p<0.05$) في اليوم الرابع والعشرين، بالإضافة إلى ذلك، ارتفع مستوى (LCAT) بشكل غير معنوي في المجموعة الثانية مقارنة بالمجموعة الأولى وللأيام المتماثلة. تمت مناقشة التأثيرات الفسيولوجية لهذه النتائج وفقا لتأثيرات مراحل الدورة الشهرية وتقدم العمر التي ربما أدت الى هذه التغيرات في علامات الاكسدة ومضاداتها وكذلك في انخفاض كفاءة المبيض.

الكلمات الدالة: بيروكسيد الهيدروجين، الكاتالاز، الليسيثين–الكوليسترول أسيل ترانسفيراز.