

ORIGINAL A R T I C L E

Effect of Frequent Use of Ovulation Stimulants drugs on, Total Cholesterol, Triglycerides, High density lipoprotein and Total Antioxidants

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Abstract

Background Letrozole, an aromatase inhibitor, inhibits the final stage of conversion of androgens into estrogens, affecting organs and tissues such as the ovaries, breasts, adipose tissue, and bone. This mechanism greatly reduces the effects of estrogen. Estrogens are important for controlling the metabolism of fats and lipoproteins, influencing total protein, total antioxidants, and total cholesterol. FSH stimulation can benefit patients with pituitary dysfunction and is used to promote ovulation in women who have not become pregnant. It also provides controlled stimulation of ovarian hyperstimulation, which increases the number of follicles in in vitro fertilization.

The Aim To assess the difference in the level (total cholesterol, Triglycerides, High density lipoprotein and total antioxidants) of infertility treatment among the three study groups, the group that injected by FSH, the group that took Letrozole, and the control group.

Material and Method A study was conducted between October 2022 and May 2023. It involved one hundred and twenty patients, divided into three groups: those who took Letrozole continuously for more than one month, those who were injected by FSH continuously for more than one month, and the control group who did not take any drugs to induce ovulation.

Results The results of this study showed an increase in the total antioxidant levels and total protein capacity levels in FSH compared to the other LET groups and the control group. Our study showed a significant difference (p value < 0.0001) in cholesterol concentrations, and total antioxidant capacity, compared to all studied groups, and an increase in total cholesterol levels was observed, as there was a significant difference (p value = 0.0012) in comparison to all studied groups.

Keywords: Ovulation; FSH; Letrozole; Total cholesterol; Total antioxidant.

1 Introduction

The ability to reproduce is critical to the long-term survival of humanity. However, infertility can arise from various reproductive problems affecting both male and female partners, usually after 12 months and

more of unprotected sexual activity [1]. Infertility can be categorized into primary infertility, in which the couples have never conceived, and secondary infertility, in which the couples have previously become pregnant but are struggling to conceive again [2].

Several factors contribute to the occurrence of female infertility, with sexually transmitted diseases such as gonorrhea and syphilis. In addition, obesity and addiction among youth, along with conditions such as diabetes, high blood pressure, and hypothyroidism, have also contributed to the increased prevalence of infertility [3]. It is important to note that women are responsible for more than half of infertility cases, with different factors including issues related to ovulation, fallopian tubes, endometriosis, and unexplained factors [4].

There are many treatment options available for women experiencing infertility, including lifestyle modifications, medications, assisted reproductive technologies, and surgical procedures. Ovulation induction and superovulation are the two common infertility treatments. The primary goal of treating anovulatory women is to stimulate the production of at least one follicle, while in cases of other types of infertility, ovulation boost or controlled ovarian hyper stimulation is used to increase the number of follicles [5, 6].

Evaluation is the first step in treating infertility, as it helps identify specific causes and determine the most appropriate course of action. While a thorough history and physical examination provide valuable information, the use of ovulation triggers is often necessary. Clomiphene citrate, Letrozole, and gonadotropins are among the drugs most commonly used to stimulate ovulation [7].

Clomiphene citrate has traditionally been the drug of choice for the treatment of women who are infertile due to anovulation. However, its use can increase the chances of conceiving twins due to ovarian stimulation. It is necessary to be careful as hyper stimulation of the ovaries may occur, necessitating medical attention. As a precaution, Clomid should not be repeated or the dose should not be increased without consulting a doctor, in order to reduce the risk of such side effects. Letrozole has emerged as a commonly used alternative to Clomid [8].

Letrozole is an aromatase inhibitor that mainly acts on the last step of converting androgens into estrogens. It inhibits the aromatase enzyme by an average of 80 to 90%, which results in decreased estrogen availability in various organs and tissues, including the ovaries, breasts, adipose tissue, and bone. This mechanism is particularly important in the context of ovarian stimulation, as Letrozole significantly reduces the effects of estrogens. Estrogen plays an important role in regulating the metabolism of fats and lipoproteins. They affect how these substances are made, used, and cleared in the body. Therefore, the decrease in the level of estrogens, as observed with the use of Letrozole, can have an effect on the indicators of total protein, total antioxidants, and total cholesterol in the body [9, 10].

By reducing the availability of estrogens, Letrozole has the potential to cause changes in lipid metabolism. Dysregulation of cholesterol indicators may occur as a result of modulating the effect of estrogen on the metabolism of fats and lipoproteins [9]. More research is needed to understand the specific effects of Letrozole on cholesterol profiles and the implications for metabolism in general.

Patients who do not have normal pituitary function and need help getting to ovulation can also benefit greatly from Follicle Stimulating Hormone FSH. Along with intrauterine insemination, FSH has also been used to treat typically ovulating women who have not become pregnant using traditional methods. In this case, intrauterine insemination is used in conjunction with FSH stimulation in an effort to enhance the number of eggs that ovulate and, thus, the chance of pregnancy [11]. Additionally, the hormone FSH is utilized to provide controlled ovarian hyper stimulation, which increases the number of follicles produced in vitro fertilization. Follicles are the fluid-filled sacs where eggs are developing [12].

Overall, the mechanism of action of Letrozole, as an aromatase inhibitor, and its ability to reduce estrogen availability contribute to its therapeutic efficacy in various conditions.

However, it is important to consider and closely monitor the potential effect on cholesterol indicators during treatment with Letrozole.

2 Materials and hormones

The female hormones fluctuate predictably across the menstrual cycle in women who are naturally cycling; these hormones influence many other physiological systems [13].

Female hormones play a role in metabolism. The ability of female hormones to alter plasma lipid and lipoprotein levels is important because these factors are significant indicators of cardiovascular risk in women. Numerous studies have consistently shown the influence of exogenous sex hormones on lipid and lipoprotein levels, but studies of the effects of menstrual cycle phases on circulating lipid and lipoprotein levels have not shown a consistent pattern [14].

Due to the cycling nature of circulating levels of sex hormones in premenopausal women and their possible impact on levels of lipids and lipoproteins [15]. Estrogen may provide cardiovascular protection through direct vascular effects such as increasing arterial vasodilatation and increasing perfusion, also it has a favourable effect on lipid metabolism. This explain the antiatherogenic effects seen in females of circulating levels of endogenous sex hormones in women of reproductive age, and their possible impact on levels

of lipids and lipoproteins, and hence the risk of Coronary Heart Disease (CHD) [16].

In this study, change in TC, TG and HDL level have been noted in patient on Letrozole therapy, which is a nonsteroidal aromatase inhibitor. It lowers serum estrogen levels by inhibiting the peripheral conversion of androgens to estrogens. This increases the risk of heart disease because the estrogen hormone affects the lipid profile in the blood. Also, female hormones estrogen and progesterone, during the menstrual cycle regulate protein metabolism [17].

3 Methodology

During the period from October 2022 to May 2023, a total of one hundred and twenty patients attending

the Women's and Children's Hospital participated in this study. Consent was obtained from the women to use their samples in this study.

Women were divided into three groups. The first group consisted of 45 patients who took Letrozole continuously for more than one month. Group 2 included 45 patients who were injected with FSH continuously for more than one month. The third group, referred to as the control group, consisted of thirty women who did not take any drugs to induce ovulation. The women's age ranged from 20 to 29 years.

To collect blood samples, gel tubes were utilized and were left to clot at the room temperature for 30-60 minutes.

Subsequently, the tubes were centrifuged at 3000 rpm for 15 minutes and stored at -80 °C in the main blood bank for future retrieval.

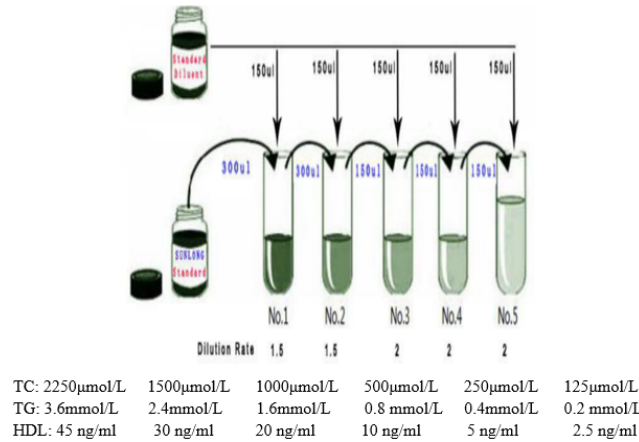


Figure 1: Dilution of Standards.

Table 1: Dilution of Standards of TC, TG and HDL

TC		
1500 $\mu\text{mol/L}$	Standard No.1	300 μl Original Standard + 150 μl Standard diluents
500 $\mu\text{mol/L}$	Standard No.3	150 μl Standard No. 2 + 150 μl Standard diluents
250 $\mu\text{mol/L}$	Standard No.4	150 μl Standard No. 3 + 150 μl Standard diluents
125 $\mu\text{mol/L}$	Standard No.5	150 μl Standard No. 4 + 150 μl Standard diluents
TG		
2.4 $\mu\text{mol/L}$	Standard No.1	300 μl Original Standard + 150 μl Standard diluents
1.6 $\mu\text{mol/L}$	Standard No.2	300 μl Standard No. 1 + 150 μl Standard diluents
0.8 $\mu\text{mol/L}$	Standard No.3	150 μl Standard No. 2 + 150 μl Standard diluent
0.4 $\mu\text{mol/L}$	Standard No.4	150 μl Standard No. 3 + 150 μl Standard diluents
0.2 $\mu\text{mol/L}$	Standard No.5	150 μl Standard No. 4 + 150 μl Standard diluents
HDL		
30 $\mu\text{mol/L}$	Standard No.1	300 μl Original Standard + 150 μl Standard diluents
20 $\mu\text{mol/L}$	Standard No.2	300 μl Standard No. 1 + 150 μl Standard diluents
10 $\mu\text{mol/L}$	Standard No.3	150 μl Standard No. 2 + 150 μl Standard diluents
5 $\mu\text{mol/L}$	Standard No.4	150 μl Standard No. 3 + 150 μl Standard diluents
2.5 $\mu\text{mol/L}$	Standard No.5	150 μl Standard No. 4 + 150 μl Standard diluents

3.1 Procedure

1. Add 10 μL of sample and 40 μL of sample dilution buffer to each well of the sample plate.
2. Following the application of the sealer, the plate was incubated at 37 °C for 30 minutes.
3. The membrane on the closing plate was gently removed and washed away with water. The washing steps were repeated three times.
4. Added 50 μL of the reagent conjugate to HRP, except the control well that is blank.
5. The plate was coated with the sealer and subjected to incubation at a temperature of 37 °C for a duration of 30 minutes.
6. The membrane on the closing plate was gently removed and washed away with water. The washing steps were repeated three times.
7. Each well was supplemented with 50 μL of Chromogen Solution B and 50 mL of Chromogen Solution A, which were then gently mixed and incubated at 37 °C for 15 minutes.
8. The wells received the addition of 50 μL of stop solution. It finally took fifteen minutes to finish.
9. The OD value was determined using the plate reader at 450 nm

3.2 Measurement of Total Anti-Oxidant Capacity

Principle

The total antioxidant and antioxidant enzyme levels in the samples are measured using this kit. Fe^{3+} -TPTZ (tripyridyltriazine) is reduced to blue Fe^{2+} -TPTZ in an acidic environment; this color reaction represents the complete antioxidant capability.

3.2.1 Preparation of solution

1. Standard: To make a 20 μL concentrated sulfuric acid (H_2SO_4) and 0.9 mL distilled water (FeSO_4) standard solution at a concentration of 40 $\mu\text{mol}/\text{mL}$, combine the two.
2. Solution Mixture: Reagent 1: Reagent 2: Reagent 3 = 7:1:1, incubate at (37 °C) for (10min) before use.

3.2.2 Procedure

1. The reagent was mixed with 100 μL of distilled water, which serves as a blank control, and 100 μL of standard solution.

2. was well mixed for 10 minutes.
3. Absorbance was measured at 593 nm.
4. According to the equation $\Delta A = AS - AB$

4 Results

In this study, women were split into three groups, each group consisted of 45 women: Group 1 consisted of women who used Letrozole for a month or longer in a succession, Group 2 consisted of women who took FSH for a month or longer in a run, and Group 3 consisted of thirty control women who did not take ovulation inducing medications. The women were between the ages of 20 and 39. The drawn blood samples were put into gel tubes, allowed to clot for 30 to 60 minutes at the room temperature, centrifuged for 15 minutes at 3000 rpm, and then recovered at -80 °C in the main blood bank.

4.1 Total cholesterol

The measurement of serum total cholesterol concentration for the two groups in the first month after FSH and LET administration revealed no significant difference as compared to the control group as shown in Figure 2. There was also no significant difference between FSH and LET.

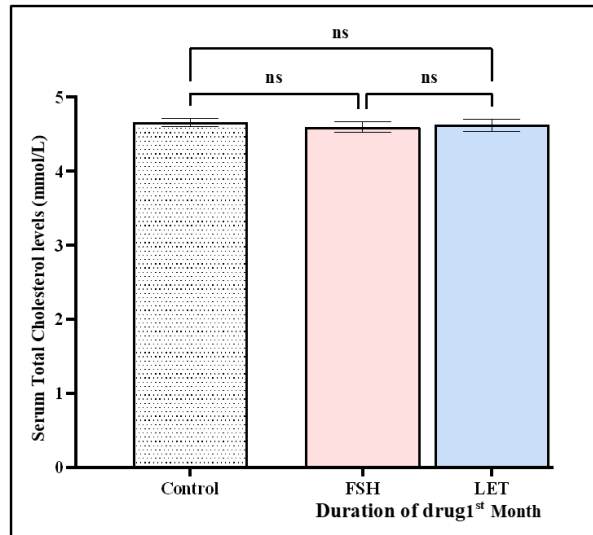


Figure 2: Estimation of serum total cholesterol concentration in mmol/L for the three groups in the first month.

In the second month of using FSH and LET the level of serum cholesterol showed a significant difference as compared to the control group, and they were respectively, 4.933 ± 0.347 mmol/L, 5.025 ± 0.443 mmol/L, and 4.66 ± 0.288 mmol/L as shown in Figure 3. There was no significant difference between FSH and LET.

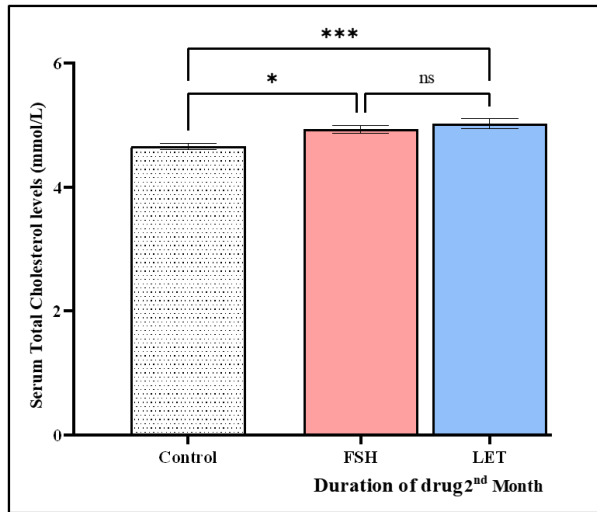


Figure 3: Estimation of serum total cholesterol concentration in mmol/L for the three groups in the second month.

The measurement of serum total cholesterol concentration for the third month of using FSH and LET revealed a significant difference as compared to the control group, and they were respectively, 5.26 ± 0.47 mmol/L, 5.29 ± 0.28 mmol/L, and 4.66 ± 0.288 mmol/L, as shown in Figure 4. There was no significant difference between FSH and LET.

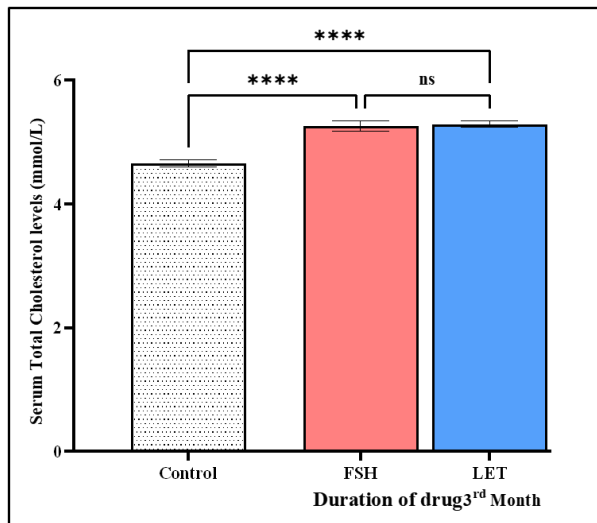


Figure 4: Estimation of serum total cholesterol concentration in mmol/L for the three groups in the third month.

4.2 Triglycerides

The measurement of serum Triglycerides concentration for the two groups in the first month after FSH and LET administration reveal no significant difference as compared to the control group as show in Figure 5. There was also no significant difference between FSH and LET.

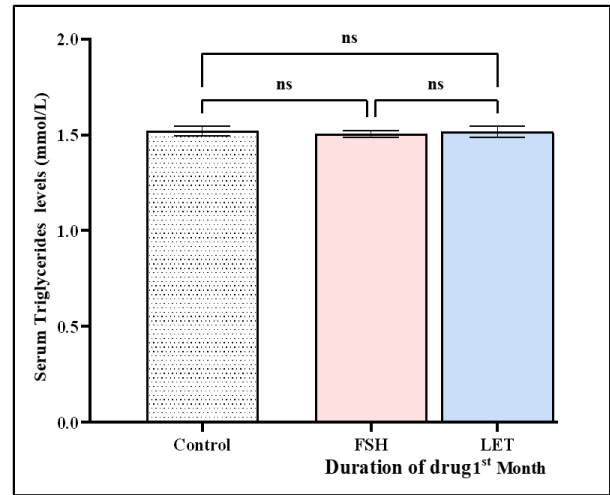


Figure 5: Estimation of serum Triglycerides concentration in mmol/L for the three groups in the first month.

In the second month of using FSH and LET the level of serum Triglycerides showed a significant difference as compared to the control group, and they were respectively, 1.626 ± 0.155 mmol/L, 1.672 ± 0.2056 mmol/L, and 1.52 ± 0.13 mmol/L as show in Figure 6. There was also a significant difference between FSH and LET.

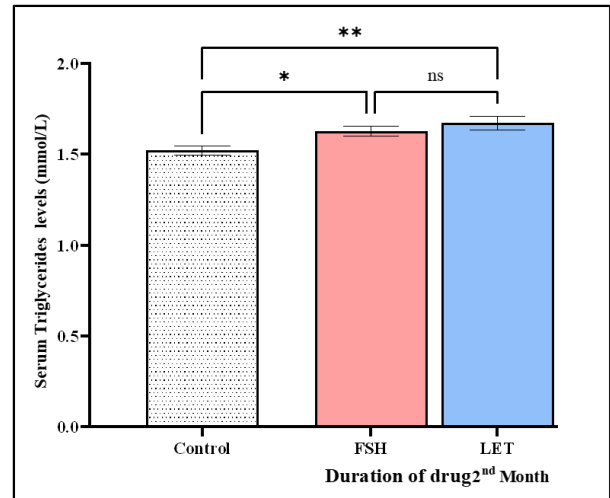


Figure 6: Estimation of serum Triglycerides concentration in mmol/L for the three groups in the second month.

The measurement of serum Triglycerides concentration for the third month of using FSH and LET reveal a significant difference as compared to the control group, and they were respectively, 1.626 ± 0.155 mmol/L, 1.808 ± 0.1732 mmol/L, and 1.913 ± 0.1774 mmol/L as show in Figure 7. There was also a significant difference between FSH and LET.

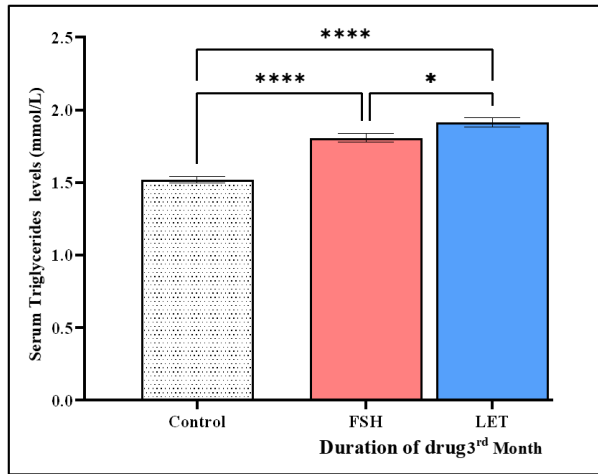


Figure 7: Estimation of serum Triglycerides concentration in mmol/L for the three groups in the third month.

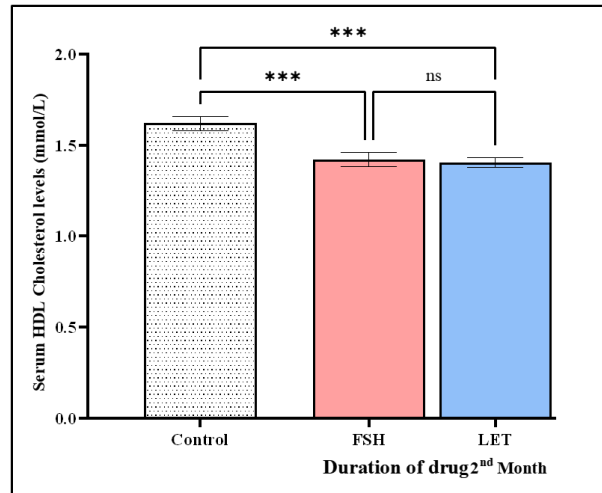


Figure 9: Estimation of serum HDL cholesterol concentration in mmol/L for the three groups in the second month.

4.3 HDL cholesterol

The measurement of serum HDL cholesterol concentration for the two groups in the first month after FSH and LET administration reveal a significant difference as compared to the control group, and they were respectively, 1.54 ± 0.16 mmol/L, 1.57 ± 0.13 mmol/L, and 1.62 ± 0.22 mmol/L as show in Figure 8. There was no significant difference between FSH and LET.

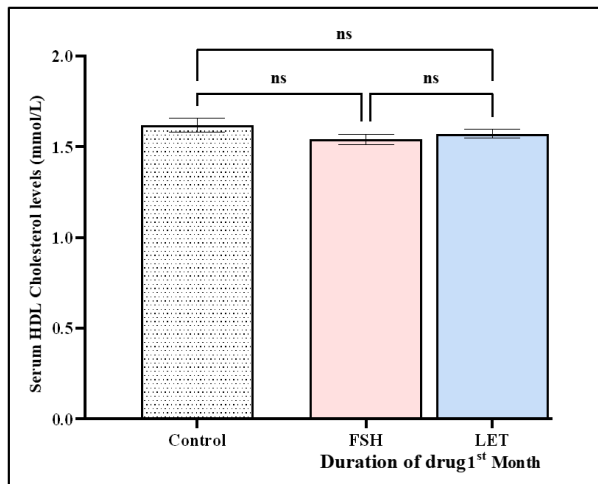


Figure 8: Estimation of serum HDL cholesterol concentration in mmol/L for the three groups in the first month.

In the second month of using FSH and LET the level of serum HDL cholesterol showed a significant difference as compared to the control group, and they were respectively, 1.42 ± 0.2156 mmol/L, 1.402 ± 0.1485 mmol/L, and 1.62 ± 0.22 mmol/L as show in Figure 9. There was no significant difference between FSH and LET.

The measurement of serum HDL cholesterol concentration for the third month of using FSH and LET reveal a significant difference as compared to the control group, and they were respectively, 1.338 ± 0.1466 mmol/L, 1.365 ± 0.1585 mmol/L, and 1.62 ± 0.22 mmol/L as show in Figure 10. There was no a significant difference between FSH and LET.

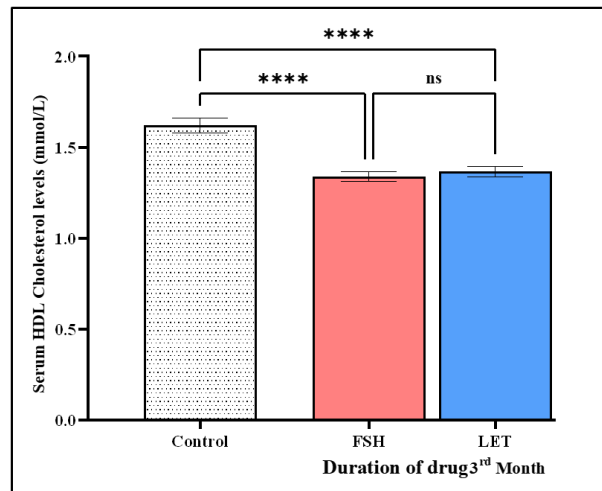


Figure 10: Estimation of serum HDL cholesterol concentration in mmol/L for the three groups in the third month.

4.4 Measurement of total antioxidant capacity

The measurement of serum total antioxidant capacity concentration for the two groups in the first month after FSH and LET administration revealed a significant difference as compared to the control group, and they were respectively, 341.5 ± 13.53 μ mol/L, 242.2 ± 15.88 μ mol/L, and 384.4 ± 21.15 μ mol/L, as shown

in Figure 11. There was also a significant difference between FSH and LET.

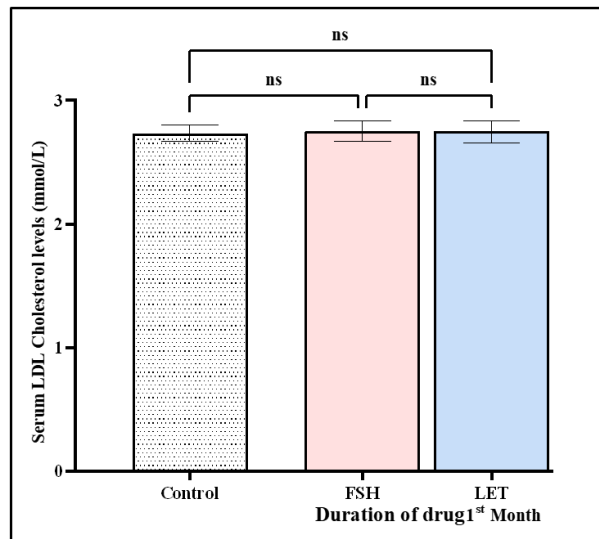


Figure 11: Estimation of serum Total Antioxidant Capacity concentration in $\mu\text{mol/L}$ for the three groups in the first month.

In the second month of using FSH and LET the level of serum total antioxidant capacity showed a significant difference as compared to the control group, and they were respectively, $365.1 \pm 4.8 \mu\text{mol/L}$, $317.1 \pm 15.61 \mu\text{mol/L}$, and $384.4 \pm 21.15 \mu\text{mol/L}$, as shown in Figure 12. There was also a significant difference between FSH and LET.

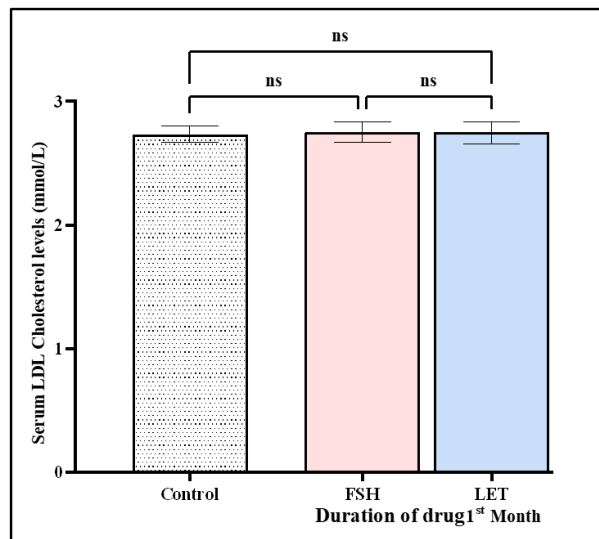


Figure 12: Estimation of serum Total Antioxidant Capacity concentration in $\mu\text{mol/L}$ for the three groups in the second month.

The measurement of serum total antioxidant capacity concentration for the third month of using LET revealed a significant difference as compared to the

control group, and they were respectively, $401.6 \pm 23.3 \mu\text{mol/L}$, and $384.4 \pm 21.15 \mu\text{mol/L}$, where there was no significant difference between FSH and control group, and they were $395.7 \pm 16.33 \mu\text{mol/L}$, and $384.4 \pm 21.15 \mu\text{mol/L}$, as shown in Figure 13. There was no significant difference between FSH and LET.

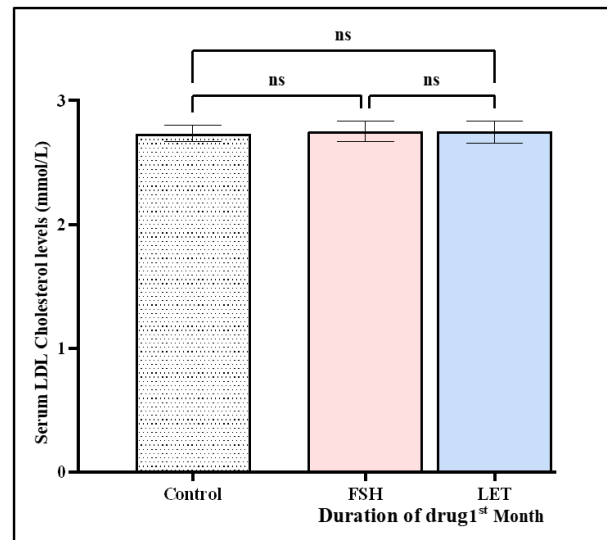


Figure 13: Estimation of serum Total Antioxidant Capacity concentration in $\mu\text{mol/L}$ for the three groups in the third month.

5 Discussion

The human body needs three basic components to ensure its functions: proteins, fats, and antioxidants. For women with fertility problems, problems are often linked to these three components. The effect of fertility hormones on protein, cholesterol and oxidative stress in women may vary from person to person and depends on the individual's response to medication and individual health conditions [18].

LET reduces estrogen levels, where estrogens orchestrate the metabolism of lipids and lipoproteins and thus a reduction in their production can imply a dysregulation of lipid indices. Aromatase inhibitors are agents that suppress the biosynthesis of estrogen and, therefore, reduce the negative feedback effect on the hypothalamic–pituitary system. This results in increased secretion of FSH that can lead to follicle selection and maturation [19].

In this study the use of induction leads to more mature follicle that means extraordinary levels of estrogen the use of induction for three-month lead to increase of lipid profile specially in the third month. In this study, the measurement of serum total cholesterol concentration for the two groups in the first month after FSH and LET administration reveal no significant difference as compared to the control group. There

was also no significant difference between FSH and LET. In the second month of using FSH and LET the level of serum cholesterol showed a significant difference as compared to the control group. There was no significant difference between FSH and LET. The measurement of serum total cholesterol concentration for the third month of using FSH and LET revealed a significant difference as compared to the control group. There was no significant difference between FSH and LET.

This results agreed with Volodymyr I. Lushchak (2014), it showed no link between high estrogen levels and hypocholesterolemia, as they found that cholesterol levels decreased with rising estrogen levels, especially after clomiphene citrate use for the third month of LEZ treatment [20]. According to Yangin et al. (2008), inhibiting FSH signaling may be a new approach to treat hypercholesterolemia throughout the menopausal period, especially in premenopausal women with increased levels of FSH injection alone [21].

In this study, the measurement of serum Triglycerides concentration for the two groups in the first month after FSH and LET administration reveal no significant difference as compared to the control group. There was also no significant difference between FSH and LET. In the second month of using FSH and LET the level of serum Triglycerides showed a significant difference as compared to the control group. There was also a significant difference between FSH and LET. The measurement of serum Triglycerides concentration for the third month of using FSH and LET reveal a significant difference as compared to the control group. There was also a significant difference between FSH and LET.

This is consistent with what was reported by Haiying Zhang et al. (2022) and Alireza Nourazarian et al. (2014), who linked increased estrogen levels with hypocholesterolemia [22, 23]. According to Rusk and Christopher (2006), the body has a lipid system, which has not been affected and no difference has been shown in the levels of TG in the body as a result of the use of FSH injection treatments [24].

In this study, the use of the induction program by LET decreased the level of estrogen to an abnormal concentration and this was associated with a decrease in the level of serum HDL. This is consistent with what was reported by Tao Cai et al., they found that LET reduces estrogen levels, affecting lipid indices because of the positive role of estrogens in modulating lipoproteins and lipids [25].

The measurement of serum HDL cholesterol concentration for the two groups in the first month after FSH and LET administration reveal a significant difference as compared to the control group. There was no significant difference between FSH and LET. In the

second month of using FSH and LET the level of serum HDL cholesterol showed a significant difference as compared to the control group. There was no significant difference between FSH and LET. The measurement of serum HDL cholesterol concentration for the third month of using FSH and LET reveal a significant difference as compared to the control group. There was no a significant difference between FSH and LET.

The results of this study are consistent with what researchers Wen Zhang and others found, as they linked low FSH to low levels of HDL in a direct relationship, and vice versa, that is, when FSH is high, HDL levels increase [26].

The measurement of serum total antioxidant capacity concentration for the two groups in the first month after FSH and LET administration revealed a significant difference as compared to the control group. There was also a significant difference between FSH and LET. In the second month of using FSH and LET the level of serum total antioxidant capacity showed a significant difference as compared to the control group. There was also a significant difference between FSH and LET. The measurement of serum total antioxidant capacity concentration for the third month of using FSH and LET revealed a significant difference between LET and control group, where there was no significant difference between FSH and control group. There was also no significant difference between FSH and LET.

oxidative stress characterized by the imbalance between pro-oxidants and antioxidants molecules, which involved in the pathogenesis of subfertility in females. oxidative stress plays an essential physiological role in the modulation of a full spectrum of reproductive functions, such as oocyte maturation, ovarian steroidogenesis, formation of the corpus luteum and luteolysis, fertilization, embryo development and pregnancy. oxidative damage has been implicated as a causal factor in the oocytes quality. While the use of induction in this study leads to more mature follicles and thus increase fertility.

The effect of LET on oxidative stress has not been fully studied in women. Some general fertility research suggests that ovarian stimulation may increase oxidative stress in the body due to hormonal changes. Oxidative stress occurs when the number of free radicals exceeds the number of antioxidants in the body and can lead to damage to the body's cells. However, some evidence suggests that a diet rich in antioxidants, such as fruits, vegetables, and nutritional supplements, may help fight oxidative stress [27].

Michael J. et al. discovered that whereas oral HRT regimens may improve the synthesis rates of albumin, there was no beneficial effect of hormone replacement therapy (HRT) on rates of total body protein turnover, nor was there a harmful effect of ovarian

hormone deficit concomitant with the postmenopausal state [28]. So the use of LET and FSH injection are useful to stimulate follicular maturation but the recurrent administration of induction program could lead to a very serious hormonal changes that might effects the general metabolic pathways it need further studies to identify the possible ways to avoid those complications.

6 Conclusions

In conclusion, the recurrent use of ovulation induction drugs can have a significant impact on various biochemical parameters, including total protein, lipid profile, and total antioxidant levels. Several studies have investigated the effects of these drugs on women undergoing fertility treatments, shedding light on their potential consequences. It has been observed that the use of ovulation induction drugs can alter the levels of total protein in the body. These medications, which commonly include synthetic hormones, may affect protein synthesis routes and levels.

Conflict of Interest: No conflicts of interest exist between the authors and the publication of this work.

Ethical consideration: The ethical committee approved the study at University of Al-Qadisiyah, Al-Qadisiyah, Iraq.

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