

# The Effect of FSH and Letrozole Treatment on The Lipid Profile in Women Being Treated for Fertility

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## ABSTRACT

**Background:** Letrozole, an aromatase inhibitor, affects the ovaries, breasts, adipose tissue, and bone by preventing androgen-to-estrogen conversion. This drastically reduces estrogen's effects. Estrogens regulate fat metabolism by influencing lipid and lipoprotein metabolism. FSH stimulation, which induces ovulation in non-pregnant women, may help pituitary dysfunction. Regulated ovarian hyperstimulation stimulation increases follicles during in vitro fertilization. **Background:** Letrozole, an aromatase inhibitor, affects the ovaries, breasts, adipose tissue, and bone by preventing androgen-to-estrogen conversion. This drastically reduces estrogen's effects. Estrogens regulate fat metabolism by influencing lipid and lipoprotein metabolism. FSH stimulation, which induces ovulation in non-pregnant women, may help pituitary dysfunction. Regulated ovarian hyperstimulation stimulation increases follicles during in vitro fertilization. **The aim:** To assess the difference in the level of fat (total cholesterol, triglycerides levels, HDL, LDL, and VLDL) of infertility treatment among the three study groups, the group that received HSF, the group that took Letrozole, and the control group. **Methods:** From October 2022 to May 2023, research was carried out. It featured 120 women who were split into three groups: those who took Letrozole consistently for a month or more in a row, those who received FSH injections continuously for a month or more in a row, and the control group who did not take any medications to promote ovulation. **Results:** The results show increased levels of total cholesterol, triglycerides, LDL cholesterol, and VLDL cholesterol in LET compared with other groups FSH and control. Our study showed a significant difference ( $p$ -value  $< 0.0001$ ) in the concentrations of TG compared to all studied groups, when the results show decreased levels of HDL cholesterol in LET compared with other groups FSH and control, a significant difference is showed ( $p$ -value  $< 0.0001$ ) in the concentrations of HDL cholesterol compared to all studied groups. **Conclusion:** Letrozole and FSH has modulated lipid profile via increasing triglyceride, cholesterol, HDL, LDL, and VLDL, with greater impact achieved by FSH and letrozole.

**Keywords:** Ovulation, FSH, Letrozole, Cholesterol, Triglycerides, HDL, LDL, VLDL.

## 1 INTRODUCTION

For mankind to survive over the long run, reproduction is essential. However, infertility considered after 12 months or more of unprotected sexual intercourse, infertility can develop from a variety of reproductive issues affecting both male and female partners [1]. Primary infertility, in which the pair has never conceived, and secondary infertility, in which the couple has once given birth but is having trouble getting pregnant again, are two different types of infertility [2]. Female infertility is a common problem, and syphilis and gonorrhea are two sexually transmitted illnesses that have a role in it.

Additionally, the prevalence of infertility has grown as a result of illnesses including diabetes, high blood pressure, and hypothyroidism as well as teenage obesity and addiction [3]. It is significant to remember that women account for more than half of instances of infertility, with a variety of causes including endometriosis, problems with the fallopian tubes, challenges linked to ovulation, and unexplained causes [4]. For women struggling with infertility, there are several treatment options available, including dietary changes, drugs, assisted reproductive technologies, and surgical treatments. The two most popular infertility therapies are ovulation induction and superovulation. In cases of other kinds of infertility, ovulation boost or con-

trolled ovarian hyper stimulation are used to increase the number of follicles, but the primary objective of treatment for anovulatory women is to promote the creation of at least one follicle [5,6].

The first stage in treating infertility is evaluation since it enables the identification of particular reasons and helps choose the best course of action. Ovulation triggers are frequently required, even though a complete history and physical examination yield useful information. Among the medications most frequently used to promote ovulation are gonadotropins, letrozole, and clomiphene citrate [7]. Letrozole, an aromatase inhibitor, primarily affects the last phase of turning androgens into estrogens. Ovaries, breasts, adipose tissue, and bone are just a few of the organs and tissues that experience a reduction in the availability of estrogen as a result of its typical 80–90% to 90% inhibition of the aromatase enzyme. Given that letrozole considerably lessens the effects of estrogens, this mechanism is particularly critical in the context of ovarian stimulation. Estrogen is crucial in controlling how lipids and lipoproteins are metabolized. They have an impact on how the body produces, utilizes, and excretes these compounds. Letrozole usage was associated with a drop in estrogen levels, which can have an impact on fat-related indicators [8,9]. Letrozole has the potential to alter lipid metabolism by lowering the availability of estrogens. Modulating the impact of estrogen on the metabolism of fats and lipoproteins may lead to dysregulation of fat markers [10].

Follicle stimulating hormone (FSH) is also very helpful for those who do not have normal pituitary function and need assistance ovulating. FSH has also been utilized to treat normally ovulating women who have not conceived naturally using conventional procedures, along with intrauterine insemination. In this instance, intrauterine insemination and FSH stimulation are utilized in an effort to increase the number of eggs that ovulate and, consequently, the likelihood of conception [11]. In order to boost the quantity of follicles generated during in vitro fertilization, the hormone FSH is also used to deliver controlled ovarian hyper stimulation. The fluid-filled sacs called follicles are where eggs develop [12].

Overall, letrozole's therapeutic effectiveness in a variety of illnesses is a result of its mode of action as an aromatase inhibitor and its capacity to decrease estrogen availability. However, it is crucial to take into account and carefully monitor any potential impact on fat markers during FSH and letrozole treatment. Elevated levels of triglycerides in the blood have been found to have a significant correlation with cardiovascular disease (CVD) mortality [13].

Monitoring triglyceride levels is important in assessing the risk of CVD and maintaining cardiovascular health. Increased cholesterol in the bloodstream increases the risk of plaque buildup in the arteries and the development of coronary artery disease [14]. HDL cholesterol is considered beneficial for cardiovascular health due to

its protective effects on the arteries. Having lower levels of LDL cholesterol is generally considered beneficial for vascular health, as it reduces the risk of plaque formation and related cardiovascular complications [15,16]. LDL acts as an internal transport system for lipids in the body, facilitating their delivery to various tissues and cells [17].

### 1.1 The aim

To assess the difference in the level of fat (total cholesterol, triglycerides levels, HDL, LDL, and VLDL) of infertility treatment among the three study groups, the group that received HSF, the group that took Letrozole, and the control group

## 2 MATERIALS AND METHODS

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, where the patient was asked whether she took ovulation induction treatment and whether it was LET or FSH, and they were asked about the treatment period. Samples were collected from 15 women who took LET treatment in the first month, and 15 other women in the second month, and the same number of other women in the third month. In the same way, samples were collected for women who were injected with FSH for three months and for different women. The number of patients in the study is 120. Women were divided into three groups: The first group consisted of 45 females who took Letrozole for a month or more in a row; Group 2 included females who were injected with FSH for a month or more in a row. The third group, referred to as the control group, consisted of 30 women who did not take any drugs to induce ovulation. The women's ages 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.

Measurement of Lipid profile: As per manufacturer instruction the serum cholesterol, triglyceride, and HDL were measured using ELISA techniques by using kit supplied by Sunlong (China) (cat No. SL3264Hu, SL2557Hu, and SL0878Hu) respectively. LDL calculated by equation ( $LDL-C = (Total\ Cholesterol) - (HDL-C) - (TGs/5)$ ) and VLDL calculated using equation ( $VLDL = \frac{1}{5} (Total\ Cholesterol - HDL-C - LDL-C)$ )

## 2.1 Statistical analysis

The statistical analysis conducted using GraphPad software using One-way ANOVA test. Data expressed as mean $\pm$ SD. P<0.05 is considered significant.

## 3 MEASUREMENT OF TC, TG AND HDL

### 3.1 Principle

This ELISA kit employs the Sandwich ELISA technique, which comprises pre-coating a Micro Elisa strip plate with an antibody that is specific to (TC, TG, HDL). The Micro Elisa strip plate has one antibody and either standards or samples in each well. Then, the Micro Elisa strip plate is incubated with an HRP-conjugated antibody that is specific to TC, TG, and HDL. Fill up every well with the TMB substrate solution once you've removed any extraneous items, but only in the wells that contain the (TC, TG, HDL) and HRP-conjugated (TC, TG, HDL) antibodies. We used spectrophotometry to quantify the optical density (OD).

### 3.2 Procedure

Dilute the standard by small tubes first, then pipette the volume of 50ul from each tube to the microplate well, each tube uses two wells, total of ten wells.

1. Add 10  $\mu$ L of sample and 40  $\mu$ L of sample dilution buffer to each well of the sample plate.
2. Following the application of the sealer, the plate was incubated at 37  $^{\circ}$ 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  $\mu$ L 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  $^{\circ}$ 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  $\mu$ L of Chromogen Solution B and 50 mL of Chromogen Solution A, which were then gently mixed and incubated at 37  $^{\circ}$ C for 15 minutes.
8. The wells received the addition of 50  $\mu$ L of stop solution. It finally took fifteen minutes to finish.
9. The OD value was determined using the plate reader at 450 nm

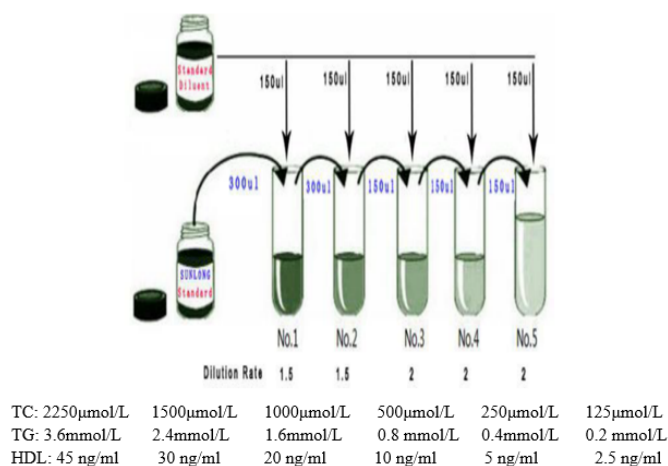


Fig. 1. Dilution of standards.

Table 1. Dilution of standards.

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

### 3.3 Measurement of LDL and VLDL

LDL and VLDL are not directly measured in a standard lipid panel. Instead, they are typically estimated or calculated using specific equations based on other lipid measurements obtained from a blood test.

The Friedewald equation is commonly used to estimate LDL cholesterol:

$$\text{LDL}(\text{mg/dL}) = \text{TC} - \text{HDL} - \text{VLDL} \quad (1)$$

This equation assumes fasting conditions and has certain limitations, particularly when triglyceride levels are very high (above 400 mg/dL) or when non-fasting samples are used. VLDL cholesterol is not directly measured but can be estimated by dividing triglyceride levels by a factor of 5, as VLDL contains approximately 20% of triglycerides.

$$\text{VLDL} = \frac{\text{triglycerides}}{5} \quad (2)$$

## 4 RESULTS

### 4.1 Total cholesterol

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 as show in Fig.2. There was also no significant difference between FSH and LET.

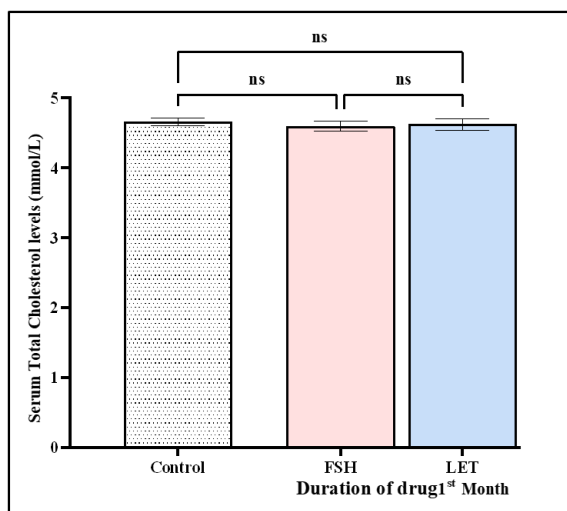


Fig. 2. Estimation of serum total cholesterol concentration in mmol/L for the three groups in the first month.

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,  $4.933 \pm 0.347$  mmol/L,  $5.025 \pm 0.443$  mmol/L, and  $4.66 \pm 0.288$  mmol/L as show in Fig.3. There was no significant difference between FSH and LET.

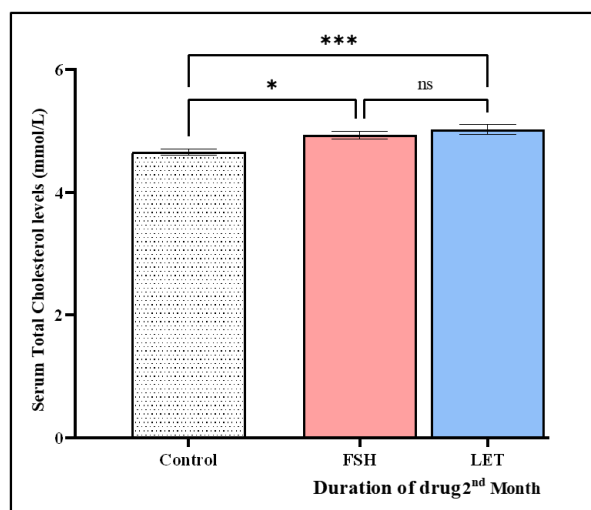


Fig. 3. Estimation of serum total cholesterol concentration in mmol/L for the three groups in the second month.

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

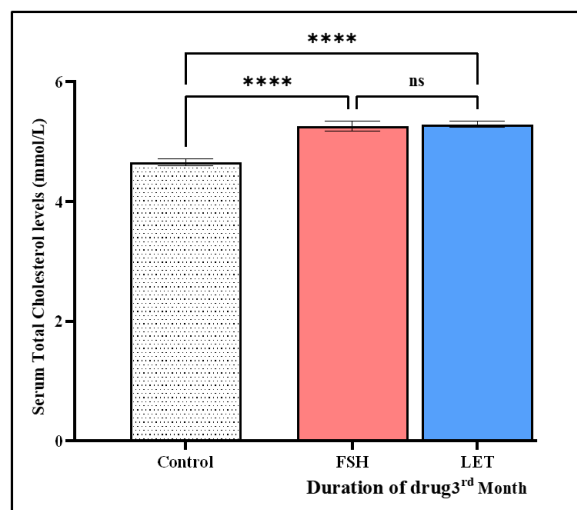


Fig. 4. Estimation of serum total cholesterol concentration in mmol/L for the three groups in the third month.

### 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 Fig.5. There was also no significant difference between FSH and LET.

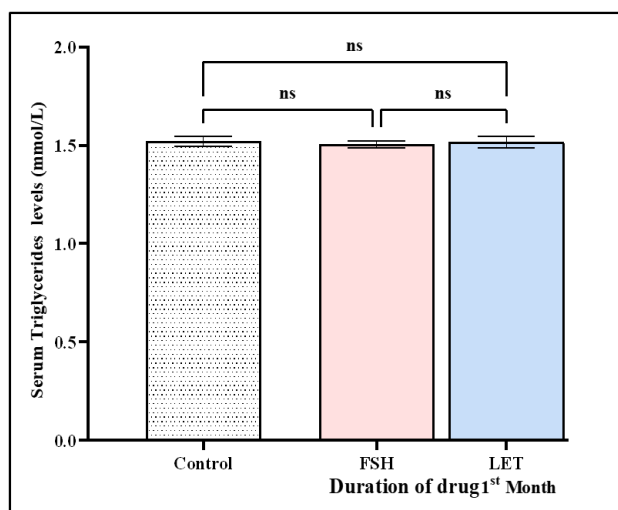


Fig. 5. Estimation of serum Triglycerides concentration in mmol/L for the three groups in the first month.

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,  $1.626 \pm 0.155$  mmol/L,  $1.672 \pm 0.2056$  mmol/L, and  $1.52 \pm 0.13$  mmol/L as show in Fig.6. There was also a significant difference between FSH and LET.

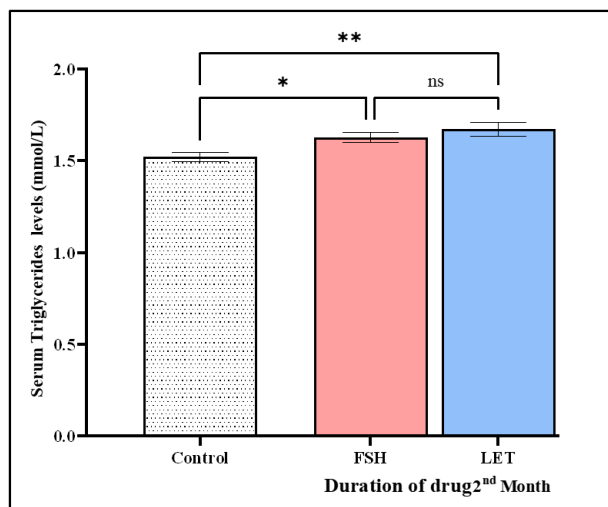


Fig. 6. Estimation of serum Triglycerides concentration in mmol/L for the three groups in the second month.

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,  $1.626 \pm 0.155$  mmol/L,  $1.808 \pm 0.1732$  mmol/L, and  $1.913 \pm 0.1774$  mmol/L as show in Fig.7. There was also a significant difference between FSH and LET.

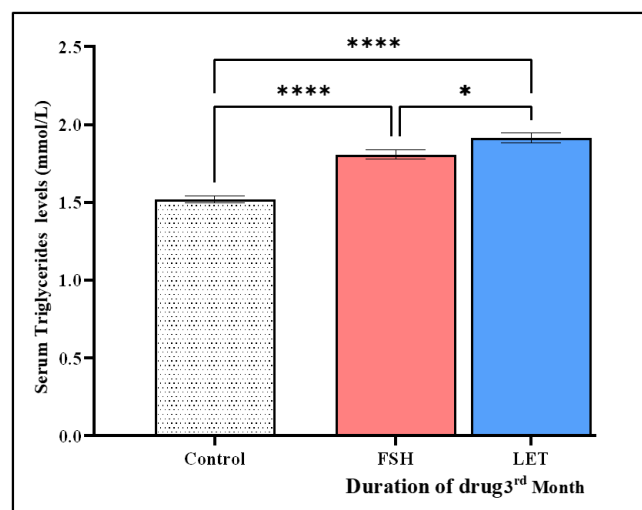


Fig. 7. Estimation of serum Triglycerides concentration in mmol/L for the three groups in the third month.

### 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,  $1.54 \pm 0.16$  mmol/L,  $1.57 \pm 0.13$  mmol/L, and  $1.62 \pm 0.22$  mmol/L as show in Fig.8. There was no significant difference between FSH and LET.

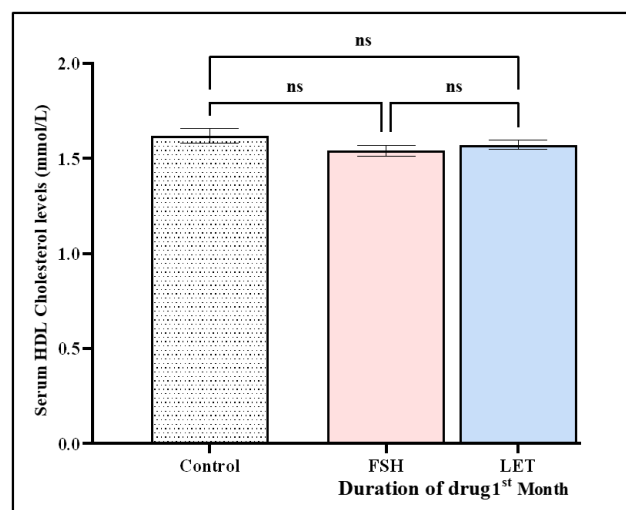


Fig. 8. Estimation of serum HDL cholesterol concentration in mmol/L for the three groups in the first month.

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,  $1.42 \pm 0.2156$  mmol/L,  $1.402 \pm 0.1485$  mmol/L, and  $1.62 \pm 0.22$  mmol/L as show in Fig.9. There was no significant difference between FSH and LET.

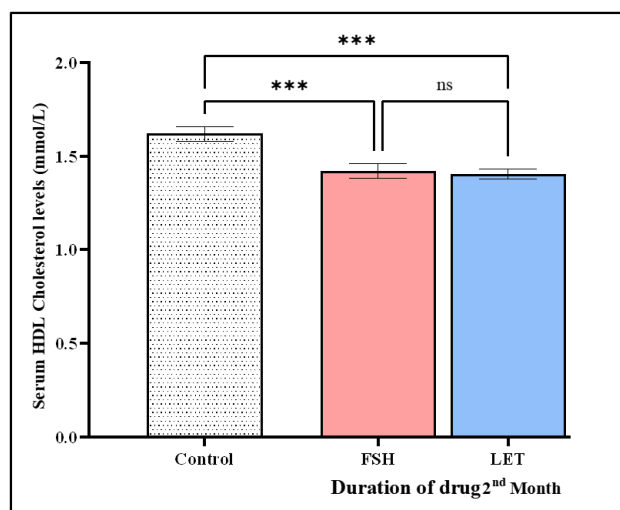


Fig. 9. Estimation of serum HDL cholesterol concentration in mmol/L for the three groups in the second month.

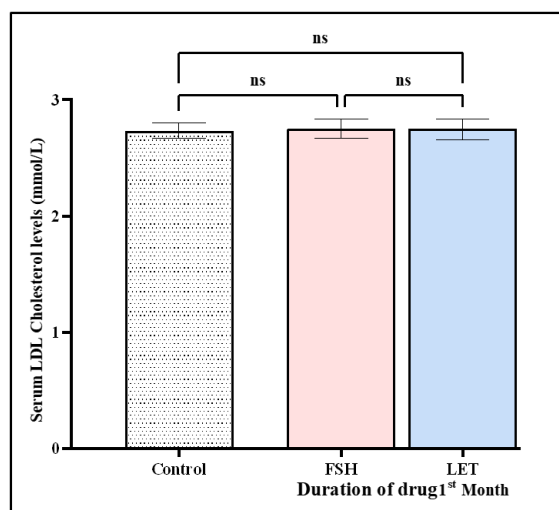


Fig. 11. Estimation of serum LDL cholesterol concentration in mmol/L for the three groups in the first month.

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,  $1.338 \pm 0.1466$  mmol/L,  $1.365 \pm 0.1585$  mmol/L, and  $1.62 \pm 0.22$  mmol/L as show in Fig.10. There was no a significant difference between FSH and LET.

In the second month of using FSH and LET the level of serum LDL cholesterol showed a significant difference as compared to the control group, and they were respectively,  $3.211 \pm 0.45$  mmol/L,  $2.89 \pm 0.46$  mmol/L, and  $2.73 \pm 0.37$  mmol/L as show in Fig.12. There was also a significant difference between FSH and LET.

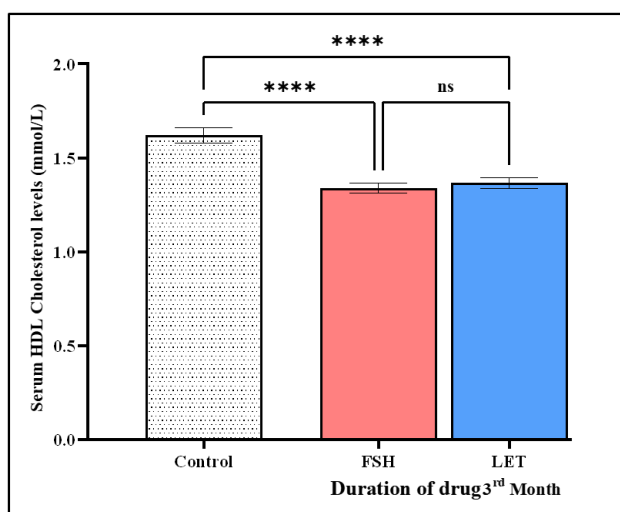


Fig. 10. Estimation of serum HDL cholesterol concentration in mmol/L for the three groups in the third month.

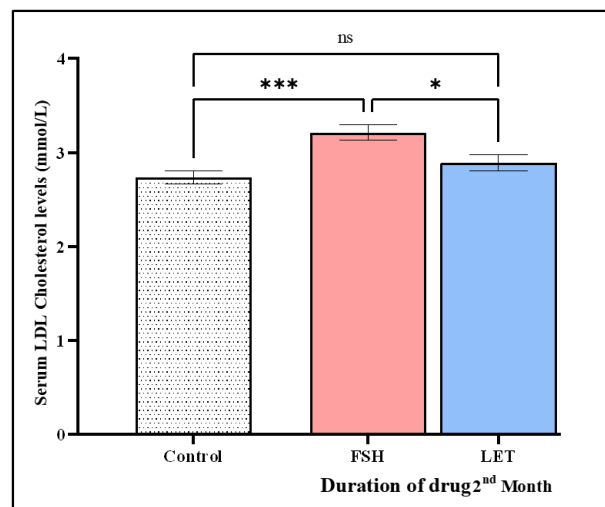


Fig. 12. Estimation of serum LDL cholesterol concentration in mmol/L for the three groups in the second month.

#### 4.4 LDL cholesterol

The measurement of serum LDL 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 as show in Fig.11. There was also no significant difference between FSH and LET.

The measurement of serum LDL 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,  $3.551 \pm 0.5397$  mmol/L,  $3.288 \pm 0.4787$  mmol/L, and  $2.73 \pm 0.37$  mmol/L as show in Fig.13. There was also a significant difference between FSH and LET.

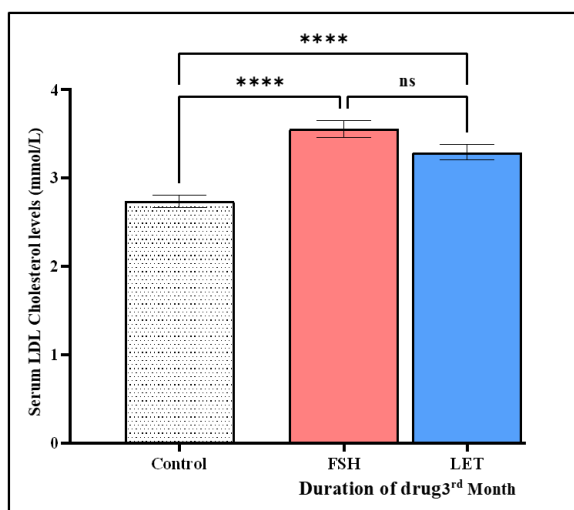


Fig. 13. Estimation of serum LDL cholesterol concentration in mmol/L for the three groups in the third month.

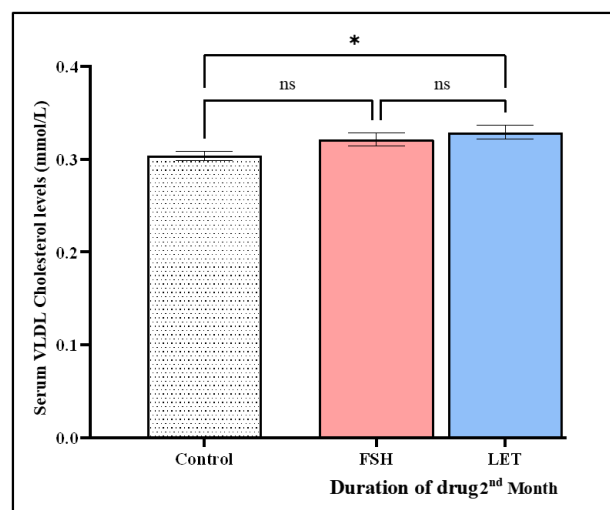


Fig. 15. Estimation of serum VLDL cholesterol concentration in mmol/L for the three groups in the second month.

#### 4.5 VLDL cholesterol

The measurement of serum VLDL 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 as show in Fig.14. There was also no significant difference between FSH and LET.

The measurement of serum VLDL 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,  $0.3705 \pm 0.04449$  mmol/L,  $0.3712 - 0.04014$  mmol/L, and  $0.304 \pm 0.0261$  mmol/L as show in Fig.16. There was no significant difference between FSH and LET.

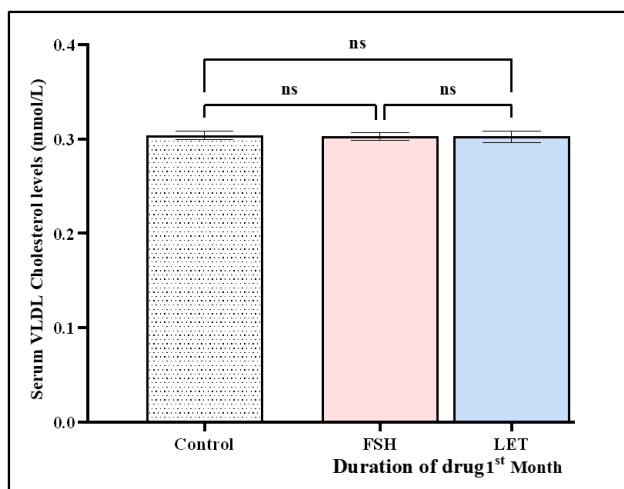


Fig. 14. Estimation of serum VLDL cholesterol concentration in mmol/L for the three groups in the first month.

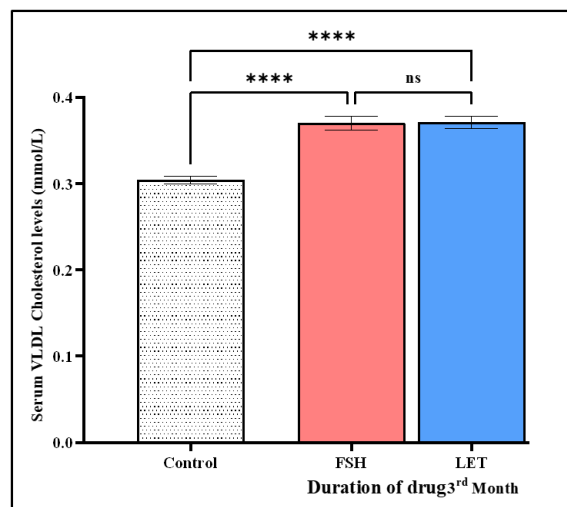


Fig. 16. Estimation of serum VLDL cholesterol concentration in mmol/L for the three groups in the third month.

In the second month of using FSH and LET the level of serum VLDL cholesterol showed a significant difference as compared to the control group, and they were respectively,  $0.322 \pm 0.037$  mmol/L,  $0.322 \pm 0.037$  mmol/L, and  $0.304 \pm 0.0261$  mmol/L as show in Fig.15. There was also a significant difference between FSH and LET.

## 5 DISCUSSION

Fats are essential building blocks for maintaining the body's activities. These three factors often cause concerns for women who have problems conceiving.

Letrozole may have different effects on fat in women depending on each person's reaction to the medication and health issues. According to some research, letrozole may

slightly raise blood fat levels. These subtle alterations have been observed in letrozole-induced ovarian stimulation and fertility experiments. However, these alterations are usually considered modest and may be related to underlying health problems. According to Rusk and Christopher (2006), the body has a lipid system that has resulted in a slight increase in body fat as a result of the use of ovarian stimulation treatments [17,18]. Low estrogen levels may increase the risk of hyperlipidemia and subsequent onset of cardiovascular disease in women, according to Kuwabara et al. (2009) and Kuznetsov (2020), who confirmed that the increase in blood lipid levels is caused by a decrease in estrogen level in women ([19,20]).

Low estrogen levels and increased obesity have been linked by Gao et al. (1999) and Nelson (2005) [21, 22]. In contrast, studies conducted by Stammler (2000) and Sarwar (2007) found no link between increased or decreased estrogen and obesity [23,24].

This study discovered that, especially after the third month of letrozole treatment, lipid levels rise while estrogen levels fall.

As a result of accelerating the breakdown of LDL, estrogen is essential for regulating lipid levels, as pointed out by Goulsen (2020), Montino, and Appetre (2021). It has been discovered that pharmacological doses of estrogen can mediate LDL absorption and lower its content [25,26].

In this study, application of a Letrozole and FSH induction program caused an endogenous decrease in estrogen level to an inappropriate concentration, which was associated with a modest increase in blood lipid levels. Letrozole can therefore be used to encourage follicular maturation, although repeated stimulation programs may cause very significant hormonal changes that can disrupt general metabolic pathways; Further study is needed to identify potential strategies to reduce these consequences.

## 6 CONCLUSION

The use of letrozole and FSH in reproductive medicine has been found to modulate the lipid profile by impacting various lipid parameters. These medications have been associated with an increase in triglyceride, cholesterol, LDL, and VLDL levels, and decrease in HDL level with letrozole often demonstrating a greater impact. It is crucial for healthcare professionals to be aware of these effects and consider lipid monitoring and management strategies in individuals undergoing treatment with letrozole and FSH to ensure optimal patient care and minimize any potential risks associated with altered lipid profiles.

**Conflict of Interest:** The authors declare no conflict of interest.

**Financing:** The study was performed without external funding.

**Ethical consideration:** The study was approved by

University of Al-Qadisiyah, Al-Qadisiyah, Iraq.

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