A J Journal of Medical Sciences

AJ Journal of Medical Sciences

ORIGINAL ARTICLE

Impact of Oral Zinc and L-Carnitine Supplementation on Follicles Growth and Endocrine Fertility Regulation in Female Albino Mice

Lamyaa Abdulridha Fadhil[1*]

[1]*Department of Biology, College of Science, University of Baghdad, Baghdad, Iraq*

ARTICLE INFO

Article history:
Received 13-11-2025
Accepted 27-12-2025
Published 31-12-2025

* *Corresponding author.*
Lamyaa Abdulridha Fadhil
lamyaa.fadel1102@gmail.com

https://doi.org/10.71325/ajjms.v2i4.25.91

ABSTRACT

Background and Aim: The current study explores the effects of zinc and L-carnitine supplementation on reproductive function in female albino mice. The study primarily focuses on growth of follicles and regulation of endocrine fertility. As previous studies have mentioned, both zinc and L-carnitine are crucial for reproductive health, this study explores the combined effect on reproductive hormonal regulation and ovarian follicle development. The aim of this study is to assess the impact of combined supplementation of zinc and L-carnitine on reproductive hormone levels and ovarian follicle development in female albino mice. **Materials and Methods:** Forty adult female mice were divided into four experimental groups. Control, Zinc (25 mg/kg/day), L-carnitine (0.5 mg/kg/day) and Zn + LC. Animals received the treatment for 30 days and follicle development, hormonal levels and histological changes in the ovarian tissues were assessed. **Results:** The zinc and L-carnitine supplementation gave rise to significant improvement in the ovarian follicles numbers along with a decrease in the abnormal follicles along with the results showed significant increased ($P< 0.05$) in the serum concentrations of reproductive hormones. Histological assessment results which further confirmed the above findings were seen in all groups supplemented with Zn and L-carnitine implicating their beneficial effect on reproductive potential. **Conclusion:** The combined use of zinc and L-carnitine has an enhanced effect which improves follicular growth and hormonal balance compared to either used alone. Their synergistic action assists ovarian function by enhancing energy metabolism and decreasing oxidative stress, indicating its great potential for the management of ovarian dysfunction.

Keywords: Folliculogenesis, Zn, L-carnitine, Fertility hormones, Oxidative stress

INTRODUCTION

Oxidative stress is an imbalance between the generation of free radicals and the body's capacity to use antioxidants to neutralize or detoxify their detrimental effects[1]. DNA, proteins, and lipids are among the biological structures that can be damaged by free radicals, particularly reactive oxygen species (ROS)[2]. affecting their ability to operate and possibly decreasing the likelihood of fertilization. For example, excessive ROS may break spermatozoa DNA, reducing their ability to fertilize. Similarly, oocyte maturation, quality, and viability may be affected by oxidative stress in the ovarian microenvironment[3]. Furthermore, excessive ROS can impede embryo growth and implantation after fertilization. Conditions causing infertility, including endometriosis and PCOS, have also been linked to elevated ROS levels[4]. One major factor impeding female fertility is oxidative stress, which increases uterine inflammation, the chance of miscarriage, embryo quality, and the risk of reproductive diseases[5].

Zinc, a naturally abundant trace element in the human body, is an important safeguarding component and cofactor for the catalytic activity of specific enzymes[6].

Zinc and L-carnitine have well-documented positive effects on reproductive function. They have been shown to enhance oocyte growth rates and regulate fertility-associated endocrine activity in female albino rat models[7]. Studies have shown that zinc significantly influences biological functions, including the regulation of animal fertility. In an animal model, neuronal and male infertility were associated with insufficient zinc levels, and zinc supplementation through oral administration recovered both conditions. Furthermore, after oral zinc supplementation in male goats, stored spermatozoa in genital structures adopted a competent physical state to fertilize the ovulatory oocyte, whereas low zinc concentration indicated greater in vivo viability among unstored sperm[8]. This positive effect of zinc on spermatozoa protection is consistent with the results of cell fertilization investigations. In pigs, insufficient zinc led to genital disorders, whereas adequate amounts restored fertility status. This mechanism was mediated through the upregulation of antioxidant and anti-apoptotic genes and downregulation of immune system-related genes. Therefore, oral zinc supplementation plays a crucial role in animal fertility[9].

Similarly, L-carnitine enhances sperm concentration and motility, increases the number of viable and fertilizing sperm in the epididymis, and regulates blood testosterone levels. These properties indicate the potential of both zinc and L-carnitine to support embryonic growth, particularly during the critical blastocyst phase[10]. Reproductive success is closely associated with the regulation of endocrine hormones, underscoring the importance of understanding how these supplements might influence fertility regulation in female albino rats[11]. A similar impact was exerted by L-carnitine on the reproductive system and, in extension, on fertility. The protective nature of L-carnitine against oxidative stress is fundamental for the preservation of fertility[12, 13].

MATERIALS AND METHODS

Supplementation Protocol

Zinc glutamate was bought in the form of a 1000 mg tablet and 1 ml of Zn and dose of (25 mg/kg/day) was administered orally to the matured female mice for (30 days). The dose was calculated based on Liu *et al.,*[6]. In a 30-day experiment, mature female mice were orally administered 1000 mg of L-carnitine for 0.5 mg/kg, in tablet form. The dosage was calculated according to Fakhrildin and Flayyih[14].

Experimental Design

For the current study, four main experimental groups were formed in which forty adult female albino mice of 8-10 weeks aged and weight 25-28 g were taken.

Each group was made up of 10 female mice. The organization of the team is in the following way:

(A) For a period of 30 days, the control mice were administered distilled water orally through a gavage tube, thereby creating conditions similar to those of the other groups.

(B) Mice were treated orally through a gavage tube at a dose of 25 mg/kg/day of zinc for 30 days. For a period of 30 days, the LC group was given LC by a gavage tube at a dose of 10mg/kg/day orally. Mice in the D group received a combined treatment of zinc (25mg/kg/day) and LC (10 mg/kg/day) by oral gavage for 30 days.

Animal Model

The experiment was approved in 2025 by the local ethics commission for animal research (Biology Department, College of Science, University of Baghdad under protocol number CSEC/1125/0159) and complied with Iraqi guidelines. For oral zinc and L-carnitine supplementation on follicle growth and endocrine fertility regulation, female albino mice were used as experimental animal models in the experiment. The day before the experiment, a mature and in-estrus female mouse is placed with a willing female rat. Thirty days after cervical dislocation, the rat is sacrificed after being given the supplement for a previous time interval. The timing of procedures is always based on the dynamics of follicle growth and endocrine regulation mechanisms[15].

Data Collection Methods

The effects of oral zinc and L-carnitine supplementation on follicles growth and endocrine fertility regulation were studied in female albino mice. The report attempts to clarify if these supplements encourage reproductive processes meaning they may enhance fertility. The animals used in the experiment were given either oral zinc or L-carnitine for a period. The number of normal and abnormal follicles observed in each group was used to assess folliculogenesis. The blood levels of progesterone, estradiol, FSH, LH, TSH, etc. were determined by hormonal analyses. Statistical analysis was conducted on the data to test significance. Developmental exposure to either oral zinc or L-carnitine increases the number of follicles. Higher concentration of hormones in supplemented groups[15].

Endocrine hormones analysis

The rats were anesthetized with chloroform. Blood was drawn from the heart of each animal to measure serum values of TSH, FSH, LH, oestrogen, and progesterone. As per the guidelines by the manufacturer, TSH, FSH, and LH were measured using ELISA kits (El abscience Co., Houston, TX). The measurement of estradiol and

progesterone was accomplished with the help of ELISA kits (Bio Check, Inc., Foster City, CA).

Histological analysis

The excised testicular tissues were preserved for a day in 10 percent formalin buffer. Next, after fixation, the specimens were washed with distilled water followed by a number of increasing alcohol concentrations. Xylene was used for cleaning dehydrated specimens and were embedded in a paraffin block. Tissue blocks of five µm thickness were prepared for sectioning. Sections were subjected to dehydration and staining with Hematoxylin and Eosin for standard analysis. A light microscope was utilized for histological examination in this regard[16].

Statistical Analysis

Using IBM SPSS Statistics software version 20, analyses were performed. Shapiro–Wilk test was used to check the data distribution. Data that were normally distributed were expressed as mean ± SD and were further processed with the one-way ANOVA test, followed by the Tukey's honest significant difference test. The values for the pairwise tests were found to be statistically significant at p-value < 0.05. Prior to the study, the power was not estimated. The R.3.2.3 version was used to analyse the GC-MS-NIST data files of the Zn complexes which were normalized for the analysis[17].

RESULTS

Table. 1 represents the differences in reproductive and thyroid hormones among experimental groups. Progesterone levels were lower in all experimental groups compared to control. Estrogen levels were higher, with LC showing the greatest increase, followed by Zn and Zn + LC groups. Similarly, LH and FSH levels were highest in the LC group, with moderate increases in Zn and Zn with LC groups compared to control. TSH levels rose in Zn and LC groups, while Zn with LC had lower TSH than other experimental groups, though still higher than control. However, the differences among the experimental groups were not statistically significant.

Table 1: Hormonal Profile of Control and Experimental Groups

Parameters Groups	Progesterone mIU/ml	Estrogen pg/ml	LH mIU/ml	FSH ng/ml	TSH ng/ml
Control group	34.78±5.62	123.75±9.56	5.19±0.63	6.82± 1.46	2.71± 0.92
Zn group	31.48±6.22	129.84±8.27	6.11±0.72	7.19±2.08	3.60±1.13
LC group	32.61±4.87	130.22±7.41	6.48±1.37	7.32±1.98	3.52±2.56
Zn + LC group	32.83±5.17	126.53±8.92	5.91±1.74	7.20±1.75	3.47±1.73

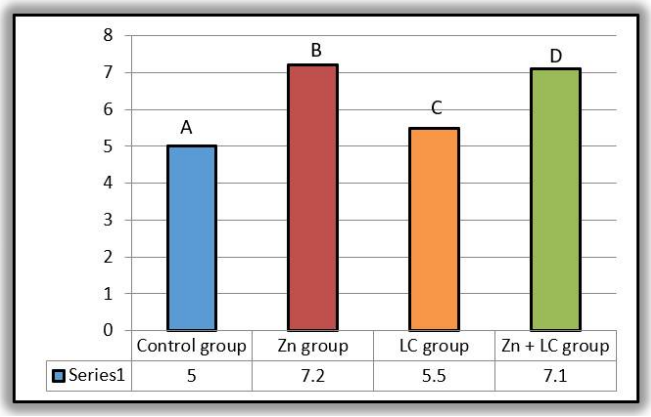

Fig. 1: Mean numbers of primordial follicles among study groups. [Different letters indicate that there are significant differences at the P ≤ 0.05 (t-Test). Same letters indicate that there are no significant differences at the P ≤ 0.05 (t-Test)]

The findings illustrated in Fig. 1 refer to the average number of primordial follicle (PF). The findings showed a significant (P ≤ 0.05) increase in the number of Primordial Follicles in the Zn group and Zn with LC group, while there was a decrease in the LC group compared to the control group (Fig. 1).

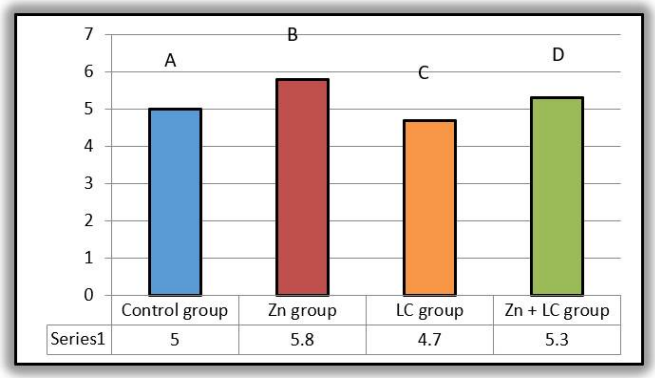

Fig. 2: Mean numbers of Primary Follicles among study groups [Different letters indicate that there are significant differences at the P ≤ 0.05 (t-Test). Same letters indicate that there are no significant differences at the P ≤ 0.05 (t-Test)]

Fig. 2 shows the mean number of Primary Follicles in Zn, LC, Zn with LC groups. The results revealed that the number of Primary Follicles was significantly ($P \leq 0.05$) increased in the Zn and Zn + LC groups and significantly decreased in the LC group compared to that in the control group.

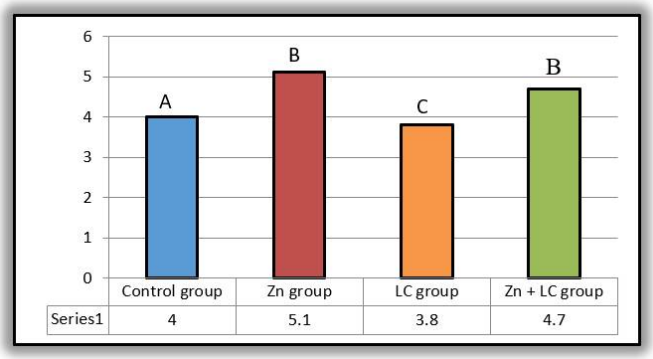

Fig. 3: Mean numbers of Graafian follicles (mature follicles) among study groups. [Different letters indicate that there are significant differences at the P ≤ 0.05 (t-Test). Same letters indicate that there are no significant differences at the P ≤ 0.05 (t-Test)]

The mean number of Graafian follicles from Zn, LC and Zn with LC groups are shown in Fig. 3. The data showed that the Graafian follicles were significant ($P \leq 0.05$) which was increased in the number of Graafian follicles of Zn group, and Zn with LC group while was slightly decreased in LC group in compared to control group (Fig. 3).

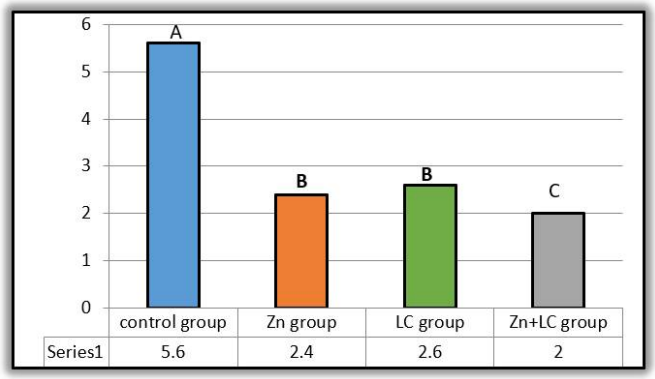

Fig. 4: Mean numbers of abnormal Follicles among study groups. [Different letters indicate that there are significant differences at the P ≤ 0.05 (t-Test). Same letters indicate that there are no significant differences at the P ≤ 0.05 (t-Test)]

In addition, as shown in Fig. 4, the results of mean numbers of abnormal Follicles in Zn, LC, and Zn with LC groups. Abnormal Follicles were significant ($P \leq 0.05$) decreased in the number abnormal Follicles of Zn group, LC group and Zn with LC group in compared to control group (Fig. 4).

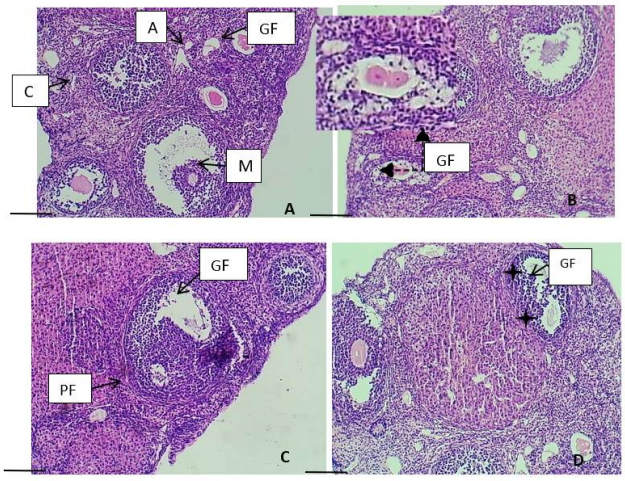

Fig. 5: Cross-section of ovarian tissue of mice in different groups showing abnormal follicles (A) control ovary: mature follicles, growing follicles, primordial follicles, corpus luteum, and atretic follicles. (B) A growing follicle with a large oocyte containing two oocytes. (C) A growing follicle merges with a primordial follicle. (D) A growing follicle containing two oocytes (star). (H&E). scale bar=100µm

As per this study, the follicles in the ovarian sections having multinucleate oocytes and/or more than two oocyte follicles (Fig. 5). We observed that Zn and LC supplementation significantly decreased the number of abnormal follicles in all treatment groups compared to that in the control group.

DISCUSSION

Zinc status has a great impact on synthesis, regulation and metabolism of progesterone. Zinc deficiency decreases the levels of progesterone in the hypophysial portal blood of ovariectomized rats[18] and the corpus luteum of zinc-deficient pregnant mice[19], and zinc excess increases concentration of receptor of this hormone in tissue of ovaries[20]. There is also a significant association between lower levels of progesterone and considerable zinc deficiency at the relatively broad range of 23-49 mg/kg in rat diets with < 4000 IU of vitamin D3. The current study has the mean within this range. The already recorded concentrations in normal and 24-hour light conditions under uncontrolled light of the environment in the past are within the range yet are not similar to the current observations. The theory of deferring is silent on the upsurge of a control group alone after experiencing reversion to normal photoperiod and light cycle of 12:12[21].

Previously it has been demonstrated that L-carnitine and acetyl-L-carnitine have positive effects on the hypothalamic-pituitary-gonadal axis and that they induce that adjustment of reproductive hormone levels in polycystic ovary syndrome. Moreover, it has been established that secretions and metabolism of gonadotropin and sex steroids are strongly affected by thyroid hormones, there is a common set of hypothalamic and pituitary pathways to modulate reproductive hormones, and that thyroid hormones have the capability to up or down regulate their receptors within these structures with systemic changes in TSH axis[22]. Considering this, it is hypothesized that in the female rat the L-carnitine can influence the secretion of the hormones of the reproductive system, which are progesterone, estrogen, FSH and TSH[23].

The 4-month intake of 60 mg LC/kg body weight/day had an impact on thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), estrogen (E2), and progesterone (P4) in female rats. The histological studies of ovaries are required to conclude whether LC supplements result in atresia of the follicles, corpus luteum degeneration, or estrus inhibition. This type of information is essential in determining the condition of the female rat reproductive system 30 minutes after sodium pentobarbital anesthesia[24]. Hormonal assay and control variables also contribute to making an experiment as one that impacted the reproductive system. The majority of the publications do not correlate FSH to TSH. The feedback of the thyroid-gonadal contributes to the level of hormones mostly during the per-pubertal stage. There are feedback levels of individual hormones. L-carnitine exhibits a coordinated display of its performance by coordination with TSH, FSH, E2, and P4[25].

The L-carnitine supplementation might stimulate secretion of FSH and/or reduce ovarian negative responses, which might effectively impact ovulation positively[26]. The hypothalamic-pituitary interactions of TSH and L-carnitine 1, which are upstream can also regulate the release of FSH. The secretion of TSH, FSH, estrogen and progesterone are crucial to reproduction. These hormones have not yet been studied in relation to secretion concomitant to L-carnitine. Evidence indicates that no effect is exerted on the baseline TSH concentration, although the potential of increased FSH production and/or reduced ovarian steroid feedback is to be investigated[27].

It would be anticipated that since FSH would decrease, TSH secretion would also be inhibited and also the secretion of ovarian estrogen and progesterone would go down. A higher concentration of FSH on the other hand would be expected to raise the secretion of TSH which may lead to an increase in the ovarian secretion of estrogen and progesterone. All these changes are indicative of an endocrine response which is in line with low nutritional stress[28]. It was involved in the present research that has tried to investigate the potential synergies of zinc and L-carnitine in protection of ovarian folliculogenesis by analyzing the histopathological and hormonal changes in the ovarian tissue following treatment.

The findings revealed that all the antioxidant defense mechanisms, ovarian morphology and follicular growth regulation were significantly improved with zinc supplementation. Similarly, L-carnitine treatment increased the quality of oocyte and also replaced the activity of the granulosa cell which shows that it acts as a free radical and mitochondrial scavenger. The deficiency of zinc can disrupt the process of meiosis and granulosa cell survival and the intracellular zinc dynamics are essential in the development of early follicles[6]. Moreover, Liu *et al.,*[29] revealed that the autophagy in ovarian tissue and the performance of mitochondrial functions are impaired by Zinc deficiency leading to the process of follicular atresia and poor oocyte quality.

On the other hand, L-carnitine lowers oxidative stress and cellular death in ovarian environment by enhancing mitochondrial b-oxidation. Xu *et al.,*[30] reported that L-carnitine enhances the expression of antioxidant enzymes and membrane potential in mitochondria to minimize human granulosa cell oxidative damage. Considering the results of the current study on healthier and increased follicles and fewer signs of degeneration, Zhao *et al.,*[31] found that oral L-carnitine supplementation improves the quality of the oocytes and embryos during the IVF cycles. Moreover, Di Emidio *et al.,*[32] highlighted the therapeutic usefulness of L-carnitine and its analogs in the field of reproductive medicine by pointing at its regulatory properties in maintenance of redox homeostasis and the enhancement of oocyte competence.

Zinc and L-carnitine supplementation could act together to prevent oxidative stress and endocrine disequilibrium. This is most likely due to the fact that zinc is a cofactor to antioxidant enzymes such as superoxide dismutase (SOD) and L-carnitine that enhances energy metabolism and the transportation of fatty acids into mitochondria. These other measures can improve the follicular environment besides stimulating angiogenesis and stabilizing the endocrine feedback such as FSH, LH, and estradiol. Minerals play a central role in the body defense mechanism to oxidative stress[33].

The results from hormonal profiling indicated that the zinc and L-carnitine treated groups had higher FSH and estrogen concentrations compared to the control group. These findings are also in line with the results of Brown and Davis[27] who observed that the ovarian receptivity and hormone production rely on optimal proportions of zinc and thyroid hormones. The outcomes of the anti-follicles

in the ovaries of females reduced significantly in both treatment groups (Zn and LC). In comparison with the control group, that included multinucleate oocytes and/or multi oocyte follicles, this could be because of the functions of the Zn and L-carnitine combination to mitigate the oxidative stress and imbalance hormones and sustain the follicles environment.

CONCLUSION

The overall findings indicate that zinc and L-carnitine can improve ovarian function by modulating hormone synthesis and mitochondrial homeostasis, which ultimately results in increased folliculogenesis. These findings confirm their potential therapeutic use to treat infertility caused by oxidative or metabolic disorders, ovarian dysfunction or premature ovarian failure.

DISCLOSURE

Funding: Nil.

Conflict of Interest: The author declared no conflict of interest.

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