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Folliculogenesis and Ovulation Enhanced by Human Recombinant IL-3 (hrIL-3) in Female Rats

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ABSTRACT
Cytokines known to their impact in ovarian physiology and follicular responsiveness being stimulated or inhibited. To investigate the role of human recombinant interleukin-3 (hrIL-3) on folliculogenesis and ovulation in female rats, we explored 48 female rats divided randomly into four equal groups (control and three treatment groups). All animals received superovulation protocols using pregnant mare serum gonadotropin (PMSG) 10 IU intra-peritoneally. After 48h, final maturation of oocytes had achieved using human chorionic gonadotropin (hCG) 10 IU intra-peritoneally. We injected hrIL-3 concomitantly with hCG in all three treated groups at doses of 15ng, 30ng, and 45ng/rat intravenously, while control group received normal saline at this time. According to killing time after 12h and 36h of hCG injection, the animals in all groups had further divided into two subgroups. Samples of ovaries were removed for histological examination. The result of this study revealed that rats from 45ng of hrIL-3 at 12h after hCG injection had significant increase ($p<0.05$) in follicles count in different stages of folliculogenesis as compared to the control group. In addition, diameters of secondary and Graafian follicles in 45ng group were higher significantly ($p<0.05$) than control. Histopathological examination to ovaries of this group demonstrated increased numbers of ovarian follicles in different stages of maturation, high count of corpora lutea, and congested blood vessels. So, we can conclude that 45ng is the most effective dose of hrIL-3, it may enhance ovulation and promoting growth of ovarian follicles in the different stages of folliculogenesis.
Keywords: *Folliculogenesis, Ovulation, hrIL-3, Ovarian follicles,Female rats.*

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INTRODUCTION

Ovarian follicle is the developmental and functional unit of the ovary. It consists of a single oocyte surrounded by layers of somatic granulosa and theca cells. Upon postnatal life, most oocytes appear as primordial follicles within a single layer of a few squamous flat granulosa cells. When follicles activated, theyundergo a series of developmental changes such as proliferation, differentiation and acquisition of a fluid-filled cavity of granulosa cells known as antrum, and formation of follicle wall(1). Pre-ovulatory follicle development is shifted away from differentiation toward luteinization after the pituitary gonadotropin luteinizing hormone (LH) surge, starting the first phases of corpus luteum formation (2).Whether or not a dominant follicle will reach ovulation depends on the frequency and amplitude of LH pulses continually induced in the pituitary (3,4). These sequential stages of folliculogenesis orchestrated by an extensive network of cytokines and growth factors which operate in response to the gonadotropin and steroid milieu (4).The midcycle surge of LH begins ovulation and is characterized by rupture of the follicular wall and the extrusion of the oocyte from ovary to the oviduct, the site of fertilization (5,6).In addition, LH surge induces terminal growth and maturation of both the dominant follicle, whose follicular fluid volume rapidly increases, and its oocyte resumes meiosis (4).

Upon folliculogenesis and ovulation, cytokines known as key regulators of ovarian physiology. They participate to provide suitable environment for follicle growth and selection (7). Granulosa cells and leukocytes can secrete numerous types of cytokines and chemokines participated in mediating ovarian functions, such as IL-1, IL-6, IL-8, tumor necrosis factor alpha (TNFα), colony-stimulating factor (CSF), granulocyte-macrophage (GM-CSF),and monocyte chemotactic protein-1 (MCP-1) (8).In the previous studies, many cytokines were studied to show their effect on ovary such as IL-1 family, IL-6, IL-8, TNFα and CSF. These studies confirmed that cytokines play a role in both follicular responsiveness to gonadotropins being stimulated and inhibited (9).The sequential release of cytokines acts to initiate and orchestrate inflammatory activity. In addition to controlling the ovulatory process, cytokines may also be

involved in ovarian cell proliferation, apoptosis, folliculogenesis, luteogenesis, oogenesis, release of hormones, response to hormonal regulators, and fertility (10). In this study, we aimed to investigate the possible role of human recombinant interleukin-3 in folliculogenesis and ovulation in female rats.

MATERIAL AND METHODS

Animals

Forty eight Wister female rats were explored in this experiment, weighted about 150±15 g and aged about 10 weeks. The animals were housed in the animal house according to the Ethics of the Veterinary Medicine at AlQadisiyiah University. They were allowed to *ad libilum* feeding and adapted for two weeks before the experiment. After adaptation, all animals of the experiment received superovulation protocol which achieved according to (11). Briefly, we injected 10 international unit (IU) intra peritoneally(I/P) of pregnant mare serum gonadotropin (PMSG) (Ovejero de, Mexico). Final maturation of oocytes performed after 48h by injection of hCG 10IU I/P (Msd Vet Co, USA).

Experimental design

To best of our knowledge, there is no scientific dose of interleukin-3 in female rats, yet. So, we used hrIL-3 (Sigma Aldrich, UK) at three upward increased doses (15ng, 30ng, and 45ng/rat) in a pilot study after superovulation to evaluate the role of IL-3 in folliculogenesis and ovulation. At the same time of hCG injection, animals were divided randomly into four groups (control and three treated groups) each grouphad 12 rats. Control group received normal saline at the same time of hCG injection. At this time, the three treated groups including T15,T30, and T45 received 15ng, 30ng, and 45ng/rat of hrIL-3I/V respectively. The animals of these four groups had been further divided into two subgroups each contained six female rats according to the time of killing including a and b subgroups after 12h and 36h of hCG injection, respectively. Right ovaries were removed from all animals of the study and fixed using neutral buffered formalin 10%. The routine histological processing and the preparation of slides was achieved according to (12). The thickness of ovarian sections about 5 micrometers. At least five sections from each ovary had examined under microscope.Then photomicrographs were captured respective to each group of animals recruited in this study.

Statistical analysis

The count of ovarian follicles (primary, secondary, tertiary(Graafian)follicles, and corpora lutea) were analyzed using two-way analysis of variance (ANOVA) with least significant difference (LSD).Two-way analysis of variance (ANOVA) explored also to analyze the diameters of follicles, thenifdata were significant undernon parametric Kruskal-Wallis test, they compared using Dunne's multiple comparisons test. Data were expressed as means ± standard errors (M± SE). Values considered statistically significant when (p<0.05).

RESULTS

According to the statistical analysis, the count of primary follicles showed significant increase (p<0.05) in T45a as compared to Ca, T15a and T30a. Secondary follicles count revealed significant increase (P<0.05) in all three treated groups (T45a, T15a, and T30a), respectively compared to Ca. Tertiary(Graafian)follicles count showed significant increase (p<0.05) in T45a group then T30a compared to Ca. While T15a had similar tertiary follicular count to that of Ca. The count of corpora lutea revealed significant increase (p<0.05) in all three treated groups compared to Ca. However, the higher significant increase had seen in T45a then T30a and T15a, respectively. The count of ovarian follicles in different stages of folliculogenesis after 12h of hCG injection was presented in (Table1).

After 36h of hCG injection, the counts of primary and secondary follicles were lower significantly(p<0.05) in the three treated groups (T15b, T30b, and T30b) compared to the control (Cb). Tertiary follicles count in T45b was equal to their count in Cb, while in T15b and T30b were lower significantly (p<0.05) than Cb. Regarding count of corpora lutea, there was no significant differences (P>0.05) between Cb and the three treated groups (T15b, T30b, and T30b). However, the corpora luteal count in the latter groups was higher than control, but did not reach the level of significant. The count of ovarian follicles in different stages of folliculogenesis after 36h of hCG injection was presented in (Table 2).

The diameters of primary follicles did not show any significant differences (P>0.05) between control and the three treated groups, both 12h and 36h (Figures1 and 2).The diameters of secondary follicles of T45a showed significant increase (P=0.009) compared to T30a after 12h. However, there were no significant differences with Ca and T45a (Figure 3). While after 36h, the diameters of secondary follicles of T45b were higher significantly than Cb and T15b (P=0.011) and (P=0.049), respectively (Figure4).The results of statistical analysis showed no significant differences(P>0.05) in the diameters of tertiary (Graafian) follicles after 12h between Ca and the three treated groups (Figure 5). At 36h, the female rats in T45b group had significant increase (P = 0.023) in tertiary follicles compared to Cb, but there was no significant

differences with the other groups (Figure 6). The diameters of corporalutea of female rats of all three treated groups did not show any significant differences(P>0.05) compared to control group both after 12h and 36h (Figure 7) and (Figure 8), respectively.

The histopathological examination of ovarian tissues in Ca group showed the presence of primary, secondary, and tertiary (Graafian) follicles, corpora lutea, medulla and blood vessels (Figure9). In Cb rats, the ovaries showed the same types of follicles, corpus luteum, medulla and blood vessels similar to these seen in Ca group (Figure10).

The ovaries of T15acharacterized by presence of corpora lutea, several small antral follicles, and congested blood vessels also evident (Figure 11).The results of histopathological evaluation of T15b group ovaries characterized by presence of huge number of primary and secondary follicles, several tertiary follicles, several regressing corpora lutea, and congested blood vessels in medulla (Figure12).

The histopathological examination of T30a ovaries showed presence of multiple corpora lutea, one large tertiary follicle, many primary and secondary follicles(Figure 13). The T30b group evaluation had indicate presence of several corpora lutea and congested blood vessels in the medulla. In this group several morphological changes of luteal cells were evident which includes hypertrophy with abundant vacuolated cytoplasm of the granulosa lutein cells along with hyalinization of the intercellular areas (Figure14). However, these changes were appeared in one section of the ovary, and the other sections were inactive functionally.

The histopathological examination of ovaries of the T45a group showed presence of huge numbers of corpora lutea and congested blood vessels in the medulla (Figure15). The T45b group showed multiple numbers of follicles in different maturation stages included primary follicles, secondary follicles, tertiary follicles, and atreticcorpora lutea, in addition to the congested blood vessels (Figure 16).

Table 1: Ovarian follicles count of the study groups (after 12h of hCG injection) shows the different developmental stages of folliculogenesis.

	Ca	T15a	T30a	T45a
Primary follicles	4 ± 0.57a	3 ± 0.24a	4 ±0.06a	8 ±0.12b
Secondary follicles	2 ±0.29a	7 ±0.26b	5 ±0.76c	10 ±0.09d
Tertiary follicles	2 ±0.64a	2 ±0.18a	5 ±0.55b	8 ±0.88c
Corpora lutea	2 ±0.00a	4 ±0.46b	5 ±0.82b	14 ±0.96c

Data presented as means± standard errors. Least significant difference (LSD) = 1.675. Different letters refer to the significant(p<0.05) differences between groups. Study groups (after 12h of hCG injection): Ca= control group received normal saline at the same time of hCG injection. T15a, T30a, and T45a= treatment groups received 15, 30, and 45ng/rat of hrIL-3 at the same time o fhCG injection, respectively.

Table 2: Ovarian follicles counts of the study groups (after 36h of hCG injection) shows the different developmental stages of folliculogenesis.

Follicles Type	Cb	T15b	T30b	T45b
Primary follicles	6 ± 0.33a	4 ±0.21b	2 ±0.38c	2 ±0.94c
Secondary follicles	10 ±0.85 a	8 ±0.11b	2 ±0.83c	7 ±0.05b
Tertiary follicles	5 ±0.70a	3 ±0.42b	2 ±0.65b	5 ±0.79a
Corpora lutea	3 ±0.36a	4 ±0.67a	4 ±0.37a	4 ±0.47a

Data presented as means± standard errors. Least significant difference (LSD) = 1.675. Different letters refer to the significant (p<0.05) differences between groups. Study groups (after 36h of hCG injection): Cb= control group received normal saline at the same time of hCG injection. T15b, T30b, and T45b= treatment groups received 15, 30, and 45ng/rat of hrIL-3 at the same time of hCG injection, respectively.

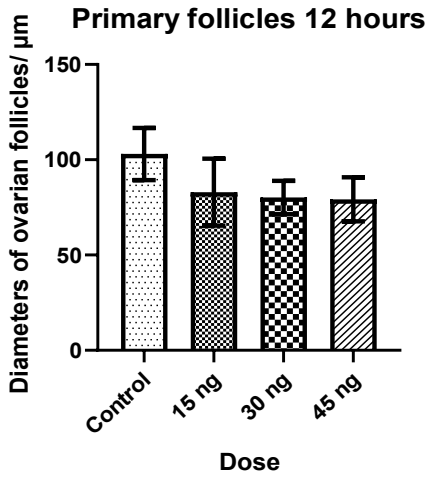

Figure1:Diameters of primary follicles (12h of hCG injection) to the control and three treatment groups T15a, T30a, and T45a that received 15, 30, and 45ng/rat of hrIL-3, respectively.

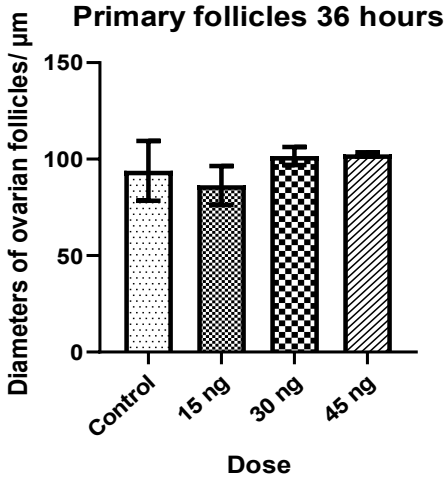

Figure 2:Diameters of primary follicles (36h of hCG injection) to the control and three treatment groups T15b, T30b, and T45b that received 15, 30, and 45ng/rat of hrIL-3, respectively.

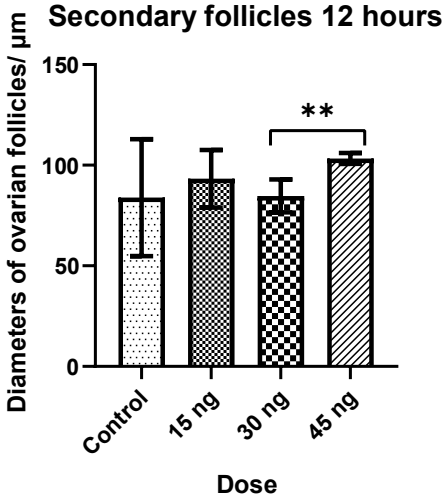

Figure 3: Diameters of secondary follicles (12h of hCG injection) to the control and three treatment groups T15a, T30a, and T45a that received 15, 30, and 45ng/rat of hrIL-3, respectively.

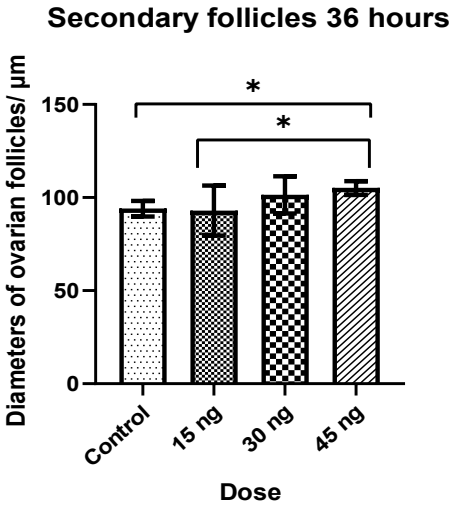

Figure 4: Diameters of secondary follicles (36h of hCG injection) to the control and three treatment groups T15b, T30b, and T45b that received 15, 30, and 45ng/rat of hrIL-3, respectively.

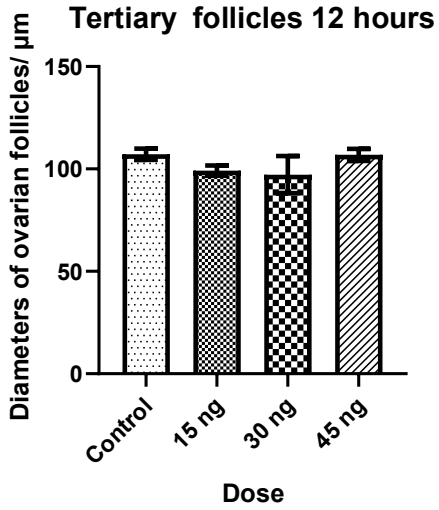

Figure 5: Diameters of tertiary follicles (12h of hCG injection) to the control and three treatment groups T15a, T30a, and T45a that received 15, 30, and 45ng/rat of hrIL-3, respectively.

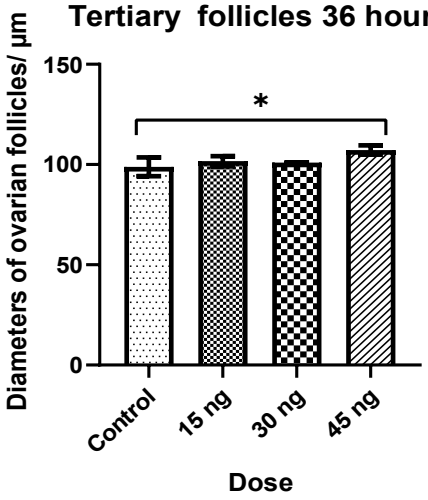

Figure 6: Diameters of tertiary follicles (36h of hCG injection) to the control and three treatment groups T15b, T30b, and T45b that received 15, 30, and 45ng/rat of hrIL-3, respectively.

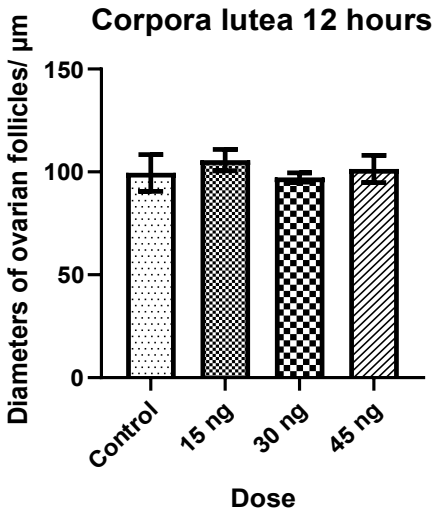

Figure 7: Diameters of corpora lutea (12h of hCG injection) to the control and three treatment groups T15a, T30a, and T45a that received 15, 30, and 45ng/rat of hrIL-3, respectively.

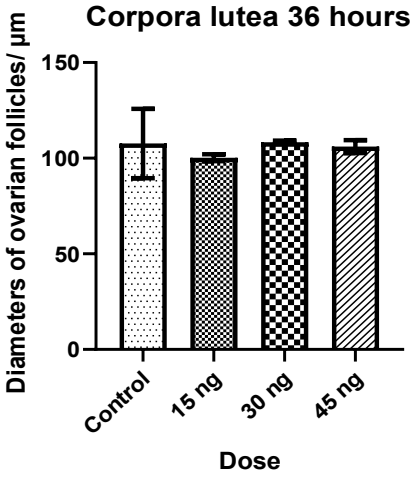

Figure 8: Diameters of corpora lutea (36h of hCG injection) to the control and three treatment groups T15b, T30b, and T45b that received 15, 30, and 45ng/rat of hrIL-3, respectively.

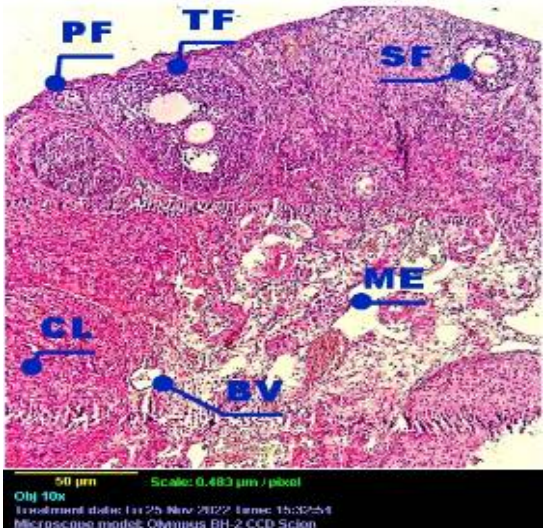

Figure 9: A photomicrograph of ovarian tissue in Ca group of rats after 12h of hCG injection (received normal saline). It shows primary follicle (PF), secondary follicle (SF), tertiary follicle (G), corpus luteum (CO), medulla (ME) and blood vessels (BV). H&E stain, X100.

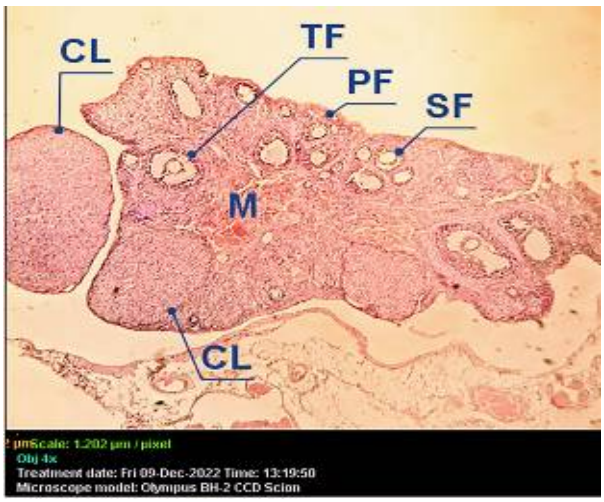

Figure10:A photomicrograph of ovarian tissue of Cb rat after 36h after hCG injection(received normal saline). It shows primary follicle (PF), secondary follicle (SF), tertiary follicle (G), corpus luteum (CO), medulla (M) and blood vessels (BV). H&E stain, 40X.

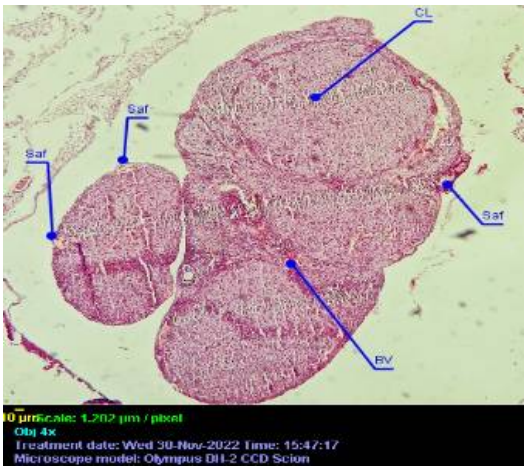

Figure11:A photomicrograph of the ovarian tissue of T15a rat 12h after injection of 15ng of hrIL-3.The ovary characterized by presence of corpora lutea (CL), several small antral follicles (Saf), and congested blood vessels. H&E, 40X.

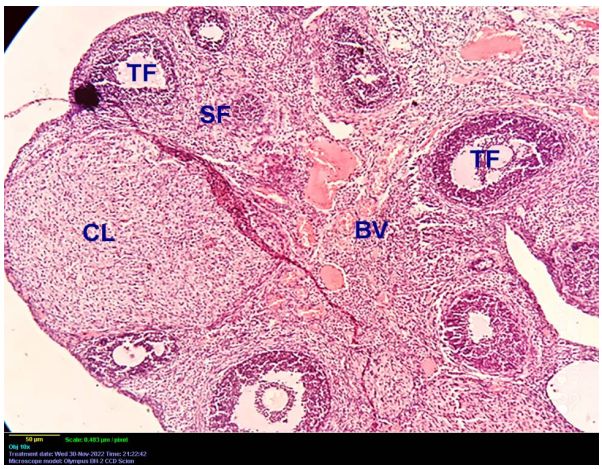

Figure12:A photomicrograph of ovarian tissue of T15b rat 36h after injection of 15ng ofhrIL-3. The ovary characterized by presence of several numbers of secondary follicles (SF), multiple tertiary follicle (TF), congested blood vessels in medulla (BV), and corpora lutea (CL). H&E, 10X.

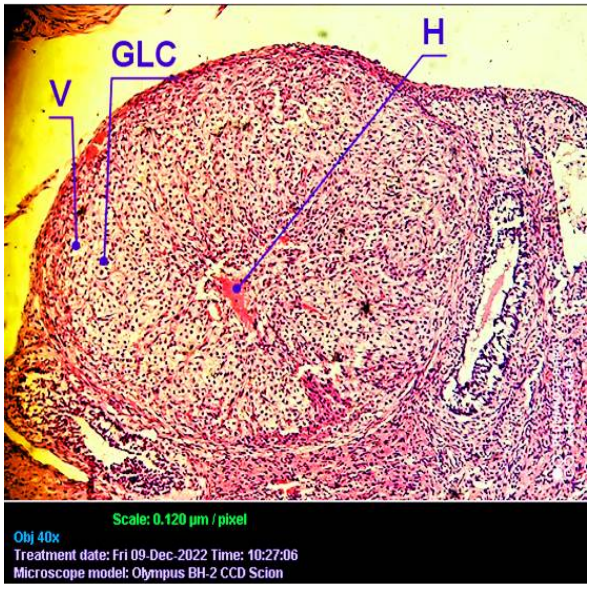

Figure13:A photomicrograph of ovarian tissue of T30a rat 12hafter injection of 30ng of hrIL-3.It shows morphological changes of luteal cells which become hypertrophied with abundant vacuolated cytoplasm (V) of the granulosa lutein cells (GLC) along with hyalinization of the intercellular areas (H). H&E, 400X.

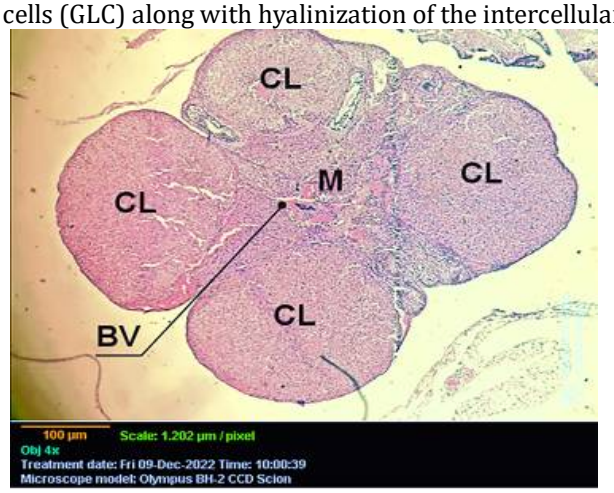

Figure14:A photomicrograph of ovarian tissue of T30b rat 36h after injection of 30ng of hrIL-3.It shows several corporalutea (CL) and congested blood vessels in the medulla. H&E, 40X.

Figure15:A photomicrograph of ovarian tissue of T45a rat 12h after injection of 45ng of hrIL-3.It shows huge numbers of corporalutea (CL) and congested blood vessels in the medulla (M). H&E, 40X.

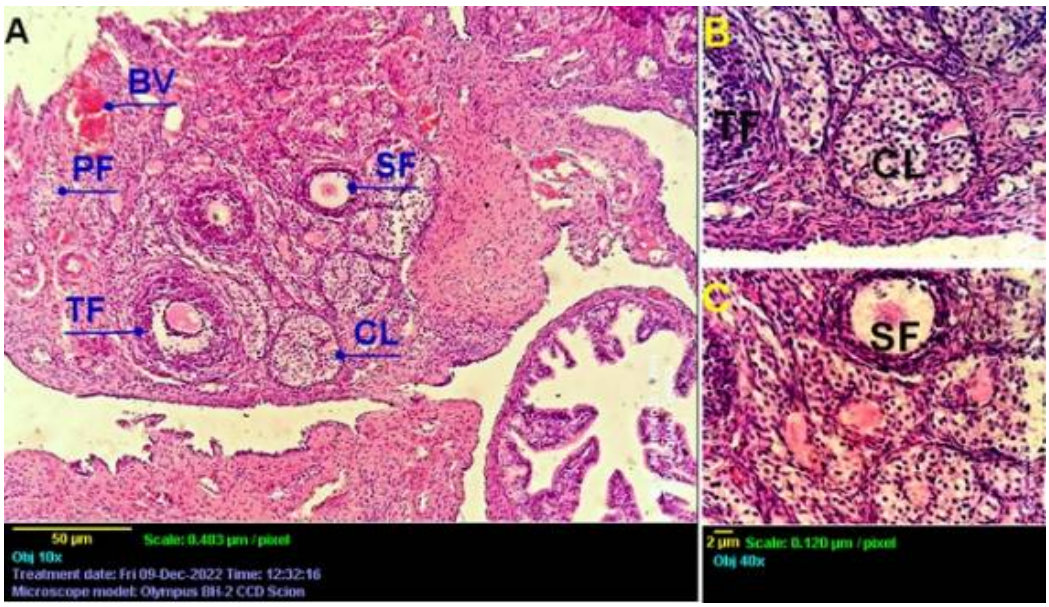

Figure 16:A photomicrograph of ovarian tissue of T45b rat after 36h of injection of 45ng of hrIL-3. It shows multiple numbers of different follicular maturation stages included primary follicles (PF), secondary follicles (SF), tertiary follicle (TF), and atreticcorporalutea (CL), and congested blood vessels (BV). H&E, (A) 40X, (B &C) 400X.

DISCUSSION

All animals in our study had undergone superovulation protocol, ovulation expected to occur in this protocol about 12-15h after hCG injection (11). So, we selected two times for animals killing 12h and 36h and considered them the beginning and the end of ovulation, respectively to show the possible effects of hrIL-3 on folliculogenesis and ovulation. The current study demonstrated that all three treatment groups that received hrIL-3 at 12h after hCG injection had follicular count higher significantly than control in different stages of folliculogenesis except the primary follicular stage.These results indicates that hrIL-3 at the beginning of ovulation increased maturation of follicles, so enhanced ovulation because ovulatory process is intimately related with maturation of oocyte. Reproduction in mammals depends on the timely ovulation of a developmentally competent mature oocyte (4, 5). When oocytes reach the final stage of development at the antral follicle stage, they acquire competence to get cytoplasmic and nuclear maturation. The antral follicle formed ideal microenvironment uniquely suited to the requirements of the oocyte as it approaches ovulation (4). However, the follicular count after 36h was lower significantly in treated groups compared to control with insignificant differences in numbers of corpora lutea. Furthermore, the diameters of follicles from primary to the corpora lutea stage in T15a, T15b, T30a, and T30b did not show significant differences with control. This may attributed to the high numbers of follicles within ovarian tissue in treatment groups. According to the results of this study, female rats that received 45ng of hrIL-3 at 12h after hCG injection showed better results compared to control besides other treated groups. For example, the significant increase in follicular count in all stages of folliculogenesis compared to control, especially the huge count of corpora lutea which reached 14 in this group versus 2 in control at the same time of hCG injection, taking into account that diameters of corpora lutea in these two groups were almost equal.

Ovarian folliculogenesisis controlled by both intraovarian and endocrine mechanisms that regulate the processes of growth of oocyte and the proliferation and differentiation of somatic cells. These interactions and oocyte-granulosa cell structure are follicle stage-specific and controlled by FSH (13).The preantral stages of follicular development require hormones and referred as gonadotropin-responsive to transform follicles from preantral to the preovulatory stage. While preovulatory antral follicles will be gonadotropin-dependent namely FSH-dependent from antral follicles to tertiary or Graafian follicle stage (14). Pituitary gonadotropins initiated ovulation following the LH surge and mediated signaling cascades by intrafollicular inflammatory mediators such as cytokines from the theca, mural, and cumulus granulosa cells, as well as the oocyte leading to follicular rupture (2,5, 6, 16). The LH/FSH surge initiates a series of events regulated breakdown of the follicular wall and extrusion of the oocyte (16). The LH surge stimulates dramatic changes in genes transcription associated with ovulation and luteinization(17). So, we think that hrIL-3 at a dose 45ng acts via LH and FSH to exert its positive effects on folliculogenesis and ovulation. The positive effect of hrIL-3 in increasing primary and secondary follicular count may

attributed to the gonadotropin-responsive follicles growth in this stage. Furthermore, the increased tertiary follicular and corpora luteal count may be due to the follicular growth in this stages of development which referred as gonadotropin-dependent especially via FSH and LH (14). However, the same dose (45ng of hrIL-3) did not show any significant differences in follicular count compared to control after 36h.

The results of histopathological examination in this study revealed that ovaries from all the three treated groups had congested and dilated blood vessels. Ovulation, a process referred as an inflammatory response due to the typical changes that occur during a classical inflammation. One of these important changes is vascular dilatation (2, 15). The increased blood flow results in tissue reddening during the LH surge, leading to increase vascular permeability causing fluid accumulation and swelling (18). The previous studies showed similar findings under the effect of other cytokines. For example, IL-1 induce ovulation by exerting cytotoxic effect on the granulosa, in addition to the stimulation of hyperemia and rupture of the follicle via nitric oxide (19). Angiogenesis is essential for the formation of corpus luteum (20). In luteinizing granulosa cells undergoing ovulation, the ovulatory LH-surge increases the gene expression of vascular endothelial growth factor (*vegf*) gene. The peak of gene expression of this gene reached at 12h after hCG injection in female rats (21).However, the mechanism by which hrIL-3 acts to increase congestion still unknown.The dilated and congested blood vessels reflects prominent changes related to ovulation (22). Histopathological examination to the sections of ovarian tissues from 45ng was another indication supported our hypothesis.

CONCLUSION

According to the results of our study, we can conclude that hrIL-3 in different doses (15ng, 30ng, and 45ng/rat) have positive role on folliculogenesis and ovulation. However, hrIL-3 a dose of 45ng at 12h afterhCG injection was the most effective dose owing to its role in promoting growth and maturation of ovarian follicles in the different stages of folliculogenesis and enhancement of ovulation may be via FSH and LH.

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CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

REFERENCES

1. UsluB, Johnson J. (2013). The In Vitro Culture of Ovarian Follicles: A Brief History and Current Considerations. In: Oocyte physiology and development in domestic animals. 1st. edition. Krisher RL. (Editor). John Wiley and sons, Inc. 21-34.
2. Richards JS, Russell DL, Ochsner S, Espey LL. (2022). Ovulation: new dimensions and new regulators of the inflammatory-like response. Annu Rev Physiol. 64:69–92
3. HennetML, and Combelles CM. (2012). The antral follicle: a microenvironment for oocyte differentiation. Int. J. Dev. Biol. 56: 819-831
4. Orsi NM, Baskind NE. Cummings M. Wilkinson N (Ed.). Pathology of the ovary, fallopian tube and peritoneum, essentials of diagnostic gynecological pathology, In: Anatomy, development, histology, and normal function of the ovary. 2014. www.https//doi.org/10.1007/978-1-4471-2942-4_1.
5. Robker RL, Hennebold JD, Russell DL. Coordination of Ovulation and Oocyte Maturation: A Good Egg at the Right Time. Endocrinol.2018; 159(9):3209–3218.
6. Duffy ME, Twenge JM, Joiner TE. Trends in Mood and Anxiety Symptoms and Suicide-Related Outcomes Among U.S. Undergraduates, 2007-2018: Evidence From Two National Surveys.2019;65(5):590-598.
7. Field S, Dasgupta T, Cummings M, and Orsi N. Cytokines in ovarian folliculogenesis, oocyte maturation and luteinisation. Mol. Reprod. Develop. 2014; 81:284–314.
8. Fujii A, Harada T, Yamauchi N, Iwabe T, Nishi Y, Yanase T, Nawata H, Terakawa N. Interleukin-8 gene and protein expression are up-regulated by interleukin-1β in normal human ovarian cells and a granulosa tumor cell line. FertilSteril. 2003; 79: 151-157.
9. Gougeon A.Intragonadal regulation of human follicular genesis: facts and hypotheses. 2012; 55(2):63-73.
10. Sirotkin AV. Cytokines: Signalling molecules controlling ovarian functions. Int J Biochem Cell Biol.2011;43, 857-861.
11. Yamamoto Y, Kuwahara A, Taniguchi Y, Yamasaki M, Tanaka Y, Mukai Y,Yamashita M, Matsuzaki T, Yasui T, Irahara M. (2015). Tumor necrosis factor alpha inhibits ovulation and induces granulosa cell death in rat ovaries. Reprod Med Biol. 14: 107–115.

12. Luna, LG. (1968). Manual of histologic staining methods of the armed forces institute of pathology. 3rd. Ed. Mcgraw-Hill Book Company. New York: 258.
13. Thomas FH, Vanderhyden BC. (2006). Oocyte-granulosa cell interactions during mouse follicular development: regulation of kit ligand expression and its role in oocyte growth. Endocrinology. 4:19.
14. Orisaka M, Tajima K, Tsang B, and Kotsuji F. (2009). Oocyte-granulosa-theca cell interactions during preantral follicular development. J. Ovarian Res. 2(9): 1-7.
15. Oliver C, Berg K, Moss J, Arron K, Burbidge C. (2011). Delineation of behavioral phenotypes in genetic syndromes: characteristics of autism spectrum disorder, affect and hyperactivity. J Autism Dev Disord ;41(8):1019-32.doi: 10.1007/s10803-010-1125-5
16. Sterneck E, Tessarollo L, Johnson PF. (1997). An essential role for C/EBPβ in female reproduction. Genes Dev. 11:2153–2162.
17. Lie JL, Misung J, Thomas E Curry J. (2011). A Role for Nuclear Factor Interleukin-3 (NFIL3), a Critical Transcriptional Repressor, in Down-Regulation of Periovulatory Gene Expression Feixue. Mol. Endocrinol. 25(3):445– 459.
18. Espey L. (1980). Ovulation as an inflammatory reaction-a hypothesis. BiolReprod. 22:73-106.
19. Mandrup-Poulsen T, Nerup J, Reimers JI, Pociot F, Andersen HU, Karlsen A, Bjerre U, BergholdtR. Cytokines and the endocrine system. I. (1995). The immunoendocrine network. European journal of endocrinology / European Federation of Endocrine Societies. 133(6), 660-671.
20. Sugino N, Matsuoka A, Taniguchi K, Tamura H. (2008). Angiogenesis in the human corpus luteum. Reproductive Medicine and Biology. 7:91–103.
21. Shinagawa M, Tamura I, Maekawa R, Sato S, Shirafuta Y,Mihara Y, MakiOkada-Matsumoto, Taketani T, Asada H, Tamura, Sugino N. (2019). C/EBPβ regulates Vegf gene expression in granulosa cells undergoing luteinization during ovulation in female rats. 9:714.
22. Aughey E, Frye FL. (2002). Comparative veterinary histology with clinical correlates. Manson publishing USA. ; 183-188.

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