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Letrozole Impact on Polycystic Ovarian Syndrome Subfertility Using Sonography and Hormonol Assay

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Abstract

Background: One of the main causes of infertility and anovulation is PCOS. the oral aromatase inhibitor letrozole has become a new and promising first-choice treatment for ovulation induction, especially in cases with PCOS and infertility due to effectiveness and acceptable adverse effect profile.

Objective: This clinical trial was intended to evaluate the impact of letrozole administration on the hormones, follicle size, and endometrial thickness among infertile women with PCOS

Patients & Methods

A study at Teba Centre for Infertility involved 100 female patients with PCOS and infertility. Data was collected before and after two months of letrozole administration, using modified Rotterdam criteria and hormone tests.

Results

Remarkable enhancements in the induction of ovulation and the modulation of hormones were noted after letrozole administration. Both follicle size and endometrial thickness increased dramatically. Relationships between the study variables were found by correlation analysis highlighting estrogen significance in differentiating between hormonal alterations.

Conclusion

Letrozole appears to be a promising treatment for infertility, by enhancing the hormonal, besides follicular, and endometrial sonographic features necessary for ovulation and successful pregnancy. To further understand causes and treatment plans, additional research is required.

تأثير ليتروزول على العقم الناتج عن متلازمة تكيس المبايض باستخدام التصوير بالموجات فوق الصوتية والفحص الهرموني

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الخلاصة

المقدمة

تعتبر متلازمة تكيس المبايض واحدة من الأسباب الرئيسية للعقم وعدم الإباضة. أصبح مثبط الأروماتاز الفموي "ليتروزول" خيارًا جديدًا واعدًا كعلاج أولي لتحفيز الإباضة، خاصة في حالات متلازمة تكيس المبايض والعقم، وذلك بفضل فعاليته وملفه الجانبي المقبول للآثار الجانبية.

الهدف

تهدف هذه التجربة السريرية إلى تقييم تأثير تناول "ليتروزول" على الهرمونات، وحجم الجريبات، وسمك بطانة الرحم لدى النساء المصابات بالعقم ومتلازمة تكيس المبايض.

العينات وطرق العمل

أجريت دراسة في مركز طيبة للعقم على 100 مريضة تعاني من متلازمة تكيس المبايض والعقم تم جمع البيانات قبل وبعد شهرين من إعطاء الليتروزول، باستخدام معايير روتردام المعدلة واختبارات الهرمونات.

النتائج

لوحظت تحسينات ملحوظة في تحفيز الإباضة وتعديل الهرمونات بعد تناول "ليتروزول". كما زاد حجم الجريبات وسمك بطانة الرحم بشكل كبير.

الاستنتاج

يبدو أن "ليتروزول" علاج واعد للعقم، من خلال تعزيز الخصائص الهرمونية، بالإضافة إلى تحسين الخصائص الجريبية والبطانية الرحمية اللازمة للإباضة والحمل الناجح. هناك حاجة لمزيد من الأبحاث لفهم الأسباب وخطط العلاج بشكل أفضل.

1. Introduction

Polycystic ovary syndrome (PCOS) affects an estimated 8–13% of reproductive-aged women and is considered the most common endocrinologic illness. Approximately, 70% of affected PCOS females remain undiagnosed universally. (Motlagh Asghari et al., 2022). The prevalence of PCOS in Iraqi women in Al-Hilla city was estimated at 33% of reproductive-aged women in a previous study. (Ban Aamer Mousa, 2020). PCOS is the most prevalent cause of anovulatory cycles and a principal cause of infertility among women ((WHO)). Polycystic ovarian syndrome is metabolic, endocrine and genetic disorders. Infertility is generally defined as the inability to conceive after one year or longer of unprotected sex. This condition can affect both men and women and may result from various factors affecting the process of conception, such as problems with ovulation, sperm quality, or the reproductive organs. (Adnan A. H. Al-Bdairi, 2021, Adnan A. H. Al-Bdairi 2023). Infertility is a common issue, with about 1 in 5 women aged 15 to 49 in the United States being unable to get pregnant after one year of trying. (Adnan A. H. Al-Bdairi 2022). Letrozole is a selective oral aromatase inhibitor for post-menopausal women with hormone-responsive breast cancer. It is a newer first-line treatment for the induction of ovulation mainly in infertile an-ovulatory women, often in conditions such as unexplained infertility and PCOS. (Chen et al., 2024). Being less harmful, more easily available, and a cheaper alternative to medications like clomiphene citrate, it has long been considered a treatment option when other traditional therapies have failed. (Yang et al., 2021). Letrozole induces mono-follicular development, and subsequently singleton pregnancies without related risk of multiple gestations. Letrozole, in addition, is beneficial in sperm motion characteristics in infertile men with pathologically reduced E2 serum profiles, resulting in improved fertility in oligospermic men. (AlJuboory et al., 2020). It also inhibits estrogen synthesis, which stimulates FSH secretion and the development of ovarian follicles. (Chen et al., 2024). Great confusion concerning the diagnosis of PCOS is caused by the broad heterogeneity of the warning symptoms experienced by patients with PCOS. Given the large number of females who suffer from PCOS and its substantial impact on the general well-being in the Middle East region, a better understanding of the contemporary burden is important. (Liu et al., 2021). Most clinic-epidemiologic surveys on PCOS have been carried out in developed states, with only restricted information existing on the burden in developing countries including Iraq. (Motlagh Asghari et al., 2022). This clinical was intended to evaluate the impact of letrozole administration on the hormones, follicle size, and endometrial thickness among infertile women with PCOS

2. Patients & Methods

2.1. Study Design

This study was designed as a prospective, randomized, single-center, controlled clinical trial, conducted at the Teba Center for Infertility and In-Vitro Fertilization, Babylon City-Iraq, from September 2023 to February 2024. It included 100 female patients with age ranges of 26.3±5.1 years who attended this center for infertility and PCOS or the diagnosis of PCOs was then made in the center. The gynecologists at the center diagnose, examine, assess, categorize, treat, and follow-up these females.

Any female with a history of infertility (primary or secondary) and PCOS, irrespective of the number of abortions they had or the regularity of their menses, age range of 18 – 35 y, was included. Any females with tubal blockage or who refused to participate were excluded from the current study. All the data about the demographic, clinical, and medical history of the included females were recorded. On the 2nd menstrual cycle day, ultrasound examinations performed by two separate specialist sonographers were reported about the follicle size and

endometrial thickness. In the meantime, hormonal assessments for FSH and estrogen were performed also. AMH assays were done only on the second day of the mens. On the 12th of the cycle and after two months of letrozole administration, ultrasound examination, and hormonal tests were repeated.

2.2. Diagnosis of PCOS

The final diagnosis of PCOS was confirmed by the gynecologists mainly in Teba Center based on history, clinical examination, hormonal studies, and ultrasound examinations, based on the "modified Rotterdam criteria" (Christ and Cedars, 2023).

2.3. Letrozole administration

Letrozole tablets (Femara®, NOVARTIS®, Basel, Switzerland) 2.5 mg, once daily after meal for 5 consequent days starting from the 2nd day of the mens for two consequent cycles. The medicine might be taken at any time throughout the day, nonetheless, it should be administered at the same time each day. The patients should swallow the tablet whole with a drink of water, and must not crush or chew it. It can be challenging to ensure that letrozole is taken precisely on "day two" of the MC in females whose MCs are irregular. (Chen et al., 2024). However, some policies can be adopted to estimate the time, such as progesterone challenge testing, serial ultrasound or hormonal monitoring, clinical decision-making, tracking the patient's own MC patterns, and baseline ultrasound and hormonal assessment. Eventually, clinical decision and flexibility are critical when dealing with patients with irregular MCs. Moreover, the team cooperates with patients, a reproductive endocrinologist, a fertility specialist, sonographers, and of course the gynecologists for optimal guidance and assistance in the management of irregular MCs.

2.4. Hormonal assays

Hormonal assessments of FSH, estrogen, and AMH were performed, which were evaluated by two-site immunoenzymometric assay using specific kits from TOSOH® Corporation, Tokyo, Japan.

2.5. Data Analyses

Statistical scrutiny was done by SPSS (V-27) and JASP (V- 0.18.3.0). The continuous parameters were written as (Means/SD). The chi-square test ($\boldsymbol{X^2}$) was utilized to expose the association between the categorical parameters. Independent samples t-test was applied to match any two groups' means. ANOVA was applied to compare the variation of the means among more than two groups. Pearson matrix correlation was applied to assess relationships between the continuous data. A p-value below 5% was significant in these analyses.

3. Results

Tables1 and Table2 show the clinical and demographic characteristics of the studied participants. The tables further break down the age distribution into three categories: < 20 years (16%), 20 – 29 years (55%), and ≥ 30 years (29%). The mean BMI increases with age, from 29.2 in the < 20 years group to 30.7 in the > 30 years group. The mean ± SD of BMI and marriage duration of the patients are 29.7±4.9, and 6.0±3.5years, respectively. The studied patients have undergone 0.6 abortions and have 0.8 children. Table 1 presents ultrasound measurements, including follicle size and number on U/S Day 2 and endometrial thickness on Day 2 and Day 12. Hormone levels, including FSH, Estrogen, and AMH, are also included in the tables. Table 2 provides insights into how various study variables vary across different age groups of the patients. However, the differences are not significant statistically ($p > 0.05$). There is a considerable variation ($p = 0.001$) in the duration of marriage across the age of the study groups. The frequency of abortions across age groups is relatively similar across all age classes ($p > 0.05$). The mean number of children increases significantly with age, from 0.2 in the < 20 years group to 1.1 in

the > 30 years group (p = 0.002). The mean follicle size and number on U/S at Day 2 across age groups are similar (p > 0.05). The mean endometrial thickness on the 2nd and 12th day of the MC across age groups remains relatively consistent (p > 0.05), for both measurements.

Table 1: Basal Demographic Features of The Studied Patients

Variables	Mean	Std. Deviation
Age	26.3	5.1
< 20 y	18.7	0.8
20 – 29 y	25.2	2.5
> 30 y	32.6	1.9
BMI	29.7	4.9
Duration of Marriage	6.0	3.5
No. of abortion	0.6	1.1
No. of children	0.8	0.9
Follicle size and no. on U/S Day 2	3.9	1.2
Endometrial thickness Day 2	3.9	5.1
Follicle size and no. on U/S Day 12	17.9	4.1
Endometrial thickness Day 12	7.8	0.5
FSH (mlU/mL)	7.2	3.1
Estrogen (pg/mL)	106.5	186.0
AMH (ng/mL)	4.5	2.9

Table2: Variations in study variables according to patient age groups: < 20 years (n = 16), 20–29 years (n = 55), and > 30 years (n = 29)

Variables	Age/year	Mean	SD	P value
BMI	< 20	29.2	4.3	> 0.05
	20 – 29	29.4	5.0	
	> 30	30.7	5.0	
Duration of Marriage	< 20	3.3	1.9	0.001
	20 – 29	6.0	3.1	
	> 30	7.4	4.0	
No. of abortion	< 20	0.4	0.8	> 0.05
	20 – 29	0.5	1.1	
	> 30	0.9	1.2	
No. of children	< 20	0.2	0.4	0.002
	20 – 29	0.7	0.8	
	> 30	1.1	1.1	
Follicle size and no. on U/S Day 2	< 20 y	4.0	1.1	> 0.05
	20 – 29 y	4.0	1.2	
	> 30 y	3.9	1.3	
Endometrial thickness Day 2	< 20 y	3.9	0.8	> 0.05
	20 – 29 y	7.9	0.7	
	> 30 y	3.7	0.7	
Follicle size and no. on U/S Day 12	< 20 y	18.9	4.0	> 0.05
	20 – 29 y	17.5	4.3	
	> 30 y	18.0	3.7	
Endometrial thickness Day 12	< 20 y	7.7	0.7	> 0.05
	20 – 29 y	7.9	0.3	
	> 30 y	7.7	0.6	

Table3 provides ultrasound findings regarding follicle size and mean endometrial thickness on the 2nd and 12th day of the MC. The data shows a substantial and statistically significant increase in follicle size from Day 2 to Day 12. The combined low p-values (0.001) for both the increase in follicle size and endometrial thickness reinforce the reliability of these changes. This rules out the likelihood that these results occurred by chance.

Table3: Ultrasound Findings of the Follicle Size and Endometrial Thickness on the 2nd and 12th Day of the Menstrual Cycle

Variable	Days of the menstruation	Mean	SD	P value
Follicle Size	Day 2	3.9	1.2	0.001
	Day12	17.8	5.1	
Endometrial Thickness	Day 2	3.9	0.8	0.001
	Day12	7.8	0.5	

Table4 presents hormonal findings of FSH and Estrogen at days 2 and 12 of the menstrual cycle. It indicates significant variations in estrogen levels between Day 2 and Day 12 of the menstrual cycle (p= 0.001), while FSH levels show no significant differences (p > 0.05).

Table 4: Hormonal Findings of FSH, and E2 at a Thickness on the 2nd And 12th Day of the Menstrual Cycle

Variable	Days of the menstruation	Mean	SD	P value
FSH	Day 2	7.1	2.6	> 0.05
	Day12	7.4	3.5	
E2	Day 2	41.4	31.4	0.001
	Day12	170.0	246.1	

Table5 presents the variation in study parameters according to the regularity of the menstrual cycle. It indicates that while there are non-significant alterations in age, BMI, and most hormonal parameters between women with irregular and regular menstrual cycles, there is a significant statistical alteration in the duration of marriage, with females experiencing irregular cycles having a shorter mean duration of marriage.

Table5: Variation in the study parameters according to the regularity of the menstrual cycle, [Regular cycle (N=61) and irregular cycle (N=39)]

Variables	Group	Mean	SD	P value
Age	Irregular	25.3	5.2	> 0.05
	Regular	27	5.0	
BMI	Irregular	29.5	4.8	> 0.05
	Regular	29.9	4.9	
Duration of Marriage	Irregular	4.9	3.2	0.03
	Regular	6.7	3.6	
No of Abortions	Irregular	0.5	1.1	> 0.05
	Regular	0.1	1.1	
No of Children	Irregular	0.6	0.8	> 0.05
	Regular	0.9	0.9	
FSH	Irregular	6.9	2.5	> 0.05
	Regular	7.2	2.7	
E2	Irregular	40.9	37.9	> 0.05
	Regular	41.6	26.9	

Numerous substantial correlations between the study variables are revealed by Spearman's correlation analysis Table6, offering insights into the interactions between various factors related to fertility and reproductive health.

Table 6: Spearman's Correlations Evaluations of the Study Variables Among Each Other

Variable		Age	Endometrial Thickness	BMI	Follicle Size	FSH	E2	AMH
Age	*R*	—						
	P	—						
Endometrial Thickness	*R*	-0.11	—					
	P	0.37	—					
BMI	*R*	0.26*	-0.16	—				
	P	0.02	0.17	—				
Follice Size	*R*	-0.03	0.898***	-0.04	—			
	P	0.83	< .001	0.72	—			
FSH	*R*	-0.08	-0.08	-0.05	-0.16	—		
	P	0.51	0.31	0.67	0.06	—		
E2	*R*	0.19	0.350**	0.09	0.36***	0.32***	—	
	P	0.10	0.001	0.46	< .001	< .001	—	
AMH	*R*	-0.21	0.06	-0.08	-0.10	-0.25*	0.17	—
	P	0.07	0.59	0.51	0.39	0.03	0.15	—
* p < .05, ** p < .01, *** p < .001								

The ability of endometrial thickness, follicle size, FSH, and estrogen to discriminate between hormonal and ultrasonic changes on days 2 and 12 of the MC following letrozole is displayed in Table7 and Fig.1 and Fig.2; along with the corresponding 95% confidence intervals (CI), specificity, sensitivity, and area under the curve (AUC). Endometrial thickness and follicle size are highly effective markers for distinguishing changes, making them valuable for monitoring menstrual cycle-related changes after letrozole administration. Estrogen has some utility but is less effective, while FSH is not a reliable marker for monitoring these changes, than endometrial thickness and follicle size.

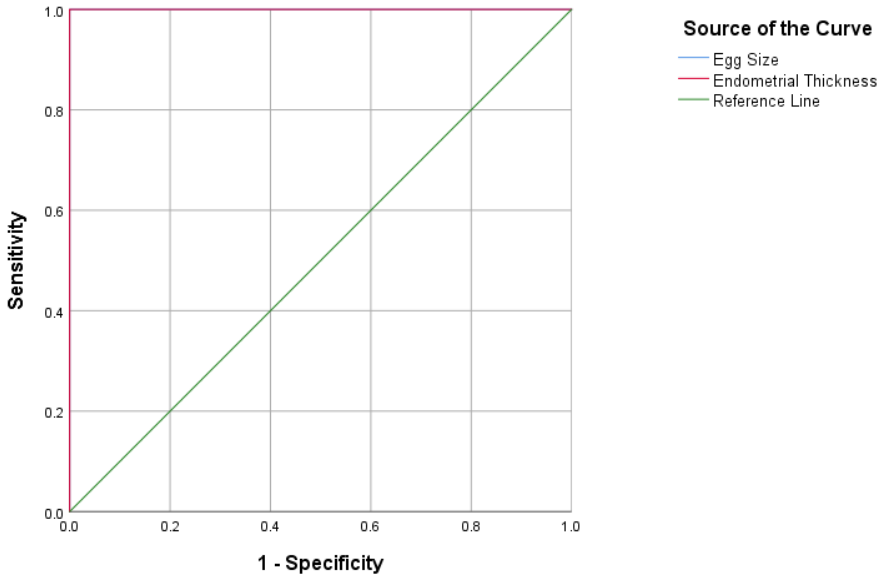

Figure1: ROC Curve Analysis of Egg Size And Endometrial Thickness as Predictors of Clinical Outcome.

The ROC curves compare the diagnostic performance of egg size (blue line) and endometrial thickness (red line), with the green diagonal representing the reference line (no discrimination). Endometrial thickness shows a perfect sensitivity and specificity (AUC = 1.0), indicating it may be an excellent predictor in this context, while egg size overlaps the same curve line, suggesting similar performance in this analysis.

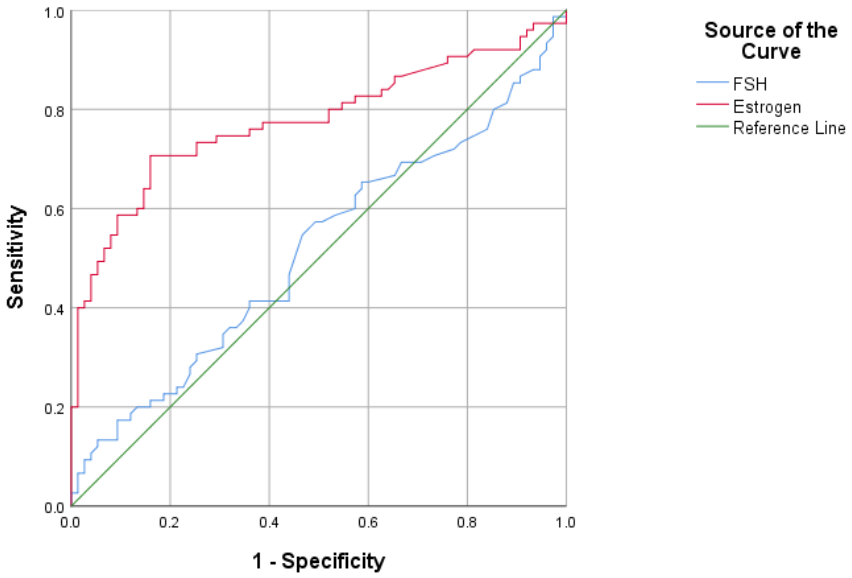

Figure2: Roc Curve Analysis of Follicle-Stimulating Hormone (**Fsh**) and Estrogen as Predictive Markers The ROC curves illustrate the diagnostic performance of FSH (blue line) and estrogen (red line) in relation to the studied outcome. The green diagonal represents the reference line indicating no discriminative ability (AUC = 0.5). Estrogen demonstrates superior diagnostic performance with higher sensitivity and specificity compared to FSH, suggesting a stronger predictive value in this clinical context.

Table 7: Ability of Endometrial thickness, follicle size, **FSH**, and Estrogen to distinguish between hormonal and ultrasonic changes on the 2nd and 12th day of the menstrual cycle

Variables	AUC	P-value	Sensitivity	Specificity	95% Confidence Interval	
Endometrial thickness	1.0	0.001	1.00	1.00	1.00	1.00
Follice size	1.0	0.001	1.00	1.00	1.00	1.00
FSH	0.515	0.752	0.578	0.508	0.422	0.608
Estrogen	0.777	0.001	0.613	0.514	0.699	0.854

4. Discussion

Letrozole therapy resulted in a marked rise in ovulation rates and endometrial receptivity, indicating a considerable gain in ovulatory and uterine activity. The current study was intended to find out the extent to which the aromatase inhibitor letrozole operates as a medication to treat infertility. Our results add to the growing volume of data that supports letrozole should be administered as a first-line treatment for infertility. (Yang et al., 2021, Chen et al., 2024, Franik et al., 2022). The study evaluated the effectiveness of letrozole to stimulate ovulation and improve fertility in women who have ovulation-related infertility. How letrozole works is it inhibits the enzyme aromatase which is responsible for synthesizing estrogen. This inhibition destroys the HPG axis' negative feedback loop. Therefore, estrogen mainly played the role of suppressing FSH in the regulation of the anterior

pituitary. Elevated FSH concentrations stimulate follicle growth and maturation, which eventually results in ovulation. (Franik et al., 2022, Eskew et al., 2019).

The authors reported that this effect was regulated simultaneously with the control of hormonal indicators such as estradiol and FSH. The hormonal oscillations regulate the complex mechanisms of growth and development of the follicles, ovulation, and the steroidogenic process finally yielding the corpus luteum, which are crucial actions for the setting up of a successful pregnancy. (Duncan, 2021, Przygrodzka et al., 2021, Reed BG).

The mean ±SD of the follicle size and endometrial thickness on Day 12 had significantly increased compared to Day 2 of the menstrual cycle after administration of letrozole. This can be explained by the fact that letrozole inhibits aromatase, which increases intra-ovarian androgen levels, especially in the early antral follicles (6-8mm) that are present on Day 3 or Day 5 of the cycle (McGrail et al., 2020). These higher androgen levels in the early follicles promote granulosa cell mitosis, increase FSH receptors, and make the follicles more resistant to atresia. This enhances follicular development and ovulation (Rose and Brown, 2020). The higher estrogen levels resulting from the increased follicular development with early letrozole initiation lead to better endometrial thickening and maturation (Franik et al., 2022). Specifically, the search results indicate the median endometrial thickness was significantly greater when letrozole was started on Day 5 compared to Day 3 (9.0mm vs 8.0mm). The improved endometrial response with early letrozole initiation may contribute to the higher conception and clinical pregnancy rates observed (Sakar and Oglak, 2020).

Proliferative thickening increased following the HRT - a rubber stamp on the fact that epithelial proliferation and reaction to hormone stimulation are taken for granted. These results may suggest a novel role for letrozole concerning improving endometrial cohesion and creating an environment that is ideal for the embryo attachment-implantation signal, and ultimately, conception (15,16).

The search results revealed no studies have compared the effect of oral letrozole starting on the second day of the menstrual cycle for two successive cycles with day 12^{th} of the second cycle regarding follicle size or endometrial thickness. However, data about the effects of letrozole on the endometrial thickness are still controversial. If letrozole was started on the fifth day of the menstrual cycle, compared to the third day of the menstrual cycle, there were greater rates of ovulation, endometrial thickness, pregnancy, and clinical pregnancy in PCOS women documented earlier. (Roy et al., 2012, Shi et al., 2022). In contrast, a study on the effect of letrozole on endometrial thickness in IVF cycles indicated that using letrozole during stimulation reduced the endometrial thickness by 0.81mm. In comparison to patients who did not get letrozole during their initial IVF cycles, those who received it had a thinner endometrium on the trigger day. The study showed that letrozole thins the endometrium, but it is still unclear how letrozole affects endometrial function. This underscores the need for more research before letrozole is prescribed for new transfers. (Ruiter-Ligeti et al., 2021).

There is a significant statistical alteration ($p = 0.001$) in the duration of marriage between age classes. Similarly, while the search results fail to demonstrate a significant difference in the duration of marriage between age groups in couples experiencing infertility due to PCOS, they do indicate that PCOS can significantly affect a couple's satisfaction with their marriage and sexual life, as well as their connections with friends and family (Navid et al., 2018, De Frène et al., 2014).

There were no significant differences in age, BMI, and most hormonal parameters between women with irregular and regular menstrual cycles. However, there is a significant difference in the duration of marriage, with women

experiencing irregular cycles having a shorter mean duration of marriage. The duration of marriage has no direct effect on PCOS women's irregular menstrual periods. Nevertheless, irregular periods after marriage can be caused by a variety of circumstances, including stress, changes in practice, weight variations, hormonal birth control, and pregnancy. The condition itself of PCOS can cause irregular menstrual cycles in women, which can impact menstrual regularity and reproductive health. (Dason et al., 2024). To address any primary worries and to obtain the proper management, females with irregular periods after marriage must visit health care specialists. (Navid et al., 2018).

Spearman's correlational investigation exposed substantial associations between different study variables, presenting clear insights into the relationship between factors affecting reproductive women's health. Nonetheless, the cautious clarification is rational to account for possible confusing confounders that may affect the associations.

5. Conclusion

The data shows that letrozole oral administration on the 2nd day of the menstruation, significantly enhances the growth of follicle and endometrium. This proposes that letrozole efficiently excites follicular development, promoting the growth of the dominant follicle(s). Additionally, letrozole boosts endometrial receptivity by stimulating endometrial maturation. These outcomes validate letrozole's worth in enhancing the main reproductive factors needed for fruitful ovulation and potential implantation in infertile females with PCOS. Moreover, the high specificity and sensitivity measures for follicular size and endometrial width highlight their ability as markers of the ultrasonic and hormonal variations induced by letrozole. Hence, these results support the latent role of letrozole among women suffering from PCOS in improving reproductive outcomes.

6. Ethical Approval

This study was approved by the Ethics Committee of the College of Pharmacy/University of Karbala on August 2, 2023. (Ref: 2023HU2). All patients provided informed consent before being enrolled in the study. The study was performed in accordance with the Declaration of Helsinki.

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