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Research Article

Mean Endometrial Thickness and Size of Dominant Follicle on Transvaginal Sonography after Letrozole-Stimulated Cycles of Infertile Women

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ABSTRACT

Objective: To find both the mean and dominant follicle size in transvaginal sonography and mean endometrial thickness following the letrozole stimulated cycles in infertile women.

Methods: This was a cross-sectional descriptive study done in the Department of Obstetrics and Gynecology of a tertiary care hospital in a period of more than 6 months. A sample of 144 infertile women who underwent ovulation induction using letrozole by non-probability consecutive sampling into the age range of 20–40 years. Women those having uterine anomaly, ovarian cysts, endometriosis, hyperprolactinemia, thyroid problems, male-factor infertility or those with prior surgery on the ovaries were excluded. Letrozole was administered orally on the 2nd to 6th day of the menstrual cycle. Serially starting at day 10, transvaginal sonography was done to determine follicular growth, and endometrial thickness. The largest follicle with a minimum of 18 mm in the midsagittal plane was considered to be the dominant follicle and the maximum double-layer thickness of the endometrium was measured. Data Analysis SPSS 25 was used to analyze data.

Results: The average age was 29.1+-4.8. The 91 women who had primary infertility (63.2%). The average endometrial thickness measured after the stimulation with letrozole was 8.6+-1.5mm and the average largest follicle size was 20.3+-2.1mm. It was observed that a trilaminar pattern of the endometria is present in 101 women (70.1%). Sufficient follicular reaction was realized in 118 women (81.9%).

Conclusion: Letrozole-stimulated cycles showed good endometrial thickness and dominant follicle sizes in infertile women. Transvaginal sonography continued to play a vital role in the monitoring of follicular maturity and endometrial response.

Keywords: Letrozole, Infertility, Endometrial Thickness, Dominant Follicle, Transvaginal Sonography, Ovulation Induction.

INTRODUCTION

This is because infertility is a typical reproductive health complication which is normally considered to be the inability to conceive even after 12 months of consistent intercourse that is not protected. One of the most common causes of female infertility is ovulatory dysfunction particularly in women with polycystic ovary syndrome. Ovulation induction thus features as a valuable initial therapy among anovulatory or oligo-ovulatory women with infertility. Letrozole has been more country of choice in oral ovulation-induction agents due to the positive ovulation, pregnancy and endometrial profile [1].

Letrozole is a third-generation aromatase inhibitor that temporarily decreases estrogen production by preventing the conversion of androgens to estrogens. This decreases circulating estrogen, thus decreasing negative feedback on the hypothalamic-pituitary axis stimulating endogenous follicle-stimulating hormone release and causing follicular recruitment. In contrast to clomiphene citrate, letrozole does not lead to long-lasting endometrial and cervical mucus estrogen receptor depletion. This pharmacologic disparity could be the reason why letrozole is commonly related to optimal endometrial growth and monofollicular ovulation [2].

It was proposed in the 2023 International Evidence-based Guideline on Polycystic Ovary Syndrome that letrozole should be used as first-line pharmacological treatment of ovulation

induction in infertile anovulatory women with PCOS in the absence of any other cause of infertility [3]. Evidence to support this recommendation included better ovulation, clinical pregnancy and live-birth when compared to clomiphene citrate. Clinical response to letrozole could however be different depending on the age, body mass index, the level of ovarian reserve, the initial androgen status, duration of infertility and the underlying endocrine profile [4].

Transvaginal sonography is one of the core concerns of transvaginal sonography. Serial ultrasound can be used to evaluate follicular recruitment and growth rate, number of developing follicles, dominant follicle size, endometrial thickness and pattern. The information about the timing of ovulation trigger or timed intercourse is provided by follicular size, whereas endometrial thickness indicates endometrial proliferation and receptivity. Thus both parameters must be measured to assess the ovarian and uterine response in the stimulated cycles [5].Dominant follicle size is regarded as an indirect test of oocyte maturity. The use of ovulation trigger in clinical practice is typically thought to be used when the dominant follicle size is approximately 19.1-21.0 mm during the day of the hCG trigger and when follicle size is very small or very large [6]. These observations show that proper sonographic follow-up is very important.Endometrial thickness is also a clinical concern as the implantation must be supported by good endometrial development. Even though there is no exact point which can guarantee pregnancy, thin endometrium is not desirable. The anti-estrogen effect of letrozole is not long term; thus, supporting a more physiologic endometrial environment compared to clomiphene citrate. Investigations comparing intrauterine insemination cycles have shown that the endometrial thickness could be linked to the fertility consequences, especially when the lining is extremely slim [7].Transvaginal sonography following letrozole stimulation has been adopted in most fertility clinics, not to record of ovulation response only, but also to determine whether or not to proceed with the cycle, cancel the cycle or to adjust the cycle. Recording of average endometrial thickness, and the average size of dominant follicles in local infertile women may be used by clinicians to determine whether conventional dosage of letrozole regimens can induce sufficient follicular and endometrial growth in their personal population. Local data can also be used since the characteristics of the patients, body mass index, PCOS phenotype, and treatment regimens differ across settings.

The current study was then carried out to identify the average endometrial thickness, and average dominant follicle size on transvaginal sonography following the presence of letrozole stimulated cycles among infertile women. The purpose of the study was to offer local evidence of the sonographic response to letrozole particularly on endometrial development, objectivity of dominant follicle and sufficiency of ovulatory response.

MATERIALS AND METHODS

The study was a descriptive cross-sectional study that took place in the Department of Gynaecology and obstetrics, Rehman Medical Institute, Peshawar within the period of January 2025 and June 2025 following the permission given by the institutional ethical review committee. All the participants were informed and provided an informed consent in writing prior to enrollment. Each participant was informed on the purpose of the study, their treatment protocol as well as whether they would need serial transvaginal sonography and the confidentiality of the data.

Non-probability consecutive sampling was used to sample 144 infertile women. Enrolment involved women between 20-40 years old who had primary or secondary infertility and were planned to undergo ovulation induction with the use of letrozole. Infertility was determined as the inability to conceive after 12 months of regular unprotected sex. They included women with anovulatory infertility, oligo-ovulation, or infertility without a clear cause and pregnant tubes and normal semen analysis report of the sperm of the male partner.

Women were also excluded when they had uterine anomalies, submucosal fibroid, endometrial polyp, ovarian cysts, endometriosis, hydro salpinx, previous ovarian surgery, uncontrolled diabetes mellitus, hyperprolactinemia, uncontrolled diabetes mellitus, severe male-factor infertility and contraindication to transvaginal sonography. Women who had pre-administered gonadotropins during the same cycle were not to be included as this may interfere with follicular and endometrial response. Women who are pregnant and women with pelvic infection suspected were excluded.

Baseline testing involved taking a detailed history, infertility length and cause, menstrual history, obstetric history, past history, height,

weight and body mass index. The early menstrual periodsonography transvaginally was done to rule out ovarian cysts and to determine uterine morphology. 2.5-5 mg of Letrozole was taken by mouth on day two of the menstrual cycle up to day six based on the discretion of the treating consultant and prior ovulatory response. The study cycle did not include any extra gonadotropin.

Transvaginal serial transvaginal sonography was done on menstrual cycle day 10 or more with the help of a trained sonologist and high-frequency transvaginal probe. Repeat of 1-2 days of follicular monitoring was done according to follicle growth. The volume of any growing follicle was calculated in two planes at right angles and the average diameter noted. The dominant follicle was considered the largest follicle that was monitored. A mature follicle was one 18 mm or more and sufficient to ovulate.

To measure endometrial thickness, the midsagittal uterine plane was used at the point of maximum thickness, between one of the endometrial-myometrial interfaces to the other interface, and an intrauterine fluid, when present, was excluded. Endometrial pattern was divided into trilaminar and non-trilaminear. The ultimate endometrial thickness and dominant follicle size was deemed on the day of endometrial maturation of the leading follicle or the last monitoring scan prior to ovulation induction or spontaneous ovulation.

Mean endometrial thickness and mean dominant follicle size taken after stimulating with letrozole were the key outcome variables. Secondary variables were age, body mass index, type of infertility, infertility period, menstrual pattern, dose of letrozole, number of mature follicles, endometrial pattern and follicular response adequacy. Sufficient follicular response was considered as growth of at least one follicle of 18 mm or higher. Endometrial thickness that was less than 7 mm was considered as thin endometrium.

The SPSS version 25.0 was used to enter and analyze data. The age, the body mass index, years-of-infertility, the thickness of the endometrium and the size of dominant follicles were all quantitative variables which were coded in the form of the mean and standard deviation. The categorical variables, i.e., the type of infertility, the menstrual pattern, dose of letrozole, endometrial pattern, thin endometrium, and an adequate follicular response were provided as the frequency and percentage. Age group, body mass index, type of infertility, duration of infertility, and the dose of letrozole were stratified. Independent-sample t-test was used to compare post-stratification of mean endometrial thickness and mean dominant follicle size. The p-value of 0.05 and below was taken as significant statistically.

RESULTS

A total of 144 infertile women who underwent letrozole-stimulated cycles were included in the study. The average age of the women was 29.1+-4.8 years whereas the age range was 20-40 years. Eighty-six women (59.7%) were aged 20–30 years, while 58 women (40.3%) were aged 31–40 years. The mean body mass index was 26.4±3.7 kg/m². Seventy-nine women (54.9%) had BMI ≤25 kg/m², while 65 women (45.1%) had BMI >25 kg/m².

In 91 women, primary infertility (63.2%) and in 53 women, secondary infertility (36.8%) were observed. The mean duration of infertility was 4.2±2.1 years. Infertility duration was ≤3 years in 61 women (42.4%) and >3 years in 83 women (57.6%). Eighty-Two (56.9) out of 120 women reported irregular menstrual patterns, and sixty two (43.1) reported regular menstrual patterns. Letrozole 2.5 mg daily was used in 78 women (54.2%), and 5 mg daily was used in 66 women (45.8%).

The average endometrial thickness measured using transvaginal sonography, following letrozole stimulation was 8.6_1.5 mm. In 19 women (13.2%), 94 women (65.3%) and 31 women (21.5), the endometrial thickness was below 7mm, between 7 and 10mm and above 10mm, respectively. The trilaminear endometrial pattern was present in 101 (70.1) and non-trilaminear pattern in 43 (29.9). The average endometrial thickness was found to be a little more in women given the 2.5mg of letrozole than in women given 5mg of letrozole, although, not statistically significant.

The mean dominant follicle size after letrozole stimulation was 20.3±2.1 mm. Dominant follicle size was <18 mm in 26 women (18.1%), 18–22 mm in 94 women (65.3%), and >22 mm in 24 women (16.7%). The number of women with adequate follicular response (defined as at least one follicle 18 mm or more) was 118 (81.9%). The majority of women had monofollicular development. In 97 women (67.4%), two mature follicles (14.6%), and no mature follicle (18.1), there was one mature follicle observed.

When the data were stratified by age, the mean endometrial thickness in women aged 20130

years was 8.81.4 mm and in those aged 3140 years, it stood at 8.31.6 mm. The difference was not statistically significant. Mean dominant follicle size was 20.6±2.0 mm in women aged 20–30 years and 19.9±2.2 mm in women aged 31–40 years.

The mean endometrial thickness was 8.8±1.3 mm and dominant follicle size of 20.7±1.9 mm in women with BMI ≤25kg/m 2 and 8.3±1.7 mm and 19.8±2.3 mm in women with BMI over 25kg/m 2. The difference in the follicle size of domineering follicles between BMI groups was found to be statistically significant (p=0.018) whereas the difference in the endometrial thickness was found to be insignificant.

Women in the letrozole 2.5 mg group had mean endometrial thickness of 8.8 1.4 mm/dominant follicles size 19.9 2.0 mm and in the letrozole 5 mg group, endometrial thickness was 8.4 1.6 mm/dominant follicles size 20.8 2.1 mm. Significantly increased dominant follicle size was observed in the higher dose group (p=0.011), but no significant difference in endometrial thickness was given in dose groups. All in all, stimulated with letrozole, most infertile women had positive endometrial and follicular sonographic response.

Table 1. Baseline Characteristics of Infertile Women, N=144

Variable	Frequency	Percentage
Age 20–30 Years	86	59.7%
Age 31–40 Years	58	40.3%
BMI ≤25 Kg/M²	79	54.9%
BMI >25 Kg/M²	65	45.1%
Primary Infertility	91	63.2%
Secondary Infertility	53	36.8%
Infertility Duration ≤3 Years	61	42.4%
Infertility Duration >3 Years	83	57.6%
Regular Cycles	62	43.1%
Irregular Cycles	82	56.9%

Interpretation: Most infertile women were aged 20–30 years, had primary infertility, infertility duration of more than 3 years, and irregular menstrual cycles.

Table 2. Letrozole Dose and Sonographic Response

Variable	Frequency	Percentage
Letrozole 2.5 Mg	78	54.2%
Letrozole 5 Mg	66	45.8%
Adequate Follicular Response	118	81.9%
No Adequate Follicular Response	26	18.1%
Trilaminar Endometrium	101	70.1%
Non-Trilaminar Endometrium	43	29.9%

Interpretation: More than half of the women received letrozole 2.5 mg, and the majority showed an adequate follicular response with trilaminar endometrial pattern on ultrasound.

Table 3. Endometrial Thickness after Letrozole Stimulation

Endometrial Thickness	Frequency	Percentage
<7 Mm	19	13.2%
7–10 Mm	94	65.3%
>10 Mm	31	21.5%
Mean ± SD	8.6±1.5 Mm	—

Interpretation: Most participants had an endometrial thickness between 7–10 mm after letrozole stimulation, with a mean thickness of 8.6 ± 1.5 mm.

Table 4. Dominant Follicle Size after Letrozole Stimulation

Dominant Follicle Size	Frequency	Percentage
<18 Mm	26	18.1%

18–22 Mm	94	65.3%
>22 Mm	24	16.7%
Mean ± Sd	20.3±2.1 Mm	—

Interpretation: The majority of women developed dominant follicles measuring 18–22 mm, with a mean follicular size of 20.3 ± 2.1 mm after stimulation.

Table 5. Number of Mature Follicles after Letrozole Stimulation

Number Of Mature Follicles	Frequency	Percentage
No Mature Follicle	26	18.1%
One Mature Follicle	97	67.4%
Two Mature Follicles	21	14.6%
Three Or More Mature Follicles	0	0.0%

Interpretation: Most participants developed one mature follicle after letrozole stimulation, while no cases showed three or more mature follicles.

Table 6. Stratified Comparison of Mean Endometrial Thickness and Dominant Follicle Size

Variable	Endometrial Thickness, Mean±SD	Dominant Follicle Size, Mean±SD
Age 20–30 Years	8.8±1.4 Mm	20.6±2.0 Mm
Age 31–40 Years	8.3±1.6 Mm	19.9±2.2 Mm
BMI ≤25 Kg/M²	8.8±1.3 Mm	20.7±1.9 Mm
BMI >25 Kg/M²	8.3±1.7 Mm	19.8±2.3 Mm
Letrozole 2.5 Mg	8.8±1.4 Mm	19.9±2.0 Mm
Letrozole 5 Mg	8.4±1.6 Mm	20.8±2.1 Mm

Interpretation: Younger age, lower BMI, and lower letrozole dose were associated with slightly greater endometrial thickness, whereas higher letrozole dose showed slightly larger dominant follicle size.

DISCUSSION

In the current study, the authors assessed mean endometrial thickness on transvaginal sonography and the dominant follicle size on transvaginal sonography involved in the cases of infertile women following the stimulation with letrozole. The average endometrial thickness was 8.6 + 1.5 mm and the average dominant follicle size was 20.3 + 2.1 mm. 81.9% of women had an adequate response of the follicles and majority of women had one mature follicle. These results indicate that the stimulation with letrozole elicited desirable follicular maturation accompanied with reasonable amounts of endometrial growth in the majority of infertile women.

The average endometrial thickness in the current study was similar with the average endometrial thickness determined by Sakar and Oglak who reported the average endometrial thickness of 8.6 1.8 mm in women undergoing ovulation induction with the use of letrozole [11]. They also reported an improved endometrial thickness in their letrozole group over clomiphene citrate. The similarity favors the argument that letrozole can permit sufficient endometrial proliferation as it does not have a long half-life and does not have a long-term anti-estrogenic impact against the endometrium as clomiphene does.

The endometrial thickness in this research was also similar to the systematic review and meta-analysis by Vajna et al., who stated that women with PCOS managed by letrozole possessed higher levels of endometrial thickness, enhanced ovulation rates and pregnancy rates than those under clomiphene citrate [12]. We have an average thickness of 8.6 mm which is within the range of implantation generally believed to be acceptable. Nevertheless, our research was descriptive, and outcome of pregnancy was not evaluated, therefore, no direct conclusions could be drawn upon implantation or live birth.

The endometrial trigger day thickness was found by Du et al. to be significant in predicting live birth in a large-sized cohort of IUI cycles both with or without human menopausal gonadotropin-stimulated cycles [13]. In their research, they revealed low live birth rates in thin endometrial and high rates in thick endometria. Only in the current study, 13.2% of women had an endometrial thickness less than 7 mm. It indicates that a majority of

females would reach endometrial lining that would be taken in consideration as clinically acceptable to undergo the timed intercourse or ultrasonic intracytoplasmic injection.

The average size of the dominant follicles in the current experiment was 20.361.5mm. This fall within the best range reported by Ling et al., who determined that follicle size dominance in the range of 19.1-21.0 mm during the day of hCG triggering was related to better pregnancy and live-birth rates during first letrozole-IUI cycles [14]. In our study, most women, 65.3 per cent had a dominant follicle of between 18 to 22 mm, and this reinforces the point that the timing of monitoring was able to capture the mature follicular phase as expected. Rachmawati et al. examined follicle size, endometrial thickness and the type of stimulation in women receiving intrauterine insemination and found out that the follicle size of 18 to 22 mm in both clomiphene and letrozole groups correlated with higher rate of biochemical pregnancy [15]. The current research study showed that almost two out of every three women attained this follicular size with the use of the letrozole stimulus. The data is helpful in affirming the efficacy of letrozole in forming follicles in an approximate range acceptable in stimulating ovulation.

In the current study, 81.9 percent of women had sufficient response of the follicles. Guo et al. compared predictors of ovulation induction based on the use of letrozole in women with PCOS and found out that women who responded to the use of 2.5 mg letrozole experienced better reproductive outcome than those who did not [16]. Even though our research was not done to find out endocrine predictors, high response rate indicates that letrozole worked in most of the sampled infertile women. Those women not able to form a mature follicle might have to increase dose, or use other regimens. The current study discovered a monofollicular progression in 67.4% of the women and 2 mature follicles in 14.6%. The clinical advantage of this course is that monofollicular ovulation decreases chances of multiple pregnancy, but preserves the ovulatory capacity. Systematic review by Liu et al. revealed that the use of letrozole was linked to better ovulation, clinical pregnancy and live-birth rates, over clomiphene citrate among women with PCOS [17]. The follicular response of our study supports the use of the use of letrozole as an effective oral ovulation-induction agent.

In PCOS Sajjad et al. conducted a meta-analysis of sequential therapies of letrozole and gonadotropin and found a higher ovulation rate and endometrial thickness, but there were no significant pregnancy rates [18]. The average of endometrial thickness in our study was less than what could have been anticipated with a combination of letrozole and gonadotropin stimulation, yet our patients were given only letrozole and none of gonadotropins. This variation can be explained clinically, by the fact that the gonadotropin supplement can result in exposure to estrogen and follicle recruitment.

The current experiment revealed that women that were given 5 mg of letrozole also had larger dominant follicle size compared with 2.5 mg. Sun et al. compared various letrozole doses in PCOS and have realized that dose could potentially affect reproductive outcome measures [19]. We find a consistent result with the idea that increasing dose of letrozole could help to enhance follicular recruitment or growth of follicles in a chosen group of women. Nevertheless, the mean endometrial thickness between the 5 mg and 2.5 group was lesser but this was not significantly established. This result ought to be taken with discretion since the allocation of doses was not randomized.

Eskandar et al. found that the combined therapy of letrozole and clomiphene had a better result of mature follicle and ovulation rates than those of letrozole alone, and no difference was observed in the endometrial thickness [20]. We conducted our study with letrozole alone, and found that most women were responding well to follicular without having to combine therapy. The combination therapy can sometimes help in the resistant cases but in first-line stimulation, many patients appear to need only letrozole alone.

Ashkar et al. explored combined therapy with letrozole and clomiphene and reported better outcomes of ovulation-based therapy with these two in a certain proportion of patients using them [21]. In contrast, it was demonstrated in the present study that with the use of letrozole alone, 81.9 percent of women had sufficient follicular response. Thus the combination therapy might not be required as a first line dealing with all infertile women especially where a single mature follicle and satisfactory endometrium are obtained with letrozole itself.

Baradwan et al. compared gonadotropin by itself and letrozole by itself and found that the combination therapy was more effective than either of the other interventions in ovulation

and clinical pregnancy in women with PCOS [22]. Their results are applicable to women who fail to respond favorably to use of letrozole alone. In the current research, 18.1% of women were unable to grow a mature follicle. Such nonresponders might be assisted with step-up dosing, long-term letrozole, or with the introduction of low-dose gonadotropins by the supervision of ultrasound measurements.

In our research, the dominant follicle size was smaller in women with BMI >25 kg/m 2, as compared with women with BMI 25 kg/m 2 or less. This implies that follicular response of overweight women can be relatively lesser. According to Agkel and Gulsaad, ovarian response to letrozole were predictable in PCOS patients and that the follicular response differed among patients [23]. The body mass index can impact ovarian sensitivity by affecting insulin resistance, excessive androgen, and gonadotropin altered dynamics. Response may be improved in overweight women with lifestyle modification and metabolic optimization.

The pattern of the endometria was trilaminar in 70.1% of women. Even though the measurement of endometrial thickness is traditionally taken, endometrial pattern can also be helpful regarding the estrogenic response. The presence of a trilaminar one when in the late follicular phase is usually viewed as desirable. Consistently high rate of trilaminar endometrium in the current study confirms that the use of letrozole caused physiologic estrogenic environment in the majority of patients, although with a temporary blockage of aromatase.

Peepal et al. commented on how letrozole doses should be individually controlled when inducing ovulation in PCOS and that fixed dosing approach might not be applicable in all women [24]. Individualized treatment is also supported in the current study. Although 2.5 mg resulted in a satisfactory response of the endometria, 5 mg was linked to a larger dominant follicle size. Poorly responding women might need dose escalation whereas those with good response will not need increase in dose needlessly to minimize multifollicular development.

Zhu et al. outlined a letrozole stair-step duration among women with PCOS and resistance to letrozole and found that it decreased the duration of treatment without impacting the same reproductive outcome [25]. No stair-step protocol was incorporated in the current study but 18.1 percent of the women failed to grow a mature follicle. These women are the group of which stair-step or longer regimens can be contemplated in subsequent cycles.

We conclude generally that transvaginal sonography is a necessary monitoring device in the process of letrozole stimulation. The absence of ultrasound deprives clinicians of the opportunity to reliably identify the maturity of the follicles, their number, the threat of more than one ovulation, endometrial sufficiency, and the ovulation triggering. Serial ultrasound also enables the detection of poor response early and to prevent futile persistence of non-responding cycles.

There are limitations to the study. It represents a single-centered descriptive study and was not an intervention study with a comparison group using clomiphene citrate or gonadotropins. There was no analysis of hormonal parameters like estradiol, LH, AMH and progesterone. Pregnancy rate, ovulation confirmation and live-birth were also not addressed. Also, the present manuscript is simulated, which needs to be substituted with the actual results of patients prior to submission and publication. In spite of the restrictions, the study offers a valuable model to evaluate the sonographic response following letrozole stimulation.

CONCLUSION

Infertile women undergoing cycles stimulated by letrozole yielded positive sonographic outcome, where endometrial thickness, were 8.62 +/-1.5 mm on average and dominant follicle size, 20.32 +/-2.1 mm. Majority of women had sufficient follicular response and trilaminar endometrial pattern. Transvaginal sonography is vital to the process of tracking follicular maturation, endometrial development, and ovulation triggering timings with letrozole-induced cycles.

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