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Original Articles

Endometrial changes in Infertile Women with Polycystic Ovary Syndrome after taking Letrozole in Comparison to Clomiphene Citrate

UMMUL KHAIR MAHMUDA[1], NILUFAR SULTANA[2], FLORIDA RAHMAN[3], SULTANA AFROJ[4], FATEMA RAHMAN[5], FORIDA YESMIN[6], MARIAM AKTER SUMI[7], SARIA TASNIM[8]

Abstract

Background: *The endometrium is a receptor organ for most of the hormones involved in fertility and therefore the study of its morphology is thought to explain the mysteries of implantation failure. Many studies showed that Clomiphene Citrate impairs endometrial development due to antiestrogenic effects and long half-life. Conversely Letrozole shows a positive effect on follicle and endometrium.*

Objective: *To assess the endometrium in infertile Polycystic Ovary Syndrome women by Transvaginal Sonography after giving ovulation induction by Clomiphene Citrate versus Letrozole.*

Materials and Methods: *This Comparative cross-sectional study was conducted on sixty diagnosed Polycystic Ovary Syndrome infertile women in the Reproductive Endocrinology & Infertility Unit of Dhaka medical College Hospital, Dhaka, from January 2021 to December 2021. The patients who took Letrozole is called Letrozole group and who took Clomiphene citrate is called Clomiphene citrate group. Serial folliculometry were done to every patient from Day 7. At day 12, the patients were assessed by Transvaginal Sonography for endometrial study. The hyporesponsive and non-responsive patients took higher dose of clomiphene citrate or letrozole in next cycle and serial folliculometry were done as before. Endometrial thickness, pattern and zone of vascularity was compared between the two groups. Preovulatory S. Estradiol was done in case of optimum response. All the relevant data were collected in a predesigned and pretested case record form. Data was processed and analyzed with the help of the computer program SPSS in version 26.*

Results: *Clomiphene Citrate and Letrozole achieved optimum response in 15(50%) and 21(70%) patients, respectively. The Letrozole group had a significantly greater endometrial thickness than the Clomiphene Citrate group (8.85±1.33 vs.7.37±1.07, p=0.001s). Moreover, the Letrozole group showed a greater number of triple line endometrium (76.2% vs 60.0%, p=0.298ns), grade A (42.9% vs 26.7%, p=0.500^{ns}) and Zone 3 vascularity (33.3%vs 22.2%, p=0.325^{ns}) than the clomiphene citrate group.*

Conclusion: *Letrozole induces significantly better endometrial development in terms of endometrial thickness than clomiphene citrate.*

Key words: *Endometrium, Polycystic Ovary Syndrome, Letrozole, Clomiphene Citrate*

1. Consultant, OSD, DGHS, Dhaka
2. Prof. & Head (Ex), Gynae & Obs. Dept., DMCH, Dhaka
3. Associate Prof., Reproductive Endocrinology & Infertility unit, DMCH, Dhaka
4. Prof. & Head, Reproductive Endocrinology & Infertility unit, DMCH, Dhaka
5. Associate Prof., Reproductive Endocrinology & Infertility unit and Gynae & Obs. Dept, DMCH, Dhaka
6. Professor (Gynae & Obs)
7. Registrar, Reproductive Endocrinology & Infertility unit, MMCH, Dhaka
8. Prof & Head, Dhaka Community Hospital, Dhaka

Address of Correspondence: Dr. Ummul Khair Mahmuda, Consultant, OSD, DGHS, Dhaka.

Introduction:

Polycystic Ovary Syndrome (PCOS) is the most obvious and common condition associated with chronic anovulation, which affects 4-6% of reproductive-age women.[1] The incidence is higher in the South Asian population, which is about 50%.[2] In Bangladesh, the prevalence of PCOS using Rotterdam criteria was 6.11% in the gynecology outpatient visits.[3]

Clomiphene citrate (CC) has been a widely used drug for the treatment of infertility since its introduction into clinical practice in the 1960s.[4] CC is an orally active non-steroidal drug with mixed estrogen agonist/ antagonist properties.[5,6] It stimulates ovulation by competitively inhibiting the estrogen (E) binding to the Hypothalamic estrogen receptor (ER), so the negative inhibition of endogenous estradiol leads to an increase in gonadotropin pulse frequency, which consecutively induces ovulation.[6] In the early clinical trials, 60-85% of anovulatory women treated with clomiphene citrate achieved ovulation but a conception rate of only about 20%.[4-8] CC has a long half-life (2 weeks), and this may have a negative effect on the cervical mucous and endometrium, leading to a discrepancy between ovulation and conception.[4,9] Several studies revealed that Clomiphene Citrate reduces endometrial receptivity, as impaired endometrial development and uterine blood flow resulting in endometrial thinning in 15-50% of patients with subsequent implantation failure and induces early pregnancy loss due to luteal phase defect.[4-10]

Letrozole was proposed as an alternative to clomiphene citrate as a highly selective aromatase inhibitor that prevents androgen to estrogen conversion.[5,11] Their mechanism is the release of the hypothalamic-pituitary axis from estrogenic negative feedback, thereby increasing gonadotropin secretion and resulting in stimulation of ovarian follicles. In addition, it has a local effect on the ovary, and androgen accumulation increases follicle sensitivity to FSH.[12] This aromatase inhibitor has a short half-life (45 hours); [4,9] thus, it is rapidly eliminated from the body. No adverse effects on estrogen receptor (ER) and endometrium are seen with Letrozole due to short half- life[7,11], unlike Clomiphene Citrate.[13]

Endometrial thickness, Triple line pattern and vascularity of endometrium are the essential determinants that can predict Endometrial Receptivity.[5,14]There is a correlation between endometrial thickness and the likelihood of conception, in the context of assisted conception. However, a very thin endometrium (below 7 mm) seems to be accepted as a reliable sign of suboptimal implantation potential.[5]

Moreover, serum hormonal Estradiol (E2) and Progesterone levels cannot always accurately predict the development of the endometrium, and other methods such as histological studies are too invasive.[15] In this regard, Transvaginal ultrasound (TVS) is a modern, cheap and noninvasive technique to monitor follicular and endometrial growth in the preovulatory phase, which can predict ovulation and endometrial receptivity.[15] By observing the effect of letrozole on endometrial thickness, we can avoid the hypoestrogenic effect of Clomiphene Citrate on Endometrium, and better chance of improving endometrial receptivity. Moreover, this can avoid misuse of clomiphene citrate and can reduce the cost. Therefore, we can develop a locally adaptable guideline for the management of the infertile PCOS women in the context of our country. With this background, the present study was designed to compare the endometrial parameters in terms of endometrial thickness, triple-line formation and zone of vascularity by Transvaginal ultrasonography in infertile PCOS women who had undergone ovulation induction by Letrozole or Clomiphene citrate.

Materials and methods

This comparative cross-sectional study was conducted in the Reproductive Endocrinology & Infertility (RE&I) unit of Dhaka Medical College Hospital (DMCH), Dhaka, from January 2021 to December 2021. Through purposive sampling, sixty (60) infertile women who attended in OPD of Reproductive Endocrinology & Infertility unit of DMCH and were diagnosed as PCOS according to Rotterdam criteria were recruited initially by inclusion criteria and exclusion criteria. The inclusion criteria include diagnosed case of infertile PCOS women according to Rotterdam consensus[18] who were selected for ovulation induction, age ranged between 18 to 35 years, BMI within18.5 to 29.9 kg/m^2, at least one fallopian tube patent and normal semen analysis. Exclusion criteria includes infertile PCOS patients who had DM or other endocrinopathies like Hypothyroidism, Hyper-prolactinaemia etc., women with a documented pelvic disease like endometriosis, any ovarian pathology other than PCO, hydro or pyosalpinx, uterine fibroids or adenomyosis and who were on current OCP or ovulation induction for last

six months. Written informed consent was taken from all women recruited in this study.

Operational definition:

Optimum Response after ovulation induction: When at least one ovarian follicle was achieved that is **e"18mm size (Dominant mature follicle)** after undergoing ovulation induction by serial folliculometry, it was called optimum response.[19]

Hypo-response after ovulation induction: When there was no development of follicle e"18mm size (Dominant mature follicle) after ovulation induction by serial folliculometry, but rather 11-17mm sized follicles were seen, it was called hypo-response.

Non-response after ovulation induction: After ovulation induction, by serial folliculometry when there was no growth of follicle was observed then it was called non-response.

Endometrial thickness: The endometrial thickness is measured from the anterior outer margin to the posterior outer margin of peripheral hyperechoic lines of the endometrium and at the thickest part of the endometrium. The thickness of the endometrium is always measured perpendicular to the central line of the endometrium.[20]

Triple Line appearance of Endometrium: A triple-line pattern endometrium is in which hyperechogenic outer lines and a well-defined central echogenic line are seen with hypoechogenic or black areas between these lines.[14]

Morphological grading of Endometrium: Morphology of the endometrium is as important as the thickness of the endometrium. Morphologically the endometrium is graded as the best, **Grade A** when it is a triple line endometrium with the intervening area as echogenic as the anterior myometrium. The endometrium is graded as intermediate or **Grade B** when it is multilayered or triple line with the almost anechoic intervening area. **Grade C** or the most unfavorable endometrium would be a homogenous isoechoic (isoechoic to myometrium) endometrium.[20]

Zone of vascularity: The zones of vascularity in the endometrium are defined according to **Applebaum** [21] as:

Zone 1, when the vascularity on power Doppler is seen only at the endometrio-myometrial junction.

Zone 2, when vessels penetrate through the hyperechogenic endometrial edge**.**

Zone 3, when it reaches the intervening hypoechoic zone.

Zone 4, when vessels reach the endometrial cavity (the central endometrial line).

Procedure of collecting data:

The study included a thorough history, thorough clinical examination, were done meticulously. Routine infertility workup on Day 2 or Day 3 including hormone assessment like FSH and LH, serum prolactin, serum TSH, baseline Transvaginal ultrasonogram and Hysterosalpingography or saline infusion sonography at day 8 to 10, were done. To exclude male factor abnormality semen analysis was done according to modified **WHO guideline** [22].

The recruited sixty (60) PCOS infertile women in this study were numbered 1-60 according to the chronology of day of enrollment. Every uneven number of enrolled women who took **100mg of CC** orally daily for five days starting from day 2 to day 6 of the first cycle were grouped as **Clomiphene Citrate (CC) group** and the patients who didn't show optimum response in first cycle were given **150mg** in the second cycle.

Every even number of enrolled women who took **Letrozole 5mg** orally daily for 5 days starting from day 2 to day 6 of the cycle were grouped as **Letrozole group**. Again, the patients who didn't show optimum response in first cycle were given 7.5mg in the second cycle.

After taking Clomiphene citrate or Letrozole, serial folliculometry was started from **Day 7** of the cycle and further folliculometry was done on Day12. Ultrasonographic measurement of the endometrial thickness and triple line formation, grading and vascularity were performed on the **Day 12**.

Thereafter, a comparison between Clomiphene Citrate and letrozole groups in terms of endometrial thickness and triple line pattern (Fig. 1A, 1B), grading and zone of vascularity (Fig. 2A, 2B and 2C) was done. Statistical analysis of the study was done by using the Statistical Package for Social Science (SPSS) version 26. The comparison was done by tabulation and scatter diagram. On univariate analysis, chi-square test and independent-sample T-test were performed to compare between qualitative and quantitative variables, respectively.

Result:

Approximately two-thirds of PCOS women were oligomenorrheic (93.3%vs.83.3%). and the mean duration of infertility (76. 7%vs.73.3%) was one to three years in the CC group and the letrozole group. Mean BMI was 26.10±2.46 in the CC group and 25.79±2.43 in the letrozole group. During baseline sonography, nearly all patients were found polycystic and prominent ovaries (Table 1).

In the first cycle, Clomiphene citrate group showed optimum response in 13(43.3%) patients, 7(23.3%) patients showed hypo-response and 10(33.3%) patients showed non-response. Conversely, in Letrozole group optimum response seen in 15(50%) patients, hypo-response seen in 10(33.3%) patients and non-response seen in 5(16.7%) patients.

In the second cycle, within the remaining 17 patients of the CC group, two patients showed optimum response, seven patients continued hypo-response, and eight patients showed no response as the first cycle. On the other hand, within the remaining 15 patients of the Letrozole group in the second cycle, six patients showed optimum response, five patients continued hypo-response, and four patients showed no response.

In the case of optimum response after ovulation induction, endometrial thickness was 8.85±1.33mm in the letrozole group and 7.37±1.07mm in the CC group. An unpaired student t-test was performed to compare between two groups, and the result is strongly statistically significant. Triple line pattern of the endometrium was mostly found in the Letrozole group (76.2%) than in the CC group (60.0%) in case of optimum response but this finding is not statistically significant. Regarding morphological grading of the endometrium, Grade A endometrium was mostly seen in the Letrozole group and Grade C endometrium was seen in the CC group. But these results are not statistically significant. Vascularity seen in Zone 2 in both groups were similar. Letrozole group showed maximum vascularity in Zone 3 and it was 7(33.3%). All the differences are not statistically significant.

Table-I

Clinical profile of PCOS patients among CC group and Letrozole group (n=60)

Variables	CC Group (n=30) No. (%)	Letrozole Group (n=30) No. (%)	p-value
Age (Years)			
Mean±SD	24.8±3.28	25.5±3.52	
Range	18 – 34	25.5±3.52	0.451
Type of infertility			
Primary	24(80.0%)	18(60.0%)	0.091
Secondary	6(20.0%)	12(40.0%)	
Duration of infertility (years)			
1-3 yrs	23(76.7%)	22(73.3%)	0.766
>3-6 yrs	7(23.3%)	8(26.7%)	
Oligomenorrhoea	28(93.3%)	25(83.3%)	
Amenorrhea	2(6.7%)	5(16.7%)	0.227
BMI (kg/m^2)			
Mean±SD	26.10±2.46	25.79±2.43	0.637
Range	20 – 29.5	19.0 – 29.0	
Hirsutism	11(36.7%)	12(40.0%)	0.791
Acanthosis nigricans	4(13.3%)	6(20.0%)	0.488
Acne	11(36.7%)	12(40.0%)	0.791
Endometrium (mm)	4.51±0.40	4.67±0.57	0.218
Right ovary volume (ml)	9.85±1.71	10.39±1.73	0.231
Left ovary volume (ml)	10.66±2.35	11.30±1.55	0.220
Bilateral PCO (no, %)	27(90.0%)	29(96.67%)	0.301
Unilateral PCO (no, %)	3(10.0%)	1(3.3%)	

Unpaired student t-test was performed to compare between two groups.

Table-II

Comparison of follicular response (Follicular size) in between two groups in First cycle of ovulation induction up to day 12 (n=60)

Follicular response (Follicular size)	CC Group (n=30) No. (%)	Letrozole Group (n=30) No. (%)	p-value
Non-response (<10mm)	10(33.3%)	5(16.7%)	
Hypo-response (10-17mm)	7(23.3%)	10(33.3%)	0.311
Optimum response(≥18mm)	13(43.3%)	15(50%)	

Table-III

Comparison of follicular response (Follicular size) in between two groups in Second cycle of ovulation induction up to day 12 (n=32)

Follicular response (Follicular size)	CC Group (n=17) No. (%)	Letrozole Group (n=15) No. (%)	p-value
Non-response (<10mm)	8(47%)	4(26.7%)	
Hypo-response (10-17mm)	7(41.2%)	5(33.3%)	0.169
Optimum response(≥18mm)	2(11.8%)	6(40%)	

Chi-square Test (χ^2) was done to analyze the data

Table-IV

Comparison of endometrial thickness, grading and vascularity in between two groups in case of optimum response in both cycles (n=36)

	CC Group (n=15) No. (%)	Letrozole Group (n=21) No. (%)	p-value
Endometrial thickness			
<8 mm	10(66.7%)	7(33.3%)	
≥8mm	5(33.3%)	14(66.7%)	
Mean±SD	7.37±1.07	8.85±1.33	0.001^{s}
Range	(5.0 -9.20)	(7.10-12.80)	
Endometrial pattern			
Triple line endometrium	9(60.0%)	16(76.2%)	
NTL endometrium	6(40.0%)	5(23.8%)	0.298^{ns}
Morphological Grading			0.500^{ns}
Grade A	4(26.7%)	9(42.9%)	
Grade B	5(33.3%)	7(33.3%)	
Grade C	6(40.0%)	5(23.8%)	
Zone of vascularity			
Zone 1	8(33.3%)	5(23.8%)	
Zone 2	5(44.4%)	9(42.9%)	0.325^{ns}
Zone 3	2(22.2%)	7(33.3%)	

NTL -Non-Triple Line

CC- Clomiphene Citrate

Chi-square Test (c^2) was done to analyze the qualitative data.

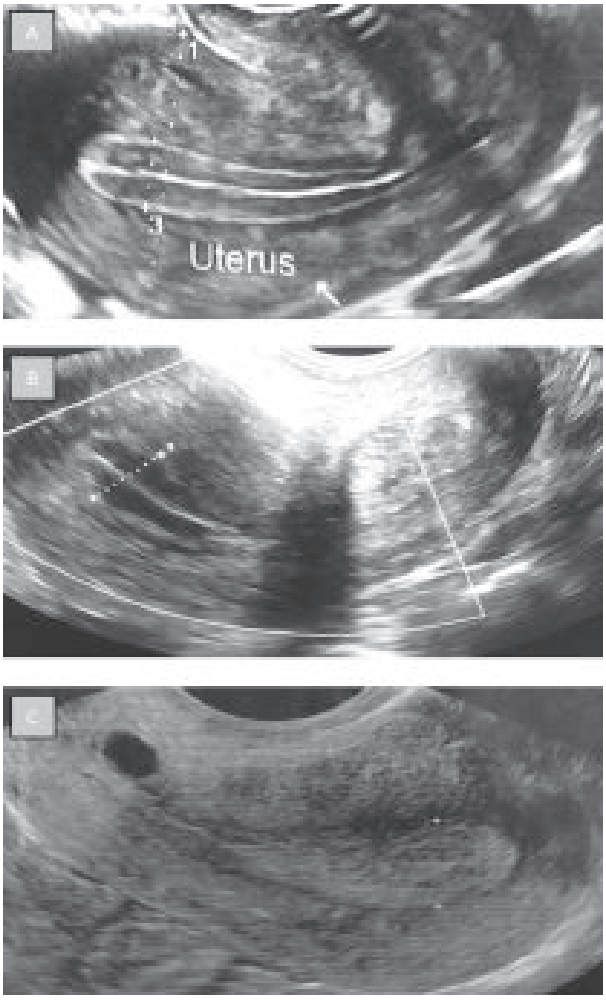

Fig.-1: *Endometrial type and grading at late proliferative phase. A) Triple line endometrium with Grade A variety; B) Triple line endometrium with Grade B variety; C) Homogenous endometrium or Grade C endometrium.*

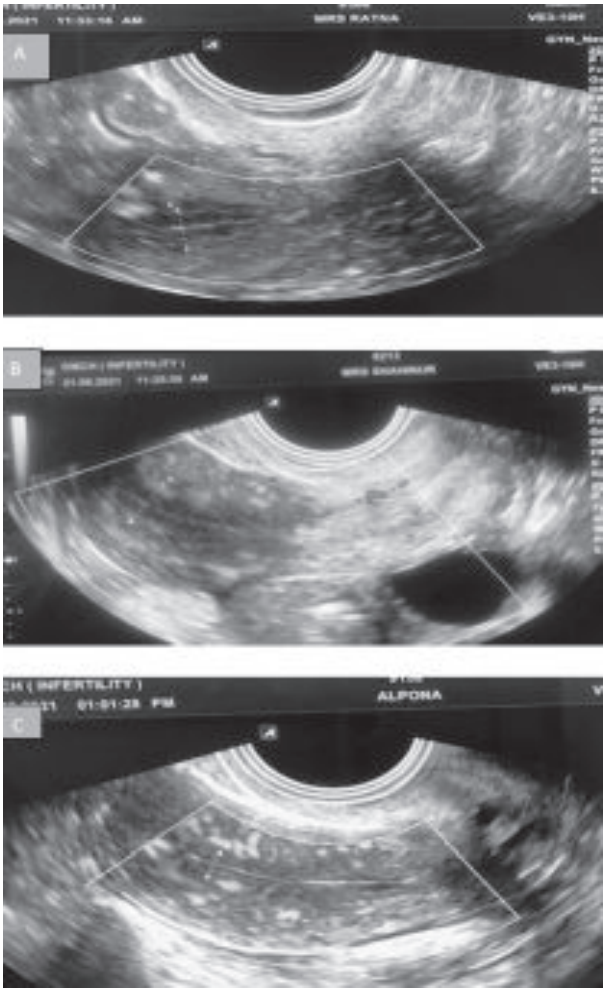

Fig.-2: *Applebaum's Zone of vascularity in case of Triple line endometrium. A) Zone 1; B) Zone 2; C) Zone 3.*

Discussion:

Since 1960, Clomiphene citrate was considered to be the sole first ovulation induction agent. However, clomiphene citrate resistance (15%-20%)[23,24], endometrial thinning, and poor cervical mucous (15%-50% of cases)[4,5,7,10] make it ineffective in many situations. No adverse effects on estrogen receptor (ER) are seen with Letrozole due to this short half-life, unlike Clomiphene Citrate[25]. Hence giving prime attention to the endometrial effect of CC and letrozole, this study revealed that the letrozole has a significant favorable effect on endometrial thickness (Letrozole 8.85±1.33 Vs. CC-7.37±1.07, p-value 0.001).

Sixty (60) diagnosed PCOS infertile women participated in this study. In our study, basic characteristics like age, duration of infertility, presenting signs and symptoms, BMI, and baseline TVS findings of the CC group and the letrozole group were similar.

We got optimum response (Mature dominant follicle ≥18mm) in 15 (50%) patients in the CC group and 21 (70%) patients in the letrozole group. The study done by Mahtab NT et al.[26] showed 50% of PCOS patients got optimum response by taking Letrozole.

Endometrial thickness (ET) measurement is a predictor for successful implantation following ovulation induction, with many studies reporting more success with a thickness of 9-10mm.[20] In the case of optimum response, ≥8mm endometrium was seen in 33.3% patients of the CC group and 66.7% patients of the Letrozole group. This result is near similar in the case

of the Letrozole group in Mahtab NT et al.[26] study. They observed e"8mm endometrium in 62.50% of all patients and 87.50% of optimum responsive patients of the Letrozole group.

In the current study, the mean endometrial thickness (ET) in optimum responsive patients was significantly thicker in the Letrozole group compared to Clomiphene Citrate (CC) group (8.85±1.33 mm vs. 7.37±1.07mm, p=0.001). The result of our study in ET(mm) is in accordance with the findings of Hegde and Maitra [17], Hussein et al.[13], Hendawy et al.[27] and Begum et al.[7] where they showed ET(mm) in Letrozole and CC group were 9.18±1.49 vs. 7.86±1.25, 8.5±0.7 vs. 7.7±0.9, 9.16±1.36 vs. 4.46±1.71, 10.37±1.2 vs. 9.03±0.89 respectively.

A triple line endometrium is the ultrasound marker that most accurately predicts the reflection of endometrial receptivity, as the triple line represents good estrogen primed endometrium which is needed for proper progesterone action for endometrial receptivity. The large randomized study done by Li Wang et al.[10] noticed a significantly increased triple line pattern in the letrozole group than the CC group (77.5% vs. 55.0%). The other studies were done by Hussein et al.[13], and Morad et al.[5] also found the same significantly increased result in favor of letrozole. However, we found more number of cases to appear triple line in the letrozole group (76.2%) than the CC group (60.0%) that were not statistically significant. Probably this result may be due to the small sample size.

Among the triple line endometrium in our study grade A endometrium was found 26.7% in the cases of the CC group and 42.9% in the cases of the Letrozole group and Grade B endometrium was found 33.3% in both group. In our study echogenic grading was not significantly different ($p=0.500^{ns}$). Similar results were noticed by Amer et al.[28] where in midcycle endometrial grading, Grade A were noticed in 36.2% vs 46.5% and Grade B were noticed in 37.0% vs 34.7% within CC and letrozole group respectively and the results were not statistically different between two groups (p=0.141). Hussein et al.[14], Morad et al.[6], found significantly increased number of Grade C or homogenouse hyperechoic endometrium in case of CC group than letrozole group and results were 23/40 vs 12/40, p= 0.024 and 50% vs 6.67%. p<0.001 respectively. However our study results were comparable with the findings of Amer et al.[28] where the grade C endometrium case difference between CC group and Letrozole group were not statistically significant and the results were 40% vs 23.8% in our study and 26.8% vs 18.8% in Amer et al.[28] study. As grade C endometrium presumably results from the hastened secretory transformation of the endometrium, so more appearance of grade C endometrium in CC group might have lower pregnancy and implantation rate.[29]

There are several reports by different groups that agree on the fact that implantation rates can be more correlated to the vascularity of the endometrium rather than the thickness and morphology of the endometrium.[29] In this current series more number cases of Zone 3 were found in the letrozole group than CC group (43.7%vs 22.2%). We didn't find Zone 4 vascularity in any group. Nagori and Panchal [29], in a retrospective study of 500 ovum donation- embryo transfer cycles found Vascularity Zone 4 for 14.47%, Zone 3 for 58%, Zone 2 for 20.73%, and zone 1 for 6.69%. After analyzing Table 4 it is seen that all the parameters of sub-endometrial and endometrial vascularization were worsened in the CC group which is comparable with the study of the results found by Li Wang et al.[10], ElKattan et al.[12], Morad et al.[5] where they found more endometrial and sub-endometrial vascularity in letrozole group than CC group defined by different sonographic indices. The study was non-randomized, and non-blinded which may affect the results. We did not repeat the scan to detect signs of ovulation and to detect endometrial receptivity parameters in the mid-luteal period. In this study, the endometrial response was analyzed in a small group of infertile PCOS women in the hope of generating some insight into the feasibility of TVS to give some attention not only to endometrial thickness but also to the quality of endometrium.

Conclusion:

Letrozole induces better sonographic parameters of endometrial development in terms of endometrial thickness than Clomiphene citrate, proven by the statistically significant increase in endometrial thickness within the letrozole group (Letrozole - 8.85±1.33 mm vs CC-7.37±1.07mm). Triple line pattern was in more quantities in the letrozole group, which are favorable parameters. Clomiphene citrate induces unsatisfactory endometrial response like endometrial thickness, and this finding should be confirmed by a further randomized, blinded clinical

trial. Therefore, a large scale, multicenter, and population-based randomized clinical trial with a big sample size is needed to identify the sonographic endometrial parameter in between CC, and letrozole stimulated cycles of PCOS women in our country.

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