Original Research Article

Efficacy of clomiphene citrate and letrozole in intrauterine insemination cycles

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Abstract

Background: There are two commonly used drugs for ovulation induction, Letrozole and Clomiphene Citrate (CC). Aim of the present study was to evaluate the efficacy of Letrozole and CC in women undergoing Intrauterine insemination (IUI) and also to compare the effects of Letrozole and CC on total number of follicles, endometrial thickness, hormone levels and pregnancy rates. **Methodology:** In our study we recruited 63 patients attending KSHEMA IVF (Fertility and Reproductive Medicine Center) and OBG OPD, Justice K.S Hegde Charitable Hospital,at Deralakatte, Mangalore between January 2018 to June 2019. There were 35 patients in Letrozole group and 28 patients in CC group. Serial TVS was performed in both the groups until a mature follicle of diameter 18 mm is seen. Gonadotropin injections were added as per the requirement of the patients in each cycle following which hCG trigger was given and after 34-36 hours IUI was performed. **Results:** The endometrial thickness in CC group was found to be more than in Letrozole Group (8.21±1.64 VS 7.36±1.25), which was statistically significant, which correlates with another finding of the study ,i.e, pregnancy rates were higher in CC group than Letrozole group(63.5% Vs 37.5%). It was found in our study that number of follicles were more in Letrozole group than CC group(61.1% Vs 38.9%). The required mean dose of Gonadotropin was found to be less in Letrozole than in CC group (104.23±56.86 Vs 168.75±77.63). **Conclusion:** CC has been considered as the first line agent for ovulation induction since years. In our study, it was found that endometrial thickness was statistically more in patients who received CC than Letrozole and pregnancy rates were higher in CC group. Also, number of dominant follicles was found more in Letrozole group. Patients in Letrozole group required less units of additional Gonadotropins.Hence we can conclude that Letrozole can be a better agent for ovulation induction, but CC might have a higher pregnancy rate than Letrozole.However it requires further study with larger sample size and sufficient study period so that the pregnancy outcomes can be studied

Keywords-Infertility, Ovulation induction, Clomiphene citrate, Letrozole, Intrauterine insemination (IUI).

Introduction

Infertility is defined as failure to achieve clinical pregnancy following one year of unprotected regular sexual intercourse. The prevalence of infertility was noted to be highest in South Asia, Central Asia, Sub-Saharan Africa, Europe and Middle East[1]. According to the estimates by WHO, the overall prevalence of primary infertility in India was between 3.9-16.3%. This estimates vary widely among the Indian states from 3.7% in Uttar Pradesh, Maharashtra and Himachal Pradesh, to 5% in Andhra Pradesh and 15% in Kashmir

Various modalities of treatment have come into existence for the treatment of infertility, IUI is one of the most cost effective and minimally invasive method of ART[2]. Ovulation induction combined with IUI is one of the approved treatment modality for cases of infertility secondary to anovulation, unexplained infertility and mild to moderate male factor. Clinical pregnancy rate following IUI was found to be 10-20%.

There are two commonly used drugs for ovulation induction, CC and Letrozole, an aromatase enzyme inhibitor.

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At physiological estrogen levels clomiphene citrate act as a competitive estrogen antagonist and is considered the first line treatment in ovulatory dysfunction and infertility. With the use of clomiphene citrate ovulation occurs in 73-87% of patients. However pregnancy rate is lower. It causes dose dependent negative effect on endometrial thickness, luteal phase defects and failure of implantation. Addition of Gonadotropins to CC decreases the dose requirement and makes it cost effective[3]. A third generation aromatase inhibitor Letrozole, is also being used for inducing ovulation. It blocks estrogen negative feedback, without depletion of ER, which increases gonadotropin secretion and as a result increases growth of follicles.It has no negative effects on endometrium and cervix, causes mono ovulation and its antiestrogenic effect is not persistent unlike CC hence estrogen receptor doesn't get depleted[4].

The present study is aimed at comparing the efficacy of Letrozole and CC with respect to endometrial thickness, number of mature ovarian follicles and pregnancy rate in IUI cycles.

Materials and methods

This prospective observational study was done at KSHEMA IVF Fertility and Reproductive Medicine Centre) OPD & OBG OPDs, Department of Obstetrics & Gynaecology, Justice K.S. Hegde Charitable Hospital, Mangalore between January 2018 and June 2019.Ethical clearance was obtained from the institution.

We enrolled 63 infertile women who were eligible for ovulation

induction and IUI. Inclusion criteria were women in the age group of 20-35 years who are infertile, women with patent fallopian tubes on hysterosalpingogram (HSG) or laparoscopy and women having body mass index (BMI) <28 and women planned for intrauterine insemination for anovulation, unexplained infertility, endometriosis and mild male factor infertility, and other indications. Exclusion criteria were male factor infertility < 10 million actively motile sperm per ml, women with bilateral tubal blockage and women having renal disease, liver disease or cardiovascular disease

The participants were observed in two groups: Clomiphene group and Letrozole group. The participants in Clomiphene Citrate group received ovulation induction with clomiphene citrate 50 mg daily on Day 2 to Day 6 of cycle of a spontaneous cycle or withdrawal bleeding after a 5 day course of 10 milligram per day medroxyprogestrone acetate. Participants in Letrozole group received ovulation induction with Letrozole 2.5mg daily on Day 3 to Day 7 of cycle of a spontaneous cycle or withdrawal bleeding after a 5 day course of 10 milligram per day medroxyprogestrone acetate . Serial trans vaginal ultrasound was performed in each cycle in both the groups from 8 th to 16 th day, depending on the ovarian response, until a mature follicle of diameter 18 mm or more and tri laminar layer of endometrial pattern is seen. Gonadotropin injections either hMG(Human Menopausal Gonadotropin) or rFSH were added as per the requirement of the patient in each cycle. 5,000IU of HCG was administered subcutaneously, once follicles attained size of more or equal to 18 mm. Also some patients were given GnRHa triggers (decapeptyl). Day 2/ day 3 Serum FSH, LH levels were documented Intrauterine insemination (IUI) was performed 34-36 hours after administration of HCG administration Urine Pregnancy Test was done with home pregnancy kits 2 weeks after HCG. The number and size of matured follicles and endometrial thickness on the day of hCG trigger in each cycle in patients with both group were documented . Participants were asked to come in case of missed periods and pregnancy was assessed by Urine pregnancy test Documentation of at least one gestational sac in USG confirmed clinical pregnancy. The mean number of dominant follicles, size of the follicles, the midcycle trilaminar layer of endometrial thickness on the day of hCG trigger and pregnancy rates were compared in both groups

Observation Chart

Table 1: Characteristics of Study Sample

Variables	Clomiphene citrate	Letrozole	P
Age, in years (Mean ± SD)	29.00±3.81	29.77±3.84	0.38
BMI, in kg/m^2(Mean ± SD)	22.80±2.39	23.13±2.22	0.51
Years of Infertility(Mean ± SD)	4.68±3.10	4.71±2.53	0.62
LH, in mIU/ml(Mean ± SD)	3.98±1.40	4.45±2.33	0.74
FSH, in mIU/ml (Mean ± SD)	6.30±1.20	5.92±1.43	0.39
Dose of Gn, in IU(Mean ± SD)	168.75±77.63	104.23±56.86	0.08
Mann Whitney test, *Statistically significant ,p<0.05			

Table 2: Distribution of the Overall Sample Based On Causes of Infertility

Ovulatory dysfunction n (%)	27(42.86%)
Endometriosis n (%)	8(12.70%)
Uterine causes n (%)	1(1.59%)
Unexplained n (%)	18(28.57%)
Mild male factor infertility n (%)	9(14.29%)
Total	63(100.0%)

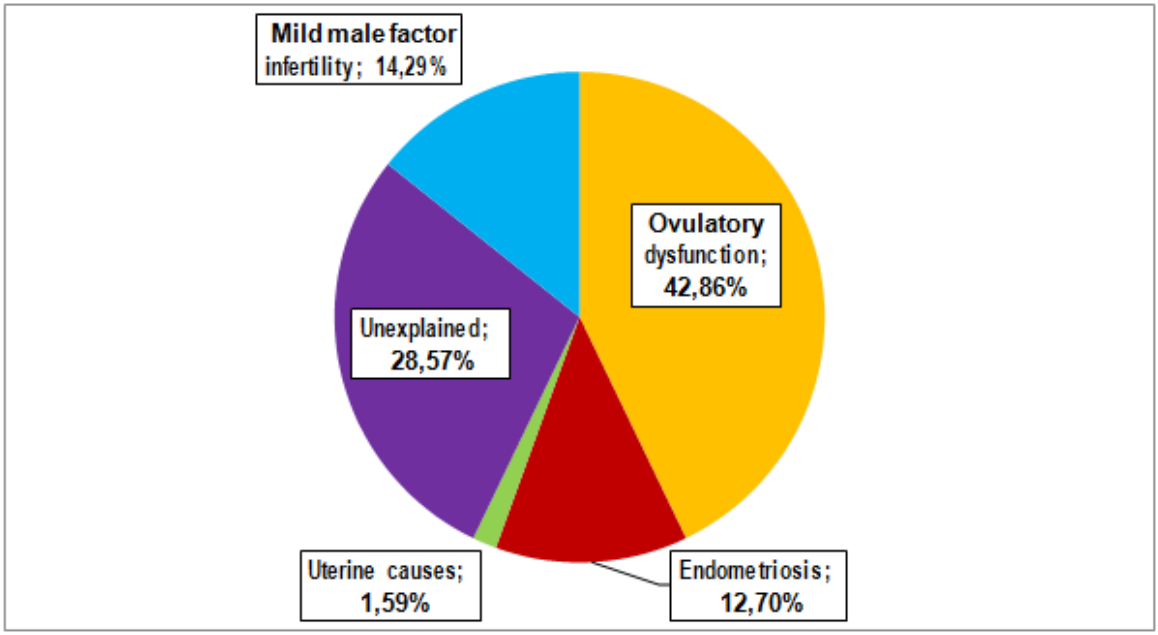

Fig. 1: Causes Of Infertility

Table 3: Comparison of Endometrial Thickness, Number And Size Of Follicles And Pregnancy Outcome Among Both The Groups

Variables		Groups	Clomiphene citrate	Letrozole	P value
Endometrial thickness		**Mean ± SD**	8.21±1.64	7.36±1.25	**0.04**
Size of follicles		**Mean ± SD**	20.04±1.87	20.61±2.32	0.36
No. of follicles >18mm size	**One**	**n (%)**	21 38.9%	33 61.1%	
	Two	**n (%)**	6 75.0%	2 25.0%	
	Three	**n (%)**	1 100.0%	0 0.0%	0.08
Mann Whitney test, Chi square test, *Statistically significant ,p<0.05					

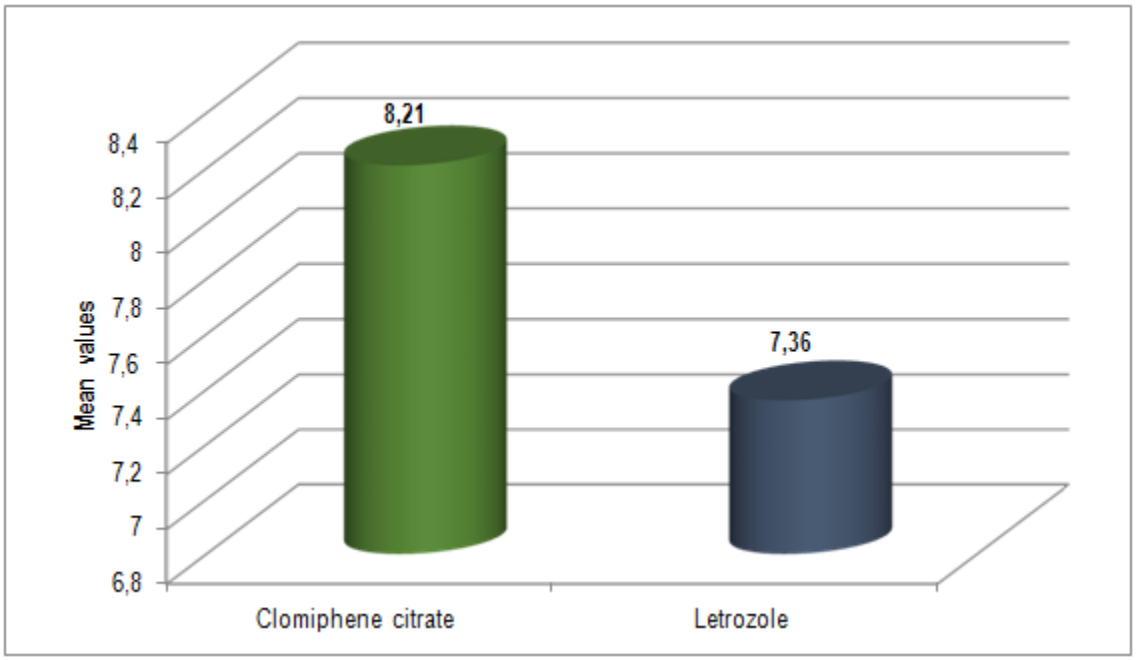

Fig. 2: Comparison of Endometrial Thickness Among Both The Groups

Table 4: Comparison of Pregnancy Outcome Among Both The Groups

Pregnancy outcome	Groups	Clomiphene citrate	Letrozole	P value
Positive	**n (%)**	5(62.5%)	3(37.5%)	
Negative	**n (%)**	23(41.8%)	32(58.2%)	0.23
Chi square test, *Statistically significant ,p<0.05				

Results

The study included 63 infertile patients after satisfying the inclusion and exclusion criteria. The mean age, BMI, years of infertilty were comparable in both the groups. Mean LH was higher in Letrozole group and mean FSH was higher in Clomiphene Citrate group. There were 21 participants who were given Gonadotropin doses. The required mean dose of Gn was higher in Clomiphene Citrate group. There was no significant difference among both the groups.

Endometrial thickness was significantly more in Clomiphene citrate group (8.21±1.64) compared to Letrozole group (7.36±1.25). When the size of follicles was measured, it was comparable in both the groups. On comparison of the no. of dominant follicles, majority of the participants had one dominant follicle, amongst which 61.1% were in the Letrozole group and 38.9% were in the Clomiphene citrate group. There was no statistically significant difference seen between both the groups when size of follicles, number of follicles and pregnancy outcome were compared.

Statistical analysis

The collected data was summarized by using frequency, percentage, mean & S.D. To compare the qualitative outcome measures Chi-square test or Fisher's exact test was used. To compare the quantitative outcome measures Independent t test was used. If data was not following normal distribution, Mann Whitney U test was used. SPSS version 22 software was used to analyse the collected data. p value of <0.05 was considered to be statistically significant.

Discussion

Ovulation induction and IUI has become one of the most empirical mode of infertility treatment as it is less expensive and less invasive technique as compared to In-vitro fertilization(IVF) /Intracytoplasmic sperm injection (ICSI). Ovulation induction along with IUI has been considered superior as compared to ovulation induction and IUI. In treatment of infertility for various indications like unexplained infertility, anovulation, Endometriosis and mild male factor infertility, Controlled ovarian hyperstimulation with IUI is used frequently. For this purpose clomiphene citrate is used frequently as a ovulation inducing agent which requires minimal monitoring. In 20% of female infertility anovulation is the cause particularly PCOS .CC remains the primary drug to induce ovulation in euoestrogenic anovulation. Letrozole has been proposed as an first line treatment and alternative to CC for ovulation induction, recently. This study aims at comparing the efficacy of CC and Letrozole for ovulation induction in patients with infertility for various indications with or without gonadotropins.

This study included 63 infertile patients in total, (35 patients in Letrozole group and 28 patients in Clomiphene group) after satisfying the inclusion and exclusion criteria. In our study there was no statistical significance in the various parameters such as age of the female partner, BMI, years of infertility, day 2 / day 3 hormone levels- FSH, LH type ofinfertility(primary/secondary) and the cause of infertility in both the study groups. There was no statistical significance among the two groups in relation to the size and no of dominant follicles prior to hCG injection for trigerring for ovulation also pregnancy rate between both the study groups were not statistically significant. The endometrial thickness on the day of hCG trigger was more in Clomiphene citrate group as compared to Letrozole group which was statistically significant. hCG triggers was given to all the participants in the study groups only after the dominant follicles has reached a size of more or equal to 18 mm.

In a study conducted by Robab Davar et al it was found that mean number of gonadotropin ampule used was comparable in both the groups (6.8±2.4 & 7.4±3.4 in Letrozole and CC group respectively), it was also found that there was no statistically significant difference in the endometrial thickness between two groups(6.9±2.5 & 7.6±1.8 in letrozole and CC group respectively, whereas in our study mean dose of gonadotropin was found to be more in CC group as compared to Letrozole (168.75±77.63 vs 101.23±56.86) also endometrial thickeness was found to be more in CC group than Letrozole group (8.21±1.64 vs 7.36±1.25) which was statistically significant (P=0.04).

In a study done by Kallol Kumar Roy et al[4] in 204 patients of PCOS, they compared the efficacy of letrozole and CC and found that the mean endometrial thickness in letrozole group was significantly higher that in CC group(9.1 ± 0.33mm vs 6.3±1.1mm) and the number of pregnancies were found to be statistically more in letrozole group that CC group (43.8% vs 26.4%)whereas in our study endometrial thickness in CC group was higher than letrozole group(8.21±1.64 vs 7.36±1.25) and pregnancy rates in CC group was 62.5% and in letrozole group was 36.5% but was statistically insignificant. The difference in the results might be because in the study conducted by Kallol Kumar Roy et al, only PCOS patients were included,whereas in our study patients with infertility due to various indications were taken into consideration.

In a study done by M P Diamond et al[5], they compared the efficacy of Letrozole, Gonadotrophin and CC in couples with unexplained infertility. They found that the clinical pregnancy rates with Letrozole was significantly lower(22.4%) than the rates with Gonadotrophin or CC (35.5 % and 28.3 % respectively). This finding was consistent with our study where pregnancy rate was found to be less in Letrozole group as compared to CC group(36.5% Vs 62.5 %), but was not statistically significant.

In a study done by S.A Amer et al[6], done in 149 participants, efficacy of CC was compared with Letrozole in subfertile women with PCOS. They found that pregnancy rates was significantly more in Letrozole group than CC group(61.2% Vs 43%). But the endometrial thickness on the day of hCG trigger was found to be significantly more in CC group as compared to Letrozole group (9.0 % Vs 8.4 %). Also the mean value of LH was more in Letrozole group (11.8 % Vs 10.2%) and mean value of FSH was found to be more in CC group than in Letrozole group (5.1% Vs 5.0%). Also ovulation per cycle was found to be statistically more in Letrozole group than CC group(75% Vs 67%). These findings were consistent with our study where endometrial thickness was statistically higher in CC group as compared to Letrozole group. Also number of mature follicles were found to be more in Letrozole group than in CC group(61.1% Vs 38.9%). FSH level was higher in CC group(6.30±1.20) compared to Letrozole group(5.92±1.43). In Letrozole group there were more number of patients with PCOS, this might be the reason for LH levels to be high in Letrozole group.

A similar randomized trial was done by Pourali L et al on clomiphene citrate versus letrozole with gonadotropins in intrauterine insemination cycles. The number of matured follicles, cycle cancellation, and abortion were the same in both groups. Endometrial thickness was higher at the time of human menopausal gonadotropin administration in letrozole group. Chemical and clinical pregnancy rates were much higher in letrozole group. Ovarian hyperstimulation was significantly higher in clomiphene group. Letrozole appears to be a good alternative to clomiphene citrate with fewer side effects[7].

Palatnik A et al did a retrospective study to determine the optimal follicular size before triggering ovulation in intrauterine insemination cycles with clomiphene citrate or letrozole. Leading follicle diameter and intrauterine insemination outcome. They concluded that the optimal size of the leading follicle in ovulation induction with CC and letrozole is similar for both drugs and is closely related to the endometrial thickness[8].

HaqNawaz F et al performed this study to investigate and compare the effects of Letrozole and gonadotrophins versus Clomiphene Citrate and gonadotrophins in women undergoing superovulation for Intrauterine Insemination (IUI).The addition of Letrozole to gonadotrophins decreases gonadotrophins requirements and improves endometrial thickness, without a significant effect on pregnancy rates. An improved pregnancy rate has been observed in older age group, >35 years with Letrozole[9].

A randomized controlled trial was done by Fouda UM et al. The aim of this randomized controlled trial was to compare the efficacy of extended letrozole regimen with clomiphene citrate in women with unexplained infertility undergoing superovulation and intrauterine insemination (IUI).Serum estradiol was significantly greater in clomiphene citrate group and the endometrial thickness was significantly greater in extended letrozole group. The pregnancy rate per cycle and cumulative pregnancy rate were significantly greater in extended letrozole group. The extended letrozole regimen had a superior efficacy as compared with clomiphene citrate in patients of unexplained infertility undergoing superovulation and IUI[10].

Yun BH et al evaluated the efficacy of minimal stimulation using discretely administered gonadotropin combined with clomiphene citrate (CC) or letrozole (LTZ) for intrauterine insemination (IUI) cycles. The clinical pregnancy rate was comparable between the CC and LTZ groups. The clinical pregnancy rate also showed no significant difference among the 4 groups.The multiple pregnancy rate was significantly higher in LTZ compared to CC group and in the LTZ+450 compared to CC+450 group.Overall, there were 15 cases of ovarian hyperstimulation syndrome (OHSS), with the prevalence being significantly lower in the LTZ compared to CC group. OHSS was more prevalent in the CC+450 compared to the LTZ+450 group .The findings suggest that minimal stimulation using two alternate-day gonadotropin with LTZ decreases the development of OHSS and multiple pregnancies, while maintaining comparable pregnancy rates in IUI cycles[11].

Zadehmodares S et al did comparison of treatment outcomes of infertile women by clomiphene citrate and letrozole with gonadotropins underwent intrauterine insemination. Patients were treated with 5 mg of letrozole daily (in letrozole group) or 100 mg of clomiphene citrate daily (in clomiphene group) for five days starting on day 3 of their menses. Dose and time of FSH was similar in the two groups. Number of follicles, endometrial thickness, Pregnancy rate and prevalence of complications were compared in the two groups. It was concluded that letrozole and clomiphene have similar outcome in infertile women under intrauterine insemination and these drugs are good alternative for each other[12].

Asgharnia M et al investigated if combination therapy with clomiphene citrate (CC) plus letrozole (L) was associated with a higher efficacy than L and CC alone in patients undergoing ovarian induction plus intrauterine insemination.In the CC group, gonadotropin dose was significantly higher but endometrial thickness was significantly lower compared with other groups. In the L + CC group, total and largest follicular size, and the rates of chemical, clinical, and ongoing pregnancy, and live birth were significantly higher compared with other groups.

Combination therapy with L + CC was superior to either L or CC for achieving pregnancy in women undergoing ovarian induction plus intrauterine insemination.In a similar study Oğlak SC et al did comparison of the efficacy of letrozole and gonadotropin combination

versus gonadotropin alone in intrauterine insemination cycles in patients with unexplained infertility[13,14].

In the newer trends on tamoxifen, Pourmatroud E et al assessed the effectiveness of tamoxifen administration with letrozole in the context of intrauterine insemination (IUI) cycles.This prospective double-blinded study included 130 patients. After randomization, 65 patients in group A received letrozole + tamoxifen and human menopausal gonadotropin (HMG), whereas 65 patients in group B received placebo instead of tamoxifen. Total dominant follicles in both groups were similar and there was higher pregnancy rate in group A ; but none of them was statistically significant. Surprisingly, endometrial thickness was significantly higher in group A. In addition to the efficacy of tamoxifen in co-administration with clomiphene citrate, it has promising effects with letrozole in induction of ovulation cycles with or without IUI[15].

Conclusion/ What this study add to existing knowledge

CC has been considered as the first line agent for ovulation induction since years. In our study, it was found that endometrial thickness was statistically more in patients who received CC than Letrozole. This correlates with another finding of this study where pregnancy rates were higher in CC group. Also, number of dominant follicles were found to be more in Letrozole group.

Patients in Letrozole group required less units of additional Gonadotropins. Hence we can conclude that Letrozole can be a better agent for ovulation induction, but CC might have a higher pregnancy rate than Letrozole. However it requires further study with larger sample size and sufficient study period so that the pregnancy outcomes can be studied.

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Limitations of the study

- The patients could not be followed up to know the outcome of the positive pregnancy result. Hence further follow-up is required to assess the live birth rate.
- Further study with a larger sample size is recommended to study the comparison of efficacy of CC and Letrozole.
- Larger sample size is required to compare the efficacy of CC and Letrozole.

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