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Comparison of Letrozole and Gonadotropins as Ovulation Inducers in Women

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ABSTRACT
Letrozole is preferable than CC in terms of side effects, ovulation, and pregnancy rates, according to several research. It is unclear whether is better and safest when used for ovulation induction in CCR: letrozole or gonadotropins. A multicenter randomized observational trial was designed to compare the effects of letrozole monotherapy and letrozole plus gonadotropin co-therapy on pregnancy outcomes, such as ovulation induction, pregnancy rate, and to assess estradiol (E2) levels and endometrial thickness in infertile women with polycystic ovarian syndrome, as well as pregnancy rates (PR) for letrozole and gonadotropins in those who were unable to conceive (PCOS).Individuals treated with letrozole or gonadotropins who failed to conceive with CC.Seventy infertile an ovulatory patient with CCR were randomly allocated into 2 groups, group I (letrozole group) and group II (Gonadotropins group). Ovulation rate and pregnancy rates were assessed.Among patients who failed to conceive with at least three cycles of CC, gonadotropins had a higher PR per cycle than letrozole. Among individuals who failed to conceive with less than three cycles of CC and whose medications were changed because of thin uterine lining or intolerable side effects, average PR per cycle for letrozole and gonadotropin treatments were equivalent. All patients conceived within three stimulation cycles with either gonadotropins or letrozole.In patients who failed to conceive with CC, gonadotropins have higher PR for ovulation induction than letrozole. However, PR was high enough with letrozole to justify its use in this population of patients. Letrozole and gonadotropins should not be used for more than three cycles without a conception.

Kaywords: Letrozole, Gonadotropins, ovarian stimulation

I. INTRODUCTION

The ovarian stimulation procedure aims to stimulate ovulation and improve the lining of the uterus. Oral medications are the first choice among medical treatments for lack of or weak ovulation. Letrozole is one of the fertility drugs that is also given orally and is used either to increase the number of eggs This drug is also used as an alternative to clomiphene citrate if severe side effects appear. Gonadotropin is one of the strongest oral medications, and is prescribed for severe cases of irregular ovulation or to increase the number of eggs produced during the ovulatory cycle. The one, it can be used with IVF and IVF procedure

1 Letrozole

Letrozole belongs to the group of drugs called aromatase inhibitors. Although it has been used to improve ovulation, it is primarily recognized for treating breast cancer. It functions by preventing the generation of estrogen and elevating the brain's (pituitary gland) stimulation of ovarian follicles (where the eggs are made) (Jacobs and Agrawal, 1998). Letrozole, an aromatase inhibitor, frees the pituitary/hypothalamic axis from estrogenic negative feedback when administered in the early follicular phase.Letrozole may be used as a second-line drug due to its higher pregnancy rates (PR) when compared to clomiphene citrate (CC) and its capacity to trigger ovulation in those who continued to be ovulatory after receiving CC. Gonadotropin is often the second-line therapy for people with CC who are unable to conceive. Gonadotropins, however (FSH) (Al-Fadhli et al., 2016).

The FDA has authorized letrozole for the treatment of postmenopausal women with estrogen-sensitive breast cancer. Letrozole has been more popular as an off-label fertility therapy in more recent years. This is because, in certain instances, it might promote (trigger) ovulation. The complicated interaction between several hormones produced at particular intervals throughout the menstrual cycle is the foundation of fertility (Holzer et al., 2012). Hormone abnormalities are one of several potential causes of infertility. In women who are an ovulatory, or not ovulating, letrozole increases this development and release of eggs. It can also promote superovulation in women who are already able to ovulate. It raises the likelihood of a natural

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conception in both situations. Hormones may be produced in certain forms of infertility at the incorrect time or in inadequate quantities to cause the release of an egg. It is impossible to become pregnant without an egg (Lenton, 2014; Speroff and Fritz, 2015).

Letrozole stimulates the brain to release more hormones required for conception, such as follicle stimulating hormone, by reducing the body's estrogen levels in premenopausal women (FSH) (Karaer et al., 2009). Follicles, which are immature eggs, expand and develop as a result of FSH.One dominant follicle develops and releases an egg during ovulation. Letrozole may be especially helpful in cases of infertility linked to PCOS (hormone imbalances are the root cause of PCOS). It may result in issues with the metabolism and reproductive system. One potential issue with PCOS is infertility. Ovulation may not occur frequently or, in some situations, at all for those who have PCOS. Additionally, testosterone levels may be greater in those with PCOS compared to those without the condition (Henderson et al., 2014; Garcia-Velasco et al., 2015).

There are several common adverse effects of letrozole (Al-Fadhli et al., 2016):

- Hot flashes
- Joint pain
- Flushing
- Tiredness
- Headache
- Dizziness

It's crucial to remember that letrozole side effects are only known for those who have breast cancer. There is a shortage of side-effect studies on fertility. Ltrozole can increase the number of follicles that form, which in turn can increase the amount of eggs produced each cycle. An egg is discharged from one follicle that has developed throughout a typical ovulatory cycle Women who got letrozole alone had a disease-free survival rate of 73.8 percent at 8 years, compared to a rate of 70.4 percent for women who received tamoxifen alone, in the intention-to-treat study (Fisher et al., 2009).

2 Gonadotropins

Gonadotropins are hormone injections that are used in fertility treatments to stimulate ovulation. Depending on the specific fertility medication, gonadotropins may contain either follicle-stimulating hormone (FSH), luteinizing hormone (LH), or both FSH and LH hormones. These two hormones are necessary for ovulation and they stimulate the ovaries to produce a follicle that contains an egg (oocyte) and to release the egg from the ovary (Speroff and Fritz, 2015).

Gonadotropins encourage the ovaries to create many follicles, which can increase the likelihood of getting pregnant (via intrauterine insemination [IUI], in vitro fertilization [IVF], or through natural sexual activity). There is an increased probability of multiple pregnancies with each of these strategies (Ryan et al., 2009; Karaer et al., 2009). The corpus luteum and the generation of progesterone by it, which is required to maintain pregnancy and promote the growth of the foetus, are stimulated by the interaction between circulating human chorionic gonadotropin and the luteinizing hormone receptors of the ovary. Specialized nerves cells in the brain's hypothalamus create and emit gonadotropin-releasing hormone. Usually, gonadotropins are used in conjunction with reproductive procedures like intrauterine insemination (IUI) or in vitro fertilization (IVF) (Holzer et al., 2012). Early in the menstrual cycle, gonadotropin injections are given to help numerous eggs develop to a mature size. Gonadotropins are hormones that encourage ovulation and stimulate the release of the sex hormones progesterone and estradiol (an estrogen) from the ovaries. Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are two examples of gonadotropins that are generated in the anterior pituitary. High amounts of folic acid consumption have the ability to lessen ovulation issues in healthy women who are attempting to conceive, as well as the placental hormone human chorionic gonadotropin (hCG). The addition of folic acid to the perfusate attenuated the drop in hCG (Mitwally and Casper, 2011; Tulandiet al., 2018), they pointed common side effects of gonadotropin include:

- Headache
- Restlessness
- Tiredness
- Irritability
- Swelling or water weight gain
- Depression
- Breast tenderness or swelling, or.
- Injection site reactions (pain, swelling, or irritation).

There are three primary types of gonadotropin fertility drugs:

(1) Menotropins, or human menopausal gonadotropin

(2) Recombinant human follicle-stimulating hormone

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(3) Human chorionic gonadotropin. These are marketed under various brand names (Sohrabvandet al., 2016).

Gonadotropins are typically injected into women once daily, in the evening (between 5 and 8 PM, for example). In the majority of situations, the injection may be administered under the skin. Hypo gonadotropic hypo gonadism, a disorder in which low levels of LH and FSH induce a lack of testosterone, is brought on by gonadotropin insufficiency (Al-Fadhli et al., 2016). The disease might be acquired, such pituitary tumors or trauma, or congenital, like Kallmann's syndrome, which is linked to olfactory system failure.LH and FSH encourage ovulation and stimulate the release of the sex hormones estradiol (an estrogen) and progesterone from the ovaries, which in turn indirectly encourages the creation of estrogen in the ovary (Al-Fadhli et al., 2016). Low LH levels might indicate that the pituitary gland is malfunctioning as a result of an eating problem or starvation. Rarely does GnRH overproduce. Elevated amounts might make you more likely to develop pituitary adenomas. Your body may produce too much follicle-stimulating hormone and luteinizing hormone as a result of these benign (noncancerous) tumors. In comparison to letrozole, gonadotropins have a greater PR for inducing ovulation (Atay et al., 2010).

II. MATERIALS AND METHODS

In order to ensure that all potential patients taking letrozole were located, a retrospective chart analysis of patients who failed to conceive due to CC and were then treated with letrozole (Femara, Novartis, East Hanover, NJ), 5 mg orally, from days 3–7 of the menstrual cycle or FSH starting on (day 3 of the menstrual cycle) was performed. Patients were regarded as having failed CC if

(1)They failed to become pregnant after at least three cycles of CC.

(2) With three cycles of CC raised to 150 mg per day, given on days 3–7 of the menstrual cycle, they were unable to ovulate.

(3) At the time of their most recent ultrasound that cycle, they had an endometrial lining thickness of less than 6 mm; or (Garcia-Velasco et al., 2015)if they experienced unbearable symptoms after receiving CC. Severe heat flashes that interfered with everyday activities, agonizing headaches, eyesight problems, and sadness were intolerable effects.

Subjects studied had PCOS-associated anovulation, unexplained infertility, or mild male factor infertility. The women with PCOS were oligo ovulatory (menstrual cycles less frequent than every 35 days) or an ovulatory and had clinical (Ferryman-Gallway score R8) or biochemical evidencetotal more than female assay maximum) of hyper androgenism.

As indicated, subjects with PCOS were evaluated for thyroid abnormalities (0.39<TSH>4.0 mIU/mL);hyper prolactinemia (morning fasting PRL <26 ng/mL); hypothalamicpituitary dysfunction and ovarian failure (1.4 <FSH>20 mIU/mL and E2>20 pg/mL); ovarian and adrenal androgen-secreting tumors (total T<200 ng/mL and DHEAS <800 mg/dL); and non-classic congenital adrenal hyperplasia(morning fasting 17-hydroxy-P <3 ng/mL).

The World Health Organization (WHO) criteria for a spouse with normal semen analysis and a strict Kruger analysis R4%, patent tubes on a hysteron salpingogram, and ovulatory menstrual cycles every 21–35 days with premenstrual molimina were all requirements for subjects who were classified as having unexplained infertility. 70 individuals with CCR who were infertile and ovulatory were divided into two groups at random: group I (the letrozole group) and group II (Gonadotropins group). Pregnancy rates and ovulation rates were evaluated (Elnasharet al., 2008).

1 Letrozole Treatment

The majority of patients receiving letrozole for ovulation induction take 5 mg per day from cycle days 3 to 7. Studies in a prospective randomized study showed that letrozole at 5 mg produced higher PR and more ovarian follicles without altering the development of the endometrium when compared to letrozole at 2.5 mg.

The results of the study by (Fadhli et al., 2016) indicate that the optimal dose of letrozole for inducing ovulation should be 5 mg.

2 Gonadotropin Medication

The FSH-treated participants got one of the following treatments: Gonal-f (Serono), Follistim (Organon), Menopur, or Bravelle (Ferring), and they were observed as previously mentioned. On the day of the b-hCG injection, the injection dosage was changed to avoid more than three follicles, serum E2 R2,500 pg/mL, and follicles with a mean diameter of 15 to 18 mm according to (Mitwally and Casper, 2011).

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2 Statistical Analysis

The statistical package for social sciences 11.0 was used for all statistical studies (SPSS Inc., Chicago, IL). The Kolmogorov-Smirnov test was employed to determine if continuous variables had a normal distribution. Results are given as the mean value minus the standard error of the mean (SE). The student's t-test was employed to compare nominal data. The data were subjected to Levene's test for equality of variances, and based on whether the variances were equal; the relevant t-test and P values were approved. The non-continuous variables were compared using the C2 and Fisher's exact tests. When cells were too tiny, corrections were made. Statistical analysis was utilized to examine the evolution of pregnancy findings. The approved level of significance was a two-sided P%.05

III. RESULTS

Gonadotropins had a greater PR per cycle than letrozole among individuals who were infertile after at least three cycles of CC. Average PR per cycle for letrozole and gonadotropin treatments were comparable in women who were unable to conceive after less than three cycles of CC and whose drugs were altered due to thin uterine lining or unacceptable side effects. Within three stimulation cycles with either gonadotropins or letrozole, all patients became pregnant.

1 Letrozole Versus Gonadotropin Stimulation

The characteristics of patients taking gonadotropins or letrozole are compared in Table 1. The mean ± SE of the mean, or the percentage of people afflicted in each group, is used to indicate these features. When comparing the two groups, there was no difference in any of the variables, including age, the number of unsuccessful CC cycles, the length of infertility, or the incidence of diagnoses. It should be noted that the maximum day 3 FSH level for both treatment groups was in the normal range for the clinic assay (<12 mIU/mL). There was no statistically significant difference between the groups in the number of true CC failures, defined as failure to conceive after three or more cycles (letrozole 53% vs. gonadotropin 51%) and those who had less than three CC cycles before initiating letrozole (47%) or gonadotropin (49%, P =75) as illustrated from table 1.

Table 1. Comparison of baseline characteristic in subjects who had failed treatment with clomiphene citrate and were subsequently treated with either letrozole or gonadotropins.

Details	Letrozole	Gonadotropin	Pvalue
Patientage(years)	35.2± 0.80.7	±0.20.2±35.50.60.7	.74
Gravity	0.06162_ ± 1.0	0.20.20.081621.066.415.43.	.78
Deliveries>36weeksgestationalage	60.5 ±	6.63.33 0.42.00.2	.93
Height(cm)	±0.32.0±0.2	22%	.63
Weight(kg)	27%	0%	.11
Numberoffailedclomiphenecycles	4%	78%	.95
Durationofinfertility(years)	68%	6.9 0.5	.79
PCOS	8.2 ± 0.6		.61
Malefactorinfertility			.52
Unexplainedinfertility			.45
Maximumday3FSH(mIU/mL)			.14

Note:PCOS¼polycysticovarysyndrome.
Quintero.Letrozolevs.FSHinclomiphenefailures.FertilSteril2007.

2 Pregnancy Outcomes in all Patients

In groups treated with letrozole or gonadotropins after failing to conceive with CC, pregnancy results for each stimulation cycle are shown in Table 2. In the gonadotropin group compared to the letrozole group, the rate of positive blood b-hCG levels per stimulation cycle 2 weeks after ovulation and the percentage of cycles with foetal cardiac motion at 6–7 weeks gestational age were higher.The miscarriage rate did not differ between the two groups. In the gonadotropin-treated patients, there were two multiple gestations, whereas there were none in the letrozole-treated subjects. However, given the small sample size and the lack of statistical significance, this was not different.

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Table 2. Comparison of pregnancy outcomes per treatment cycle among subjects treated with letrozole or gonadotropins after failing to conceive with clomiphene citrate.

Details	Letrozole	Gonadotropin	Pvalue
Positivepregnancytest	9%	28%	.002[a]
Fetalheartbeat	7%	18%	.03[a]
Miscarriagerateamongpregnancies	44%	44%	1.0

[a]Representsstatisticalsignificance.
Quintero.Letrozolevs.FSHinclomiphenefailures.FertilSteril2007.

The response per cycle among patients who were unable to become pregnant after at least three cycles of CC is compared in Table 3A. In Table 3B, the response is contrasted between patients who had less than three CC cycles prior to therapy with letrozole or gonadotropins. The cumulative results shown in Table 2 are consistent with the findings that among participants who failed to conceive with at least three CC cycles, those treated with gonadotropins were more likely to have positive pregnancy tests and foetal heart beats on ultrasound than those treated with letrozole.However, there was no difference between the participants treated with letrozole or gonadotropins among those who were unable to conceive after two or fewer CC cycles in terms of the frequency of positive pregnancy tests per cycle or the frequency of foetal heartbeats seen on ultrasound. This is explained by the fact that the FSH-treated patients had lower PRs per cycle. The PR per cycle for the letrozole-treated individuals remained unchanged, according to (Al-Fadhli et al., 2016; Mitwally and Casper, 2011).

Table 3. Comparison of pregnancy outcomes per treatment cycle among subjects treated with letrozole or gonadotropins after failing to conceive with at least three cycles (A) and with less than three cycles (B) of clomiphene citrate.

	Details	Letrozole	Gonadotropin	Pvalue
A				
	Positivepregnancytest	9%	33%	006[a]
	Fetalheartbeat	7%	26%	02[a]
	Miscarriagerateamongpregnancies	22%	45%	0.56
B				
	Positivepregnancytest	9%	22%	0.18
	Fetalheartbeat	7%	16%	0.26
	Miscarriagerateamongpregnancies	75%	42%	0.55

[a]Representsstatisticalsignificance.
Quintero.Letrozolevs.FSHinclomiphenefailures.FertilSteril2007.

3 Response to Letrozole and Gonadotropins over time

A life table analysis was conducted in the two groups—those who had had at least three CC cycles of infertility failure and those who had experienced infertility with less than three CC cycles—to assess the responsiveness to letrozole or gonadotropins per stimulation cycle. The information is displayed in Tables 4. These findings demonstrate that the PR per cycle with letrozole was similar at 3%–11% per cycle among those who had failed fewer than three cycles of CC without conception or at least three cycles. The PR with gonadotropins each cycle ranged from 10% to 19%. The cumulative PR for patients who failed to conceive after at least three cycles of CC was 37%, higher than the 27% PR for patients who failed to conceive after fewer than three cycles of CC. In those who had fewer than three CC cycles, the reduced PR per cycle seen with gonadotropins, as stated in the preceding section, was caused by none.

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Table 4. Life table analysis of clinical pregnancy rate per gonadotropin cycle (A) and letrozole cycle (B) in subjects who did not conceive with less than three clomiphene citrate cycles.

Cyclenumber	Percent clinicalpregnancypercycle	Cumulativeclinicalpregnancyrate	SEforcumulativepregnancyrate
A			
1	12	12	6
2	18	27	11
3	0	27	11
4þ	0	27	11
B			
1	3	3	3
2	6	9	6
3	11	19	11
4þ	0	19	11

Quintero.Letrozolevs.FSHinclomiphenefailures.FertilSteril2007.

IV. DISCUSSION

In several trials evaluating side effects, ovulation, and PR in a general infertile population, letrozole was found to be superior to CC (Al-Fadhli et al., 2016; Atay et al., 2010; andLenton, 2014). Letrozole has also been reported to stimulate ovulation and achieve a 25% PR in PCOS individuals who are ovulatory (Mitwally et al., 2013). Given that letrozole has a reduced risk of birth abnormalities than CC, it is now more acceptable to use it to induce ovulation (Mitwally et al., 2015). The conventional next step for patients after three to six cycles of CC that failed to result in pregnancy is gonadotropin therapy (Speroff and Fritz, 2015).Letrozole is an appealing substitute for gonadotropins because of how easily it induces ovulation orally and how inexpensive it is. Compared to gonadotropins, letrozole has a reduced risk of multiple gestations (Sohrabvand et al., 2016). It has not yet been determined how well letrozole works in people who have previously used CC without success compared to gonadotropin. Our findings imply that among women with CC who have experienced infertility, gonadotropins are more effective ovulation-inducing treatments than letrozole. In these individuals, gonadotropins had a superior mean clinical PR per cycle throughout the first three cycles of therapy (16% vs. 7%). For the aim of advising patients with CC who have previously experienced infertility, letrozole is expected to provide a PR of 3%–10% per cycle compared to gonadotropins' PR of 10%–20% every cycle. The cost of letrozole per month of stimulation should be considerably lower than that of gonadotropins. When compared to gonadotropins, letrozole requires less ultrasound surveillance and maybe fewer blood test measurements per treatment cycle, which should help lower treatment expenses. When contrasting letrozole with gonadotropins for ovulation induction, statistics on cost per pregnancy are, however, limited. Data are required to determine which is more cost-effective per live birth because to the letrozole's much lower PR (Mitwally and Casper, 2011).

There was no discernible difference in average PR per cycle between treatment with letrozole or gonadotropins throughout three cycles in participants who discontinued CC before three cycles because to intolerable side effects or a thin uterine lining. Given the anticipated reduced cost per stimulation cycle as compared to gonadotropins, our statistics imply that letrozole should be the next therapy in this patient population. Patients are hypoestrogenic during the first five days of their letrozole treatment course, but their levels soon rebound to normal, lessening some of the negative side effects of CC (Garcia-Velasco et al., 2015). Contrary to CC, letrozole shouldn't have an adverse effect on the endometrial lining (Atay et al., 2010; Al-Fadhli et al., 2016; Mitwally and Casper, 2011). However, there was no difference in the group that ceased CC before three cycles; this was not due to letrozole's ability to improve PR on a cycle-by-cycle basis, but rather to a decline in cumulative PR among gonadotropin-treated patients. In the letrozole-treated participants, there were no multiple gestations; in the gonadotropin-treated subjects, there were two multiple gestations. Even though these rates were not statistically significant, the relatively small

sample size and the low multiple gestation rates compared to historical data render any comparisons about multiple gestations based on the acquired data erroneous. Letrozole could be an acceptable substitute for CC because it can be given orally, requires less monitoring than gonadotropins, and has a low likelihood of multiple gestations. True CC failures, however, should be informed about the much-increased PR observed with gonadotropins when compared to letrozole.

V. CONCLUSION

The findings suggest that the use of gonadotropins during ovarian stimulation after unsuccessful treatment with clomiphene citrate (CC) results in higher pregnancy rates than letrozole, especially for women who did not achieve a pregnancy after three or more CC cycles. The use of gonadotropins was associated with more positive pregnancy tests and fetal heartbeats than the use of letrozole, and there was no difference in miscarriage rates between treatments. However, no clear differences existed among women who had failed less than three CC cycles. Analysis from the cumulative pregnancy rates indicates that more women are likely to conceive in a given cycle when using gonadotropins, making their use more beneficial for patients with multiple CC failures.

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