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ASSISTED REPRODUCTION

Comparison of letrozole with continuous gonadotropins and clomiphene-gonadotropin combination for ovulation induction in 1387 PCOS women after clomiphene citrate failure: a randomized prospective clinical trial

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Abstract

Purpose Letrozole, though reported to be an effective ovulation inducing agent, warrants larger randomized trials. The purpose of this study is to compare the efficacy of letrozole with that of rFSH and clomiphene citrate(CC)/rFSH for ovarian stimulation in IUI cycles.

Methods Randomized, prospective, single-blinded clinical trial. 1387 PCOS women after CC failure were randomized into three groups: Group A received letrozole, Group B received CC with two doses rFSH and Group C received continuous rFSH day 2 onwards until hCG injection.

Results Group A, B and C had an ovulation rate of 79.30%, 56.95% and 89.89% and cycle cancellation rate of 20.70%, 43.05% and 10.11%, respectively. Pregnancy rates in Group A, B and C were 23.39%, 14.35% and 17.92%, while the miscarriage rates were 13.80%, 16.67% and 14.52%, respectively.

Conclusion Letrozole appears to be a suitable ovulation inducing agent in PCOS women with CC failure and is found to be most effective when baseline estradiol level >60 pg/ml.

Capsule Letrozole appears to be an effective ovulation inducing agent as compared to clomiphene-rFSH and continuous rFSH protocols in PCOS women after clomiphene citrate failure.

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Introduction

Clomiphene citrate (CC) continues to be the drug of choice for ovarian stimulation in intrauterine insemination (IUI) cycles [1]. However, 20–25% of the women are resistant to CC and fail to ovulate [2]. In such cases, the traditional option is to administer gonadotropins, though it is associated with an enhanced risk of multiple pregnancies and ovarian hyperstimulation [3]. Several research groups have observed a higher pregnancy rate with gonadotropin therapy as compared to oral ovulation inducing agents in women failing to conceive with CC/IUI [4–6]. Recently, a consensus has been reached on the use of either exogenous gonadotropins or laparoscopic ovarian surgery in CC-resistant women as a second-line of intervention [7]. Gonadotropins (FSH/hMG) used in combination with CC decrease the dose required for optimum stimulation and make it more cost-effective in women who fail to respond to CC treatment [8]. Acceptable pregnancy rates with sequential CC and hMG ovulation induction in IUI following previous CC and IUI treatment failure are reported [9].

The concept of using aromatase inhibitors (AIs) as a new method of ovulation induction has been extensively investigated by several research groups in the past few years [10–13]. Letrozole, a highly selective AI, has been found to be effective in inducing ovulation in anovulatory and ovulatory infertile women with inadequate response to CC [14, 15]. Though higher clinical pregnancy rates were

observed with gonadotropins than with letrozole stimulation in CC-resistant women undergoing IUI [5, 6], both groups have confirmed that letrozole is associated with acceptable pregnancy rates, cost-effectiveness, decreased side-effects and patient convenience, as compared to gonadotropins.

Several published studies, both controlled and non-controlled, comparing letrozole with CC alone or in combination with gonadotropins were found in an extensive Pubmed search; however still insufficient evidence is available to recommend letrozole for routine use in ovulation induction. Most of these studies suggest that larger randomized studies are necessary to confirm the effectiveness of letrozole as an ovulation inducing agent in CC resistant infertile women [16–19].

Here, one of the largest-ever randomized clinical trials to explore the efficacy of letrozole in ovulation induction on 1387 infertile PCOS women who failed to conceive with CC treatment is reported.

Material and methods

Subject selection

This randomized single-blinded prospective controlled clinical trial was conducted in a tertiary infertility care unit, Institute of Reproductive Medicine, Kolkata, India. Approval was obtained from the Institutional Research Ethics Board. Written informed consent was taken from all women included in this study. 1387 women with PCOS, diagnosed by the Rotterdam criteria [20], who had previously failed to conceive or ovulate with CC treatment and undergoing IUI were included in the study. These women were randomly assigned three different ovarian stimulation protocols categorized as Group A, B and C. The method of simple randomization was used and the allocation was done using sealed envelopes where the person allocating was blinded to the type of protocol received by the patients. Patients who failed to ovulate or conceive despite 6 cycles of CC using 100 mg/day or showed poor endometrial development (endometrial thickness <0.7 cm on the day of hCG administration) were considered as CC failure cases. Specific inclusion criteria for the study were normal TSH and prolactin levels and normozoospermic male partners as per WHO guidelines [21]. Baseline FSH, LH and estradiol (E_2) levels, basal antral follicular count, tubal patency and male partner semen parameters were evaluated. Patients with pre-existing ovarian cyst on day 3 and previous history of ovarian drilling were carefully identified and excluded. Women with at least one of the tubes patent were considered for IUI.

Ovulation induction protocols

All infertile women with PCOS who failed to conceive or ovulate with CC were categorized as Group A, B and C. Group A (n=372) received letrozole (Letroz, Sun Pharmaceuticals, Mumbai, India) 2.5 mg twice daily, starting from day 3 of the menstrual cycle for 5 days. Group B (n=669) received CC (Ovofar, Organon India Limited, Mumbai, India) 100 mg daily from day 3 to day 7 of the menstrual cycle and two ampoules of rFSH subcutaneously, one on day 3 and the other on day 8. Each ampoule of the injection contained 75 IU of rFSH (Gonal-F, Serono, Switzerland) or 100 IU (Puregon, Organon, Oslo, The Netherlands). Women in Group C (n=346) were continuously administered one ampoule (75 IU/100 IU rFSH daily) from day 2 onwards until the day of hCG administration. Subsequent gonadotropin dose in Group C was adjusted according to the follicular response.

All patients were monitored for ovarian follicular development and endometrial thickness by transvaginal ultrasound from day 8 onwards. These women were administered 5,000 IU hCG (Profasi, Serono, Switzerland) subcutaneously as a single dose when the average diameter of the leading follicles reached ≥17 mm. Pre- and post-ovulatory IUI were performed in all patients. Patients who failed to ovulate even after 72 h of hCG injection were not subjected to post-ovulatory IUI and the cycle was cancelled. All women received 300 mg micronized progesterone (Utrogestan, Laboratories Besins International, Paris, France) intravaginally daily for 15 days for luteal support. Clinical pregnancy was defined as the presence of a gestational sac with cardiac activity as detected by transvaginal ultrasound at 7 weeks of gestation. The primary outcome measures including ovulation rate, cancellation rate, miscarriage rate and pregnancy rate were compared amongst the three groups.

Immunoassay

Serum levels of LH and FSH were measured by a two-site chemiluminescent sandwich immunoassay system (ACS:180; Bayer Diagnostics Corporation, Tarrytown, NY, USA). All samples were assayed in duplicate. LH and FSH values were expressed in terms of the reference standards (WHO 2nd IS 94/632 and WHO 2nd IS 80/552, respectively). Assay sensitivity for FSH was 0.3 mIU/ml and for LH was 0.07 mIU/ml. E_2 levels were assayed by fully automated enzyme-linked fluorescence assay system (Vidas; bioMerieux, Marcy l'El' toile, France). The minimum detection limit was 9 pg/ml. The intra- and inter-assay coefficients of variation were 3.4% and 4.8% for

Table 1 Baseline characteristics of CC failure infertile women randomly subjected to three different ovulation induction protocols: Group A received letrozole, Group B received clomiphene citrate + rFSH and Group C received continuous rFSH

Clinical characteristics	Letrozole protocol (Group A) (n=372)	CC-rFSH protocol (Group B) (n=669)	Continuous rFSH (Group C) (n=346)
Mean Age (years)	30.25±4.90	30.38±5.18	30.82±4.56
Duration of Marriage (years)	6.42±4.16	6.47±4.64	6.84±4.12
Mean BMI *Kg/m2*	24.49±3.83	24.75±4.05	24.08±3.43
FSH *mIU/ml*	5.91±8.91	6.33±7.22	6.04±2.17
LH *mIU/ml*	8.91±8.29	8.40±5.39	6.36±4.11
Estradiol (E2), *pg/ml*	54.17±35.33	62.05±37.38	57.35±39.35

FSH, 4.2% and 5.6% for LH and 4.7% and 5.8% for E_2, respectively.

Statistics

Multiple comparison using one way ANOVA and z-Test were performed, wherever appropriate, between the three groups A, B and C. Data are expressed as mean ± SD. Significance of the test was performed at the 5% level ($P < 0.05$).

Results

The clinical profile including mean age, duration of infertility, BMI, baseline FSH, LH and E_2 of patients belonging to Group A, B and C undergoing IUI are summarized in Table 1. Table 2 represents the different cycle parameters of the three groups. The ovulation rate was found to be 79.3% for Group A, 56.95% for Group B and 89.89% for Group C. The cycle cancellation rate was observed to be the least for Group C (10.11%), while Group A and Group B had a cancellation rate of 20.7% and 43.05%, respectively. The pregnancy rates in Group A, B and C were 23.39%, 14.35% and 17.92%, while the miscarriage rates were 13.8%, 16.67% and 14.52%, respectively.

Discussion

The pregnancy rate in Group A was found to be significantly higher as compared to Group B ($p < 0.0001$) in the present study. This is in good agreement with recent reports which conclude that letrozole has a better ovulation and pregnancy rate as compared to CC in patients with PCOS [22, 23]. Several smaller prospective randomized trials have also shown that letrozole may be an acceptable alternative to CC as an ovulation induction drug in women with PCOS [24–26]. An ovulation rate of 54.6% and pregnancy rate of 25% with letrozole induction in CC-resistant women with PCOS is reported [2]. We observed the ovulation rate to be 79.3% and the pregnancy rate 23.39% with letrozole.

A group of researchers have reported the pregnancy rate with letrozole and CC-hMG therapy to be comparable and suggest that their results should be confirmed in larger populations with proper randomization [18]. In our study, Group B was found to be associated with a higher cycle cancellation rate as compared to the other two groups. The prevalence of spontaneous abortion of a clinical pregnancy following CC therapy has been reported to be ~20% [27]. An ovulation rate of 56.95% and a pregnancy rate of 14.35% were observed in Group B (Table 2). This discrepancy between the ovulation and pregnancy rate

Table 2 Comparison of different cycle parameters between the three groups A, B and C: Group A received letrozole, Group B received clomiphene citrate + rFSH and Group C received continuous rFSH

Cycle parameters	Letrozole protocol (Group A) (n=372)	CC-rFSH protocol (Group B) (n=669)	Continuous rFSH (Group C) (n=346)	P value
Ovulation Rate	79.3% (295)	56.95% (381)	89.89% (311)	ab<0.0001 bc<0.0001 ca<0.001
Cancellation rate	20.7% (77)	43.05% (288)	10.11% (35)	ab<0.0001 bc<0.0001 ca<0.001
Pregnancy rate	23.39% (87)	14.35% (96)	17.92% (62)	ab<0.0001 bc NS ca NS
Miscarriage rate	13.80% (12)	16.67% (16)	14.52% (9)	ab NS bc NS ca NS

ab: Comparison between Group A and Group B
bc: Comparison between Group B and Group C
ca: Comparison between Group C and Group A
NS: Not Significant

Table 3 Characteristics of cycle parameters of women treated with alternate protocols (baseline estradiol <30 pg/ml)

Parameters Baseline E_2 (<30 pg/ml)	Parameters letrozole Group A1 n=145	CC + rFSH protocol Group B1 n=187	Continuous rFSH Group C1 n=117	P value
Pregnancy rate	3.44% (5)	2.67% (5)	23.08% (27)	ab NS bc<0.0001 ca<0.0001
Miscarriage rate	20% (1)	20% (1)	14.81% (4)	ab NS bc NS ca NS

Table 4 Characteristics of cycle parameters of women treated with alternate protocols (baseline estradiol between 30–60 pg/ml)

Parameters Baseline E_2 (30–60 pg/ml)	Letrozole protocol Group A2 n=96	CC + rFSH protocol Group B2 n=181	Continuous rFSH Group C2 n=74	P value
Pregnancy rate	25% (24)	37.37% (68)	40.54% (30)	ab<0.01 bc NS ca<0.01
Miscarriage rate	16.66% (4)	16.18% (11)	13.3% (4)	ab NS bc NS ca NS

Table 5 Characteristics of cycle parameters of women treated with alternate protocols (baseline estradiol >60 pg/ml)

Parameters Baseline E_2 (>60 pg/ml)	Letrozole protocol Group A3 n=131	CC + rFSH protocol Group B3 N=301	Continous rFSH Group C3 N=155	P value
Pregnancy rate	44.28% (58)	7.64% (23)	3.87% (6)	ab<0.0001 bc NS ca<0.0001
Miscarriage rate	12.07% (7)	17.39% (4)	16.66% (1)	ab NS bc NS ca NS

may be partly explained by the peripheral anti-estrogenic effects of CC or by hypersecretion of LH [27].

The pregnancy rate in Group A was observed to be slightly higher, though not statistically significant, as compared to Group C. A similar observation like ours has been reported by another research group where the clinical pregnancy rate per cycle in the letrozole and hMG group was found to be comparable [13]. There are, however, significantly higher pregnancy rates reported with gonadotropin (hMG/FSH) stimulation than IUI cycles stimulated with letrozole [6, 28]. Nevertheless, it is suggested that ovulation induction with letrozole is associated with a satisfactory pregnancy rate as it is more cost-effective, simple and convenient to patients when compared to gonadotropins [5, 13].

It is well established that letrozole selectively inhibits the aromatase enzyme that catalyses the rate-limiting step in the production of estrogens, i.e. the conversion of androstenedione and testosterone into estrogens, a terminal step in the biosynthetic sequence [8]. This prompted us to investigate further whether varying baseline E_2 level directly influences the IUI outcome when letrozole is used as an ovulation inducing agent. We subsequently divided each group into three sub-groups based on the E_2 level. The baseline E_2 values were selected arbitrarily as $E_2<30$ pg/ml, $E_2=30$–60 pg/ml and $E_2>60$ pg/ml. Group A was classified into Group A1 ($n=145$), Group A2 ($n=96$) and Group A3 ($n=131$). Similarly, Group B was divided into Group B1 ($n=187$), Group B2 ($n=181$), Group B3 ($n=301$) and Group C into Group C1 ($n=117$), Group C2 ($n=74$) and Group C3 ($n=155$). Pregnancy rates and miscarriage rates were compared between the sub-groups of each stimulation protocol (Tables 3, 4, 5). Letrozole and CC-rFSH protocol did not appear to be as effective as continuous rFSH when basal E_2 level was <30 pg/ml. For the baseline E_2 level between 30–60 pg/ml, the letrozole group showed a lower pregnancy rate as compared to the CC-rFSH and continuous rFSH protocol. For baseline $E_2>60$ pg/ml, a significantly higher pregnancy rate was observed with letrozole as compared to the other two protocols.

Higher pregnancy rate in women with $E_2<30$ pg/ml and $E_2=30$–60 pg/ml undergoing continuous exogenous rFSH stimulation may be due to augmentation of endogenous E_2 production by the growing follicles. It is presumed that additional amount of estrogen produced by continuous gonadotropin supplementation would stimulate follicular development. It is well known that the addition of gonadotropins in CC cycles is accompanied by a more intense ovarian response than the use of CC alone. In addition, there is a lower need for gonadotropins as compared to the GnRH agonist/gonadotropin regimes as well as an improved endometrial pattern and receptivity [29]. Having failed 6 cycles of CC therapy, it is possible that CC alone is unable to generate an optimum amount of endogenous gonadotropin (FSH) necessary for the development of competent follicles and inducing ovulation. This supports our observations in the CC-rFSH group, where a pregnancy rate of 37.37% is achieved for $E_2=30$–60 pg/ml.

On examining the three sub-groups for $E_2>60$ pg/ml, highly significant increase in the pregnancy rate of women receiving letrozole was observed as compared to the other two stimulation protocols ($p<0.0001$). This may be attributed to the fact that letrozole temporarily inhibits the production of E_2 which activates gonadotropins and, in turn, stimulates follicular growth [16].

Alternate protocols for ovulation induction in women failing to conceive with CC are more often randomly used with unpredictable outcome. A clinical/biochemical parameter is expected to help in selecting a specific type of ovulation induction protocol most suitable for achieving improved ovulation and pregnancy rates in such women. It is also suggested that ovulation induction efficiency might improve if patient subgroups with altered chances for success or complications with new or conventional techniques could be identified [30]. In the present study, rFSH alone, or in combination with CC, appears to be the most effective protocol when baseline E_2 lies between 30–60 pg/ml. In women with $E_2<30$ pg/ml, continuous rFSH stimulation is observed to be the most appropriate. For baseline $E_2>60$ pg/ml, letrozole undoubtedly emerges to be the best option as an ovulation inducing agent.

Conclusions

This study is one of the largest randomized clinical trials ever reported where the efficacy of letrozole as an ovulation inducing agent has been compared with CC-rFSH and continuous rFSH protocols. Letrozole appears to be a suitable ovulation inducing agent in PCOS women who fail to conceive with CC. This protocol was found to be most effective in women with high baseline estradiol level (>60 pg/ml).

An interesting finding has also emerged from this study which opens up the possibility of considering baseline estradiol level as a potential marker for selecting the most suitable ovarian stimulation protocol for achieving best outcome in women after failure of CC treatment.

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