Original Article

Effectiveness of recombinant luteinizing hormone/human menopausal gonadotropin/letrozole as additives to recombinant follicle-stimulating hormone in women with poor ovarian reserve undergoing controlled ovarian stimulation for *in vitro* fertilization/intracytoplasmic sperm injection

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Abstract

Background: To compare the addition of fixed dose additives namely recombinant luteinizing hormone (rLH), human menopausal gonadotropin (hMG), and letrozole to conventional doses of recombinant follicle-stimulating hormone (rFSH) on ovarian response and treatment outcome among women with poor ovarian reserve (POR) undergoing controlled ovarian stimulation for *in vitro* fertilization (IVF)/intracytoplasmic sperm injection (ICSI). **Materials and methods:** In this prospective quasirandomized study, participants ($N = 120$) were randomized into three equal groups. rFSH with one additive (rLH, hMG, letrozole) was administered to patients from day 2/3 of cycle. Clinical, ongoing, and early pregnancy rates were primary outcome measures. Total number of oocytes retrieved, number of transferable embryos, cycle cancellation, and fertilization rates were secondary outcome measures. **Results:** Group A patients had higher clinical pregnancy rate (42.5%) than group B (20%) and group C (25%) with significant differences ($P = 0.030$) between groups A and B. Ongoing pregnancy rates were higher in group A (35%) compared to group B (12.5%) and group C (22.5%) with significant difference between groups A and B ($P = 0.010$). Number of patients with early pregnancy loss was numerically equivalent in all three groups. Group C showed significantly decreased levels of estradiol compared with other groups. No significant differences in secondary outcomes were observed among the groups. **Conclusion:** The current study demonstrates benefits of rLH in early stages of stimulation in patients with POR in terms of improvement in IVF/ICSI-associated outcomes. Further larger randomized studies are required to confirm this effect, given a modest sample size in this study.

Keywords: Controlled ovarian stimulation, follicle-stimulating hormone, human menopausal gonadotropin, letrozole, luteinizing hormone, poor ovarian reserve

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INTRODUCTION

Globally, 9% to 24% of poor ovarian reserve (POR) women who undergo *in vitro* fertilization (IVF)/ intracytoplasmic sperm injection (ICSI) respond poorly to controlled ovarian stimulation (COS).[1-3] Additives to recombinant follicle-stimulating hormone (rFSH), aid in improving ovarian response. Recombinant luteinizing hormone (rLH) stimulates follicular growth and ovulation,[4] human menopausal gonadotropin (hMG) has better ovarian response[5-7] and letrozole inducing ovulation and reducing estradiol (E2).[8,9] There is no consensus on superiority of additives owing to insufficient evidence.[10] The present study is first of its kind to assess the effectiveness of rLH/hMG/letrozole as additives to rFSH in patients with POR undergoing COS for IVF/ICSI.

MATERIALS AND METHODS

Study design and eligibility criteria

This study was performed as a prospective quasirandomized trial on infertile patients with POR undergoing COS for IVF/ICSI at the Centre of IVF and Human Reproduction, Sir Ganga Ram Hospital, New Delhi, India from September 2017 to December 2018. Out of 124 women participants, 120 eligible participants were included in the study and were randomized into 3 groups of 40 each (Group A, rFSH + rLH; Group B, rFSH + hMG; Group C, rFSH + letrozole).

Inclusion criteria

Women who fulfilled all the following criteria were included in the study:

(1) Infertile women of all ages with POR undergoing COS for first or second IVF/ICSI cycles
(2) Serum anti-Müllerian hormone (AMH) values <1.1 ng/mL
(3) Antral follicular count (AFC) values <7 (transvaginal ultrasound monitoring was performed on cycle days 2 to 4 to evaluate the number of follicles correlating to poor response)

Exclusion criteria

Women who met any of the following criteria were excluded from the study:

(1) Intramural fibroid or adenomyoma >4 cm
(2) Untreated hydrosalpinx >1 cm

Determination of sample size

Sample size was calculated to compare mean number of oocytes retrieved among the three stimulation protocols using unpaired *t* test. Based on mean and standard deviation values reported earlier,[11,12] sample size was estimated for each pair and minimum sample size was determined for each group. Considering a significance level of 5% and statistical power of 80%, minimum sample size was estimated to be 36 for each group to detect a difference of 1 in mean values of number of oocytes retrieved.

Ethical approval and informed consent

Subsequent to approval (letter number EC/08/17/1251, dated August 30, 2017) by the research ethical board, the study commenced. Prior to enrolment in the study, eligible patients voluntarily signed the written informed consent form.

Methodology

Patients were evaluated for eligibility in accordance with the inclusion and exclusion criteria. Sealed envelope randomization method was followed to avoid bias between patient groups. Antagonist protocol was followed for COS in all patients. Basal (day 2) gonadotropin levels and other endocrinopathy during the cycle preceding the existing cycle were evaluated.

Stimulation protocols and monitoring

The rFSH was administered to all patients from day 2 or 3 of cycle along with one additive (rLH, hMG or letrozole) till 1 day prior to human chorionic gonadotropin (hCG) administration [Table 1]. Depending on the follicular recruitment, dose of rFSH was modulated in all three groups after day 5 of stimulation. From day 5 or 6 of stimulation onwards, follicle size was monitored using ultrasound; also, plasma levels of hormones estradiol (E2) and LH were measured at every visit. Once the leading follicle reached a size of >13 to 14 mm, a multiple dose flexible gonadotropin-releasing hormone (GnRH) antagonist protocol was initiated in all the 3 groups. On transvaginal scanning, when at least two or more follicles reached a size of ≥18 mm in diameter, 250 μg of hCG was administered. Oocytes were aspirated 35 to 36 hours after hCG administration.

IVF/ICSI

Retrieved oocytes were inseminated with spermatozoa under conditions specified in stimulation protocol. Upon assessment by embryologist and clinician, embryo was transferred on day 2/3/5. All patients received daily divided doses of 800 mg micronized progesterone intravaginally, during the luteal phase

Table 1: Baseline and stimulation characteristics of the patients included in the study

Parameters	Group ArFSH + rLH ($N = 40$)	Group BrFSH + hMG ($N = 40$)	Group CrFSH + letrozole ($N = 40$)	*P*-value
Dose of additive used along with rFSH 225–300 IU (from day 2/3 of cycle till 1 day prior to hCG administration)	rLH 75 IU	hMG 150 IU	Letrozole 2.5 mg for 5 days	
Baseline characteristics				
Age (years)	34.52 ± 3.92 (25–43)	34.82 ± 4.75 (26–46)	35.35 ± 3.80 (27–43)	0.672 (NS)
BMI (kg/m^2)	26.54 ± 3.64 (21.00–35.74)	26.96 ± 3.69 (20.70–36.05)	25.61 ± 3.32 (21.93–39.79)	0.224 (NS)
AFC	5.25 ± 1.54	4.98 ± 1.23	5.15 ± 1.27	0.547 (NS)
AMH (pmol)	4.79 ± 1.98	4.79 ± 1.98	4.79 ± 1.94	0.995 (NS)
Women with previous failed cycles	50%	37.5%	35%	0.343 (NS)
Stimulation characteristics				
Endometrial thickness (mm)	9.12 ± 1.97	9.12 ± 1.97	8.72 ± 1.70	0.669 (NS)
Serum E2 levels (pg/mL)	1356.12 ± 687.05	1460.05 ± 823.07	884.22 ± 492.03	<0.001 (HS)
Dose of total rFSH used (IU)	2573.75 ± 512.12	2566.25 ± 690.79	2955.0 ± 853.71	<0.020 (S)
Dose of additives used (ampoules)	9.38 ± 1.58	9.98 ± 1.74	NA	0.111 (NS)
IVF/ICSI (*x*/*y*)	6/34	10/30	7/33	NA

rFSH, recombinant follicle-stimulating hormone; hMG, human menopausal gonadotropin; rLH, recombinant luteinizing hormone; hCG, human chorionic gonadotropin; N = total number of patients; BMI, body mass index; AFC, antral follicle count; AMH, anti-Müllerian hormone; E2, estradiol; S, significant; NS, nonsignificant; HS, highly significant; NA, not applicable; IVF, *in vitro* fertilization; ICSI, intracytoplasmic sperm injection; *x*, number of patients who underwent IVF procedure; *y*, number of patients who underwent ICSI procedure.

until serum hCG test was performed. Luteal-phase support was continued till 10 weeks in cases of positive clinical pregnancy test.

Parameters assessed

Primary outcomes: Clinical pregnancy rate, ongoing pregnancy rate, and early pregnancy loss rate.

Secondary outcomes: Cycle cancellation rate, total number of oocytes retrieved, fertilization rate, and number of transferable embryos.

Clinical pregnancy was confirmed with the presence of a gestational sac when an ultrasound scan was performed 4 to 5 weeks after embryo transfer. Ongoing pregnancy was confirmed based on an ultrasound scan performed at 12 weeks. Cycle cancellation was considered when follicle was not formed or oocytes were not retrieved or embryo was not formed for transfer.

Statistical analysis

All continuous variables were analyzed using Kruskal–Wallis test or analysis of variance test and categorical variables were analyzed using Chi-squared test or Fisher exact test as applicable. A *P*-value of <0.05 was considered statistically significant. Results are reported as number of events, mean ± standard deviation, range, or percentage where ever appropriate.

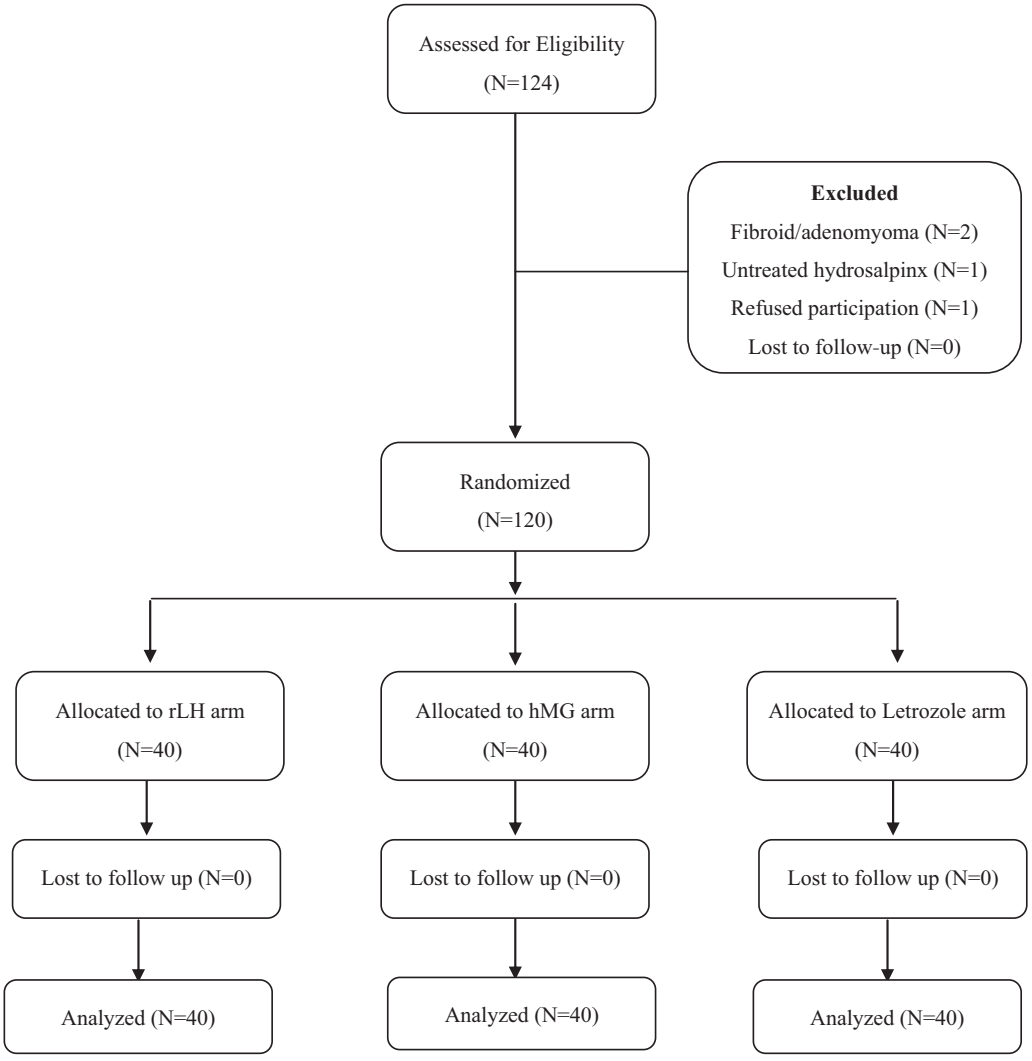
RESULTS

This study evaluated 124 women patients with POR for eligibility as per CONSORT guidelines [Figure 1]. Four patients who did not meet eligibility criteria were excluded (fibroid/adenomyoma, two patients; untreated hydrosalpinx, one patient; refused participation, one patient). A total of 120 patients who fulfilled the inclusion and exclusion criteria were randomized into 3 groups of 40 each. In all the groups, patients were not dropped out or lost during follow-up.

Patients with previous failed cycles were higher in group A (50%) compared to group B (37.5%) and group C (35%). Other baseline characteristics such as age, body mass index, AFC, and AMH levels were statistically insignificant among all the three groups [Table 1].

Stimulation parameters were also assessed based on outcomes between the groups. Patients in group C had significantly decreased serum E2 levels ($P < 0.001$) compared to group A and group B. Endometrial thickness did not differ significantly between groups. Dose of total rFSH used differed significantly ($P < 0.020$) between groups [Table 1].

The primary outcomes of the study are reported in Table 2. Patients in group A had higher clinical



rLH- Recombinant luteinizing hormone; hMG- Human menopausal gonadotropin

Figure 1: CONSORT flowchart (recruitment, follow-up, and drop outs over the course of the study). hMG, human menopausal gonadotropin; rLH, recombinant luteinizing hormone.

pregnancy rate (42.5%) than group B (20%) or group C (25%); clinically significant difference ($P = 0.030$) was observed between groups A and B. Ongoing pregnancy rates were higher in group A (35%) compared to group B (12.5%) and group C (22.5%) with clinically significant difference between groups A and B ($P = 0.010$). Clinical pregnancy rate and ongoing pregnancy rate was statistically insignificant among groups A versus C and B versus C. The number of patients with early pregnancy loss was equivalent in all three groups.

The secondary outcomes evaluated in the study are reported in Table 3. On assessment, secondary outcomes [cycle cancellation rate, number of oocytes retrieved, number of metaphase II (MII) oocytes retrieved, fertilization rate and number of transferable embryos] did not differ significantly between groups. Cycle cancellation rate was higher in group B (12.5%) and group C (10%) compared to group A (2.5%). Additives administered were well tolerated by patients and no cases of anaphylactic reactions were observed during the study.

DISCUSSION

Within the field of COS, there is still a need for better clarity on the diverse effects of gonadotropins on ovarian response. To our knowledge, the present study is the first of its kind to prospectively assess the effectiveness of addition of fixed doses of rLH/hMG/letrozole to conventional doses of rFSH on ovarian stimulation parameters and treatment outcome in patients with

Table 2: Primary outcomes of interest in women with poor ovarian reserve undergoing controlled ovarian stimulation

Parameters	Group ArFSH + rLH (*N* = 40)	Group BrFSH + hMG (*N* = 40)	Group CrFSH + letrozole (*N* = 40)	*P*-value
Clinical pregnancy rate (*n*/*N*)	42.5% (17/40)	20% (8/40)	25% (10/40)	A vs. B: 0.030 (S)A vs. C: 0.090 (NS)B vs. C: 0.590 (NS)
Ongoing pregnancy rate (*n*/*N*)	35% (14/40)	12.5% (5/40)	22.5% (9/40)	A vs. B: 0.010 (S)A vs. C: 0.210 (NS)B vs. C: 0.230 (NS)
Early pregnancy loss rate (*n*/*N*)	17.64% (3/17)	37.5% (3/8)	10% (1/10)	A vs. B: 0.344 (NS)A vs. C: 0.589 (NS)B vs. C: 0.275 (NS)

rFSH, recombinant follicle-stimulating hormone; hMG, human menopausal gonadotropin; rLH, recombinant luteinizing hormone; *n*, number of patients with defined outcome; *N*, total number of patients; S, significant; NS, nonsignificant.

Table 3: Secondary outcomes of interest in women with poor ovarian reserve undergoing controlled ovarian stimulation

Parameters	Group ArFSH + rLH	Group BrFSH + hMG	Group CrFSH + letrozole	*P*-value
Cycle cancellation rate (*n*/*N*)	2.5% (1/40)	12.5% (5/40)	10% (4/40)	0.242 (NS)
Number of oocytes retrieved	6.03 ± 3.125	5.10 ± 3.334	5.12 ± 3.115	0.211 (NS)
Number of MII oocytes retrieved	5.08 ± 2.740	4.28 ± 2.602	4.10 ± 2.158	0.227 (NS)
Fertilization rate	70.74 ± 24.89	67.46 ± 29.89	65.13 ± 25.13	0.643 (NS)
Number of transferable embryos	1.87 ± 0.85	1.80 ± 1.01	1.65 ± 0.864	0.659 (NS)

rFSH, recombinant follicle-stimulating hormone; hMG, human menopausal gonadotropin; rLH, recombinant luteinizing hormone; MII, metaphase II; *n*, number of patients with defined outcome; *N*, total number of patients; NS, nonsignificant

POR undergoing COS for IVF/ICSI. Our findings indicate higher clinical pregnancy rates in group A with rLH as additive in comparison to group B with hMG and group C with letrozole. Clinically significant difference was observed in the primary outcome for clinical pregnancy rate and ongoing pregnancy rate among group A versus group B. No significant difference was observed in the secondary outcomes among groups.

A meta-analysis conducted on 70 studies compared efficacy of mostly used gonadotropin combinations in assisted reproductive technology (ART). The combined use of FSH + LH-reduced FSH dose required for oocytes retrieved and increased the pregnancy rate by about 1.2-fold when compared with FSH alone, despite lower number of oocytes retrieved.[13] A systematic review and meta-analysis was conducted on 6443 patients (including normal and patients with POR) to study the possible clinical effect of rLH supplementation. The data suggested a relative increase in clinical pregnancy rates by 9% in the overall population and 30% in poor responders.[14] The present study results demonstrated higher incidence of clinical pregnancy rates (42.5%) with rLH as additive during IVF which are in accordance with these published meta-analysis.

To date, very limited studies are available comparing rLH and hMG in patients with POR undergoing IVF.[15] Although hMG improves the yield of mature oocytes, number of embryos, and increases implantation rate, addition of rLH leads to higher pregnancy rate.[13] A literature review was conducted for all relevant articles reporting IVF/ICSI treatment outcome after ovarian stimulation using hMG or rFSH + rLH. The available studies are mostly observational, using different daily doses and modes of administration of hMG or rFSH + rLH. No statistically significant differences were observed in ovarian stimulation variables, clinical pregnancy, and live birth rates when hMG was compared with rFSH + rLH.[16] As our study results show no difference in the number of retrieved oocytes, MII oocytes, transferable embryos, and endometrial thickness, the reason for rLH having better clinical pregnancy rate compared to hMG is difficult to determine. Therefore, we believe the observed results could be due to subtle factors.

Letrozole as an aromatase inhibitor combines the benefit of significant reduction in estrogen levels and gonadotropin dose and increases the intraovarian androgen concentrations achieving a good number of matured oocytes enhancing ovarian response.[9,17] A retrospective case–control study conducted on 214 women who underwent ART strongly suggests that the higher E2 level induced by COS has adverse effects on the maternal coagulation and fibrinolysis systems, which could enhance the hypercoagulable state during pregnancy.[18] Significant correlation was observed in IVF outcomes between higher E2 levels associated with lower clinical pregnancy and implantation rates including high miscarriage rate and lower birth weight.[9,19,20] A retrospective cohort study was conducted on 90 women with POR in previous GnRH antagonist cycles versus letrozole as adjunct in the early follicular phase in subsequent cycle. Letrozole group required reduced gonadotropin with improved

implantation and ongoing pregnancy rates. As letrozole did not improve oocyte quality, it indicated a possibility of improving oocyte quantity without adversely affecting the endometrium.[21]European Society of Human Reproduction and Embryology (ESHRE) consensus equally recommends the use of rFSH and hMG for ovarian stimulation. hMG and rFSH + LH appear to result in an equal probability of pregnancy in GnRH agonist protocols. However, the risk of ovarian hyperstimulation syndrome appears to be higher with the use of rFSH + rLH. Current study results of letrozole are in line with the recommendation of ESHRE consensus. With or without addition of letrozole to gonadotropins in stimulation protocols, improvement in efficacy of ovarian stimulation and significant difference in clinical pregnancy rates or in number of retrieved oocytes could not be established. In the present study, women administered with letrozole had lower pregnancy outcomes (25%).

Few ongoing trials which assess the influence of LH on oocyte maturity (NCT01595334) by comparing the efficacy and safety of two brands of highly purified hMG (CTRI/2009/091/000854), and evaluating the efficacy, safety, and cost effectiveness of minimal stimulation protocol (CTRI/2009/091/000086) might help to further identify the novel treatment strategies in IVF/ICSI. To optimize stimulation, a clinical trial (NCT01250821) evaluated the use of highly purified hMG and individualized standard protocol in Denmark. The efficacy of dual ovarian stimulation in the same IVF/ICSI cycle with hMG and letrozole as cotreatments was analyzed for number of retrieved oocytes in poor ovarian responders (NCT02732808). A prospective, randomized clinical trial comparing efficiency and safety of letrozole and rFSH on mild ovarian stimulation and COS in women with POR (NCT01926210) might help to further understand their effect on clinical pregnancy rate. The main limitation of our study is small sample size, and hence we suggest further larger randomized trials before rLH is routinely included in stimulation protocols for treating women with POR.

CONCLUSION

According to current study results, addition of rLH may improve the outcome of IVF/ICSI in patients with POR during early stages of stimulation. The results are evident with the highest clinical pregnancy rate when rLH was used as an additive with rFSH. In conclusion, we suggest designing future research with larger randomized studies to further establish the present findings.

Authors' contributions

RA, AM, SG were involved in planning and conceptualization of the study. All authors discussed the results and commented on the manuscript. DG was involved in doing structural changes in the manuscript. The manuscript has been read and approved by all the authors, the requirements for authorship as stated earlier in this document have been met, and each author believes that the manuscript represents honest work and information is not provided in another form. All data generated or analyzed during the study are included in this article and the data sets used during the current study are available from the corresponding author on reasonable request.

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Conflicts of interest

There are no conflicts of interest.

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