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"A COST-EFFECTIVE ALTERNATIVE TO CONVENTIONAL IVF PROTOCOL: AN ANALYSIS OF LETROZOLE AND GONADOTROPIN PROTOCOL VS CONVENTIONAL PROTOCOL IN IVF"

Obstetrics & Gynaecology

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ABSTRACT

Aim: Comparing the cost effectiveness and clinical pregnancy rate achieved with letrozole and gonadotropins with conventional (only gonadotropins) protocol. **Material & Methods:** Two groups of 45 patients each were studied. Study group (1) received letrozole plus gonadotropins and control group (2) received only gonadotropin as a stimulation protocol. The clinical pregnancy rate, gonadotropin dose and cost effectiveness, number of oocytes retrieved, implantation rate, fertilisation rate, abortion rates and ongoing pregnancy rates were compared. **Results:** Clinical pregnancy rates were comparable (24.3% vs 38.6%, p value 0.27). Dose of gonadotropins were significantly lower in study group (p value <0.001), leading to significant decrease in cost of the cycle by 36.4%. The total number of follicles on day of trigger were less in study group (9.78 vs 11.69; p value 0.151). The number of oocytes retrieved were lower in study group (7.3 vs 10; p value 0.036). The fertilisation rate in both groups were comparable (53.8% vs 58.3%; p value 0.219). Implantation rate was also comparable in both the groups (8.8% vs 14.6%; p value 0.23) and the ongoing pregnancy rates were (10.8% vs 20.4%; p value 0.41). **Conclusion:** The study shows the efficacy of letrozole plus gonadotropin as a affordable IVF protocol, the pregnancy rates were less in letrozole plus gonadotropin group without any statistical significance compared to gonadotropin only group. **Clinical significance:** Use of letrozole with gonadotropin lower the cost and dose of gonadotropins which was clinically significant. The pregnancy rates were comparable in both groups which makes letrozole and gonadotropin as good alternative to conventional protocols.

KEYWORDS

IVF, Letrozole, Gonadotropin

INTRODUCTION

Infertility is defined as the failure to conceive after 12 months or more of regular intercourse without contraception[1].Ovarian stimulation is a key component of ART. Various methods for ovarian stimulation are being used like natural cycle, modified natural cycle, mild stimulation and conventional methods. Conventionally only pure follicle stimulating hormone(FSH), only human menopausal gonadotropin(HMG) or combination of these have been used to get ideally 8 to 15 number of oocytes in each cycle of In Vitro Fertilization. Such regimens are associated with risk of complications such as Ovarian Hyperstimulation Syndrome. Therefore, mild stimulation was started. This was achieved with the use of clomiphene citrate and letrozole with or without gonadotropins.

More than a decade ago concept of aromatase inhibitor in ovulation induction was given by Robert Casper and Mohammed FM Mitwally[2]. There was a setback to letrozole use in year 2005 in infertility. Letrozole lost the approval by Central Drugs Standard Control Organization (CDSCO) in the last decade, now it has been approved for the use, after establishing its safety. It has been recently introduced in Indian market and approved by CDSCO for use in Assisted Reproductive Technology. There is paucity of literature about letrozole. In the last ten years and only recently it has been approved in India. Currently there are few evidences for use of aromatise inhibitor in IVF and very few studies have been conducted.

AIMS AND OBJECTIVES

The aim of the study is to compare the cost effectiveness and clinical pregnancy rate achieved with letrozole and gonadotropins with conventional (only gonadotropins) protocol. The secondary objective was to compare implantation rate, no. of oocytes retrieved, fertilisation rate and gonadotropins used.

MATERIALS AND METHODS

Sample Size:

The study was conducted in a tertiary care centre. The pregnancy rate was reported in a study by Garcia-Velasco et al., 2005 as 22.4% in letrozole and gonadotropin group as against 15.2% in the gonadotropin group. Based on these reference values, a minimum sample size of 461 patients in each group would be necessary to achieve a statistical significance of 5% and a power of 80%."

Formula used:

$$n = \frac{p_1(1-p_1)+p_2(1-p_2)}{(p_1-p_2)^2} C_{p,power}$$

where

n -number of subject required in each group

p_1 -success rate in letrozole and gonadotropin group

p_2 - success rate in gonadotropin group

$C_{\alpha, power}$ - constant defined as values chosen for the α level of significance and given power

Calculations:

$p_1 = 0.224$

$p_2 = 0.152$

$C_{5\%,80\%} = 7.9$ for the $\alpha = 5\%$ and power = 80%

However, a convenient sample size of minimum 90, 45 each group were enrolled in the study.

Study Population: All women of age group 23-43 years having infertility and planned for IVF were randomised into two groups using random number table:

Inclusion Criteria-

- Age: 23-43 years old.
- Women with indication of IVF and fit to undergo the procedure of IVF.

Exclusion Criteria-

- History of allergy to study drugs.
- With autoimmune, inflammatory or genetic abnormalities.
- History of 3 or more failed IVF.
- Medically not fit to undergo procedures.

METHODOLOGY

Group 1-Letrozole given 2.5mg/day from D2-D6. On D6 overlap with FSH was initiated with lower gonadotrophin doses (150 IU/day) and then increased to higher doses (225-300 IU/day) and HMG(37.5-75IU/day) on subsequent follow-up, according to response of follicles. GnRh antagonist added when follicle size 12-14mm.

Group 2-FSH (150-225 IU/day) given for 5 days from D2-D6. GnRh antagonist added when follicle size 12-14mm. Follicle stimulating hormone(225-300 IU/day) and HMG(75-150 IU/day) tailored according to need.

In both the groups, 10000IU Human Chorionic Gonadotropin (HCG) trigger is given when follicle size is > 16-17mm. After 34-36hrs ovum pick up was done and embryo transfer was done on D3 or D5 of ovum pick up as per convenience.

In the initial cases we had given gonadotropin on D5 of letrozole, later

on realised results were not good therefore after 5 cases we started gonadotropin on D3 of the cycle.

The patients were followed up with standard protocol and urine pregnancy test/HCG assay was done to confirm pregnancy. The outcome of pregnancy was noted till it reaches 14-16 weeks.

Outcome Measures:

Primary-

- Cost-Effectiveness
- Clinical pregnancy rate.

Secondary-

- Amount of gonadotropins used.
- Number of oocytes retrieved.
- Implantation rate, fertilisation rate, abortion rates and ongoing pregnancy rates.

OBSERVATION AND RESULTS

Majority of women had the tubal factor, 17(37.8%) and 24(53.3%) in group 1&2 respectively. Total 5 patients were having male factor, (11.1%) and 6(13.3%) in group 1&2 respectively. Five in group 1 and four in group 2 had unexplained infertility. 3 patients had decreased ovarian reserve(DOR) in group1&2. Six and one with polycystic ovarian syndrome in group 1&2 respectively. Endometriosis was seen in 3 patients in group1 and 2 each. Combined factor was in 6 patients in gp1 and 4 in gp2. Hence all factors were included in the study making it heterogenous study.

Estrogen (pg/ml) levels were compared on day 2 and trigger day. The mean E2 levels on D2 were 41.2 and 37.03 in group 1&2 respectively. Mean estrogen level on the day of trigger was 1404.95 and 1867.67 in group 1&2 with p value 0.036. Total E2 levels on day of trigger were significantly lower in group1.

The two groups did not differ significantly in endometrial thickness. The mean thickness in group 1 was 7.4 +/- 2.1 and 7.4 +/- 1.5 in group 2. Despite the significantly lower E2 levels in group 1, the endometrial thickness was not statistically significant (P value - 0.922).

The mean number of embryos freezed in group 1 was 1.31 and group 2 was 1.53 which was not significant statistically (p value 0.793). The fertilisation rate was 53.8% in group1 and 58.3% in group2 (p value 0.219) and the implantation rate was 8.8% in group1and 14.6% in group2 (p value 0.230) showing no statistical significance.

There were 45 patients in group1, 4 cycles were cancelled, out of which 2 were converted to IUI as tubes were patent and number of follicles produced were 1-2 only. Other 2 were cancelled as no dominant follicle produced and both the patients were poor ovarian reserve.

There were 41 ovum pick up, out of which 4 patients did not undergo embryo transfer as oocytes were not fertilised/degenerated therefore 37 embryo transfer of at least one or more good embryo done.

In group1, 37 embryo transfer were done, 9 were UPT positive. In group2, 44 embryo transfer done but only 17 were UPT positive.

Around 56.7% double embryo transfer done in group1 and 52.2% in group2. Whereas 29.7% triple embryo transfer was done in group1 and 40.9% in group2, rest were single embryo transfer. The mean embryos transferred in group1 was 1.78 and in group 2 was 2.27, p value 0.008 which was statistically significant.

Embryo freezing was done in 26 cases out of 37 cycles in group 1 and in 32 cases out of 44 cycles in group 2 which was around 70.2% and 72.7% in group1 & 2 respectively with p value 0.807.

In group2, 44 cycle continued as one case had degenerated oocytes. Out of 45 women in group1, 9 were UPT positive, whereas 17 out of 45 women in group2 were UPT positive. In group1, all 9 UPT positive cases were positive for clinical pregnancy. In group2, 17 UPT positive cases were positive for clinical pregnancy.

a. The **clinical pregnancy** rate- presence of intrauterine G-sac with or without cardiac activity. 24.3% vs 38.6% in group1&2 respectively (**p-value 0.27)**
b. The **ongoing pregnancy rate** which was followed up to 12 weeks of gestation. 10.8% and 20.4% in group1&2 respectively. As 4 patients out of 9 in group 1 continued pregnancy and 9 out of 17 in group 1**(p value 0.411)**
c. The **abortion rate**-presence of intrauterine g-sac with crown-rump length >/= 7mm with no heartbeat or mean sac diameter >/= 25mm with no embryo. 13.5% &18.1% in group1& 2 p value 0.56.

Table 1: Outcome of cycles

Outcome	Group 1	Group 2
Total patients	45	45
Cycle cancelled	4	0
Converted to IUI	2	0
Cycle continued	41	45
ET done	37	44
UPT positive	9	17
Clinical pregnancy rate	9/37(24.3%)	17/44(38.6%)
Abortion rate	5 /37(13.5%)	8/44(18.1%)
Ongoing pregnancy rate	4/37(10.8%)	9/44(20.4%)

Patients with UPT positive, ultrasound was done 4-5 weeks after embryo transfer in order to confirm the pregnancy, site of pregnancy and cardiac activity. Clinical pregnancy rate was the number of the patients with clinical pregnancy out of total number of the patients who underwent ET.

Out of 9 UPT positive cases, cardiac activity was detected in 4 patients and 5 were missed abortion, in group1. Two patients were converted to IUI and had negative UPT, 2 cycle were cancelled and rest had negative UPT. Out of 17 UPT positive cases, cardiac activity was detected at the time of scan in 9 and 8 were missed abortion, in group2.

There was significant decrease in cost of the cycle by 36.4%. (P value <0.001)

The clinical pregnancy rate in group 1 was 24.3% and in group 2 was 38.6% which was higher in control group, with no statistical difference. (P value- 0.271)

Table 2:

Variable	Group1		Group2		P value
	Mean	SD	Mean	SD	
Total follicles on day of trigger on USG	9.78	5.94	11.69	6.57	0.151
Oocytes retrieved	7.3	5.8	10	6.2	0.036
No. of embryo transferred	1.78	1.00	2.27	0.69	0.008
No. of embryos freezed	1.31	1.59	1.53	1.56	0.51
Gonadotropin dose	1427.78	509.27	2878.49	889.21	<0.001
Cycle Cost	14851.11	4128.98	23376.67	7015.05	<0.001

DISCUSSION

Letrozole and gonadotropins when combined with antagonist protocol limits the gonadotropin dose. Although there was a significant reduction of the gonadotropin dose in the letrozole-gonadotropin group, and a significant reduction in the cost of treatment, the outcomes, including pregnancy rates, were comparable. This is consistent with studies by Mitwally and Casper where they achieved a 45-55% reduction in the gonadotrophin requirement in letrozole-gonadotropin cycles.[2,3,4] Our observation of a significant reduction in terminal E2 levels also supports the findings of Verpoest et al[5]., Garcia-Velasco et al[6]., and Schoolcraft et al[7]. These findings supports the theory that aromatase inhibitors increase intraovarian androgen and FSH receptors gene expression by blocking androgen conversion, leading to increased FSH sensitivity to exogenously administered FSH.[8,9] We observed a decrease in mean endometrial thickness on the day of hCG in the study group, which correlates with the observation of Garcia-Velasco et al.[6], Davar et al.[10], and Ozmen et al.[11] However, there was no statistical significance (P value-0.922). The study done by Tal Lazer et al.[12], showed a higher clinical pregnancy rate in the gonadotropin-only protocol which is comparable to our study.

Although clinical pregnancy rate was less in group1 (24.3%) than group2 (38.6%) but it remained statistically insignificant (p value-0.27). Similarly, abortion rate though increased (13.5%) in group1 than group2 (18.1%) also remained insignificant statistically (p value 0.56). The ongoing pregnancy rates were 10.8% and 20.4% in group1&2 respectively with p value 0.411. Similar findings were reported in other

studies such as those conducted by Schoolcraft *et al*[7], Davar *et al*[10], Ji Hee Yoo *et al*[15] and Jigal Haas *et al*[16] in which they used letrozole as ovulation induction agent and observed pregnancy outcome in IVF. Studies conducted by Verpoest *et al*[5], Garcia- Velasco *et al*[6], *Ozmen et al*[11] Tal Lazer *et al*[12], S.K. Goswami *et al*[13], S.Mukherjee *et al*[14] letrozole plus gonadotropin group showed higher pregnancy rates than gonadotropin only group. To limit the gonadotropins dose and ultimately reducing cycle cost we added gonadotropins on day 2 of letrozole leading to gonadotropins to act slightly later to letrozole. As seen in earlier studies[12,14,17] gonadotropins and letrozole were started on same day or after completion of letrozole dose, there was no such statistical difference in the outcomes. So we tried to limit our dose by one day.

The dose of gonadotropin used was significantly lower (50.3%) in group1 compared to group2 with p value <0.001. These findings were same as shown by Mitwally and Casper[2] and S.K Goswami et al[13] in IVF. There were few limitations to this study like the sample size was small therefore more studies are needed with broader population. The patients were also followed till 12 weeks of gestation hence full evaluation is needed for long term outcomes of each protocol. As the study did not have stringent exclusion criteria, the results could be extended to a wider population. Since gonadotropin treatment requires close monitoring, and the cost of gonadotropins is high, our study's findings are reinforced. The average cost per cycle in this study was reduced by 36.4% in group1 including the cost of cancelled cycles, which corroborated with work done by S.K. Goswami *et al*.[13] The study represent a cost-saving option for patients and healthcare providers with outcomes being comparable in both groups. This is certainly an advantage for poor patients.

CONCLUSION

This study comparing letrozole plus gonadotropins with gonadotropin only in IVF cycles, involving 45 patients each, shows the effectiveness of letrozole-gonadotropin as an affordable IVF protocol. However, the pregnancy rates were less but without any statistical significance. However, cycles are cancelled more in letrozole gonadotropin group, indicating the effect on number of follicles which are significantly less compared to gonadotropin only group. Our objective to transform a costly conventional IVF protocol into an affordable one has been achieved with success even after considering cancelled cycles. Nevertheless, the lower pregnancy rates observed in the study group could potentially be attributed to variations in the number of prior IVF procedures among the participants, small sample size, difference in letrozole protocol used compared to other studies and all cases of infertility were included in the study. Therefore, we suggest letrozole is useful in normal responders, however more studies are needed for its use.

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