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Original Research Article

## A study for evaluation of two protocols comprising of clomiphene citrate, human menopausal gonadotropin with or without follicle stimulating hormone for ovulation induction in patients with infertility for intrauterine insemination

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### ABSTRACT

**Background:** To compare two protocols comprising of FSH/CC/HMG and CC/HMG for ovulation induction and IUI in women with infertility.

**Methods:** 60 women with unexplained infertility were randomized using sequentially numbered opaque envelope method. Group A received inj FSH 150 units on day 2 of menstrual cycle and clomiphene citrate 100 mg from day 3-7, followed by injection HMG 150 units on day 9 of menstrual cycle. Group B received clomiphene citrate 100 mg from day 3-7, and HMG 150 units on day 7 and 9 of the menstrual cycle. Ovulation triggered with hCG 5000 units when dominant follicle was 18mm. Single IUI was done 36-42 hours afterwards.

**Results:** Pregnancy occurred in 3 out of 30 women in 116 cycles Group A (with FSH) with a pregnancy rate of 10 percent, and 2.8% per cycle. In group B (without FSH) pregnancy occurred in 3 out of 30 women in 117 cycles with pregnancy rate of 10 percent, and 2.6% per cycle. The number of follicles per cycle was 1.36 and follicle size was 18.57 mm in group A. While in Group B numbers of follicles per cycle were 1.22, with average size of 18.9mm. Mean endometrial thickness was 7.7mm in Group A and 6.37 in Group B ( $p=.01$ , significant). Mild OHSS was observed in one woman in Group B. No other side effects were observed in both the groups.

**Conclusions:** The controlled ovarian stimulation regimes used in this study are equally effective, easy to administer, require less intensive monitoring and fewer medications, with little risk of OHSS and multiple gestation.

**Keywords:** Clomiphene citrate, Follicle stimulating hormone, Intrauterine insemination, Unexplained infertility

### INTRODUCTION

It is estimated that infertility affects 10 to 14% of the Indian population. Prevalence of infertility in couples actively attempting to conceive varies from 13.9% in Africa, 12.5% in China, 12.5% in India, 10.7% in UK to 7.2% in USA. India faces a high burden of infertility,

with 22 to 33 million reproductive age couples suffering from lifetime infertility. Female factor accounts for 40% - 50% of infertility, while male factor, which is on the rise in India, accounts for 30% to 40%. Assuming the marital rate in 2020 is similar to the current rate, the number of infertile couples could increase from 220 million in 2015 to 244 million by 2020.<sup>1</sup>

Human beings are remarkably fertile. Most women are capable of conceiving within two years of trying. However infertility has been reported since ancient times and is a common human burden. It has been established that factors contributing to infertility include both male and female factors such as increasing rates of ovulatory failures, tubal blockage and conditions such as endometriosis. Additionally, when the pregnancy is delayed to an older age when couples become less fecund also contributes to infertility.<sup>2</sup> The World Health Organization has listed infertility as a global public health issue. According to WHO, the major millennium development challenge will be to make management of infertility more accessible to the estimated 80 million couples who are unable to conceive.<sup>3</sup>

Most couples seeking infertility treatment are subfertile, with a decreased monthly conception rate, but natural pregnancy is possible. Approximately 25% of infertile women have problems with ovulation. These include inability to produce fully matured eggs or failure to ovulate. Out of all infertility cases, 30% are unexplained.<sup>4</sup>

Intrauterine insemination has demonstrated increased pregnancy rates in sub-fertile men when compared to timed intercourse in both natural ovulation and ovulation induction cycles.<sup>5</sup> Intrauterine insemination with ovulation induction has also demonstrated increased live birth rates in unexplained infertility when compared with timed intercourse and ovulation induction.<sup>6</sup> Intrauterine insemination (IUI) with husband's semen is the first line technique for many conditions of infertility including unexplained infertility and minimal or mild endometriosis. Several studies have demonstrated that IUI with controlled ovarian stimulation (COS) is better than IUI alone.<sup>7</sup>

Compared with natural cycle of IUI, ovarian stimulation may improve the treatment outcome of couples with unexplained infertility.<sup>8</sup> However, significant risks of ovarian hyperstimulation syndrome (OHSS) and multiple pregnancies remain. In addition there is small but finite risk of infection following IUI. Infertility still continues to pose a great problem in India including the state of Himachal Pradesh.

The present study is an attempt to fill the gap wherein an effort has been made to identify in detail the variables that contribute to the success of CC/HMG/IUI and CC/HMG+FSH/IUI treatments.

Objective of this study was to compare two protocols comprising of FSH/CC/HMG and CC/HMG for ovulation induction and IUI in women with infertility.

## METHODS

After approval of the "Institutional Ethics Committee", the study was conducted for a period of one year with effect from June 2016 to May 2017 in the Department of

Obstetrics and Gynecology, in association with the Department of Radio-diagnosis, at Dr Rajendra Prasad Government Medical College at Tanda, District Kangra H.P.

The couples attending the infertility clinic suffering either from primary or secondary infertility, and consenting to participate in the study were enrolled.

### Inclusion criteria

Women between 18 to 40 years age attending infertility clinic with

- At least one patent fallopian tube on hysterosalpingography
- Regular menstrual cycles
- Normal TSH and Prolactin levels
- Normospermic male partner as per WHO guidelines as under:
  - Liquefaction- complete in 60 min
  - Volume- 1.5 mL
  - Color- Opalescent white
  - Concentration (mL)- 15 million
  - Progressive motility- 32%
  - Vitality -58%
  - Morphology- 4%
  - Leukocytes (mL)- <1 million.

### Exclusion criteria

- Women with untreated endocrinological disorders in the form of thyroid dysfunction, hyperprolactinemia, cushings syndrome, and uncontrolled diabetes mellitus
- Couples not willing to participate in the study.

Preliminary workup included demographic profile; age, occupation, education, socio-economic status, history of infertility; primary or secondary infertility, duration of infertility, history of previous treatment. Menstrual history, obstetric history, sexual history, past history-hypertension, diabetes, thyroid dysfunction, renal disease, and sexually transmitted disease was also noted. Investigations included semen analysis, hormonal evaluation (serum TSH and day 2 serum prolactin), ultrasound (USG) of the pelvis, hysterosalpingogram, and laparoscopy if indicated. A total of 60 women with unexplained infertility were recruited in the study. These women were then randomized into two groups using sequentially numbered opaque envelope method (SNOSE). They then received either of the two controlled ovarian stimulation regimes as under:

Group A: Injection of purified urinary follicle stimulating hormone (FSH) 150 IU was administered intramuscularly on day two of last menstrual period and clomiphene citrate (CC) 100mg was given for 5 days (day 3-7) followed by intramuscular administration of human

menopausal gonadotropin (HMG) of 150 IU on day nine of last menstrual period.

Group B: Women were given clomiphene citrate (CC) 100 mg from day 3 to day 7, and human menopausal gonadotropin (HMG) 150 IU intramuscularly on day 7 and 9 from last menstrual period.

In both the groups, follicle monitoring was started using trans-vaginal ultrasound (TVS) from day 11 till the dominant follicle was 18-20mm. Then, ovulation was triggered by human chorionic gonadotropin (hCG) injection of 5000 IU. IUI was done 36 to 42 hours after ward. Luteal phase support was given in the form of oral or vaginal micronized progesterone 300 mg per day. A maximum of four cycles were tried. The primary outcome was to observe the pregnancy rate in two protocols proposed in the study.

**Statistical analysis**

Sample size was studied before the start of the study. Means, standard deviations, medians and ranges were calculated for descriptive purposes. Comparisons of patient characteristics, response to stimulation regimes, pregnancy rates per cycle, average number of follicles per cycle and average follicle size per cycle were done using chi-square test and student t-test. P values less than .05 were considered statistically significant.

**RESULTS**

The study comprised 60 women with unexplained infertility that underwent 233 cycles of controlled ovarian stimulation and IUI. The demographic characteristics, BMI and endocrinologic characteristics are shown in Table 1 and were similar in both the groups.

**Table 1: Demographic characteristics/ baseline characteristics of the patients with infertility in both the groups.**

Parameter	Group A	Group B	P value
Age (mean) years	30.36±3.2	29.86±3.9	.42
Duration of infertility (Range in Years)	6.8±3.1(2-15)	5.2±3.5(1-18)	.62
<b>Socio-economic status</b>			
Low socio-economic status	13 (43.3%)	19(63.3)	
Middle socio-economic status	17 (56.6%)	11(36.6)	
<b>Address</b>			
Urban	17(56.6)	19(63.3)	
Rural	13(43.3)	11(36.6)	
BMI (Kg/m <sup>2</sup> , Range)	22.2±4.6(17-30)	22.3±3.2 (18-31)	.83
TSH ( mIU/L)	2.26	3	.88
Prolactin (ng/dL)	14.05	14.05	.89
RBS (mg/dL)	96.6	95.3	.98

**Table 2: Comparison of ovulation induction cycles.**

Parameters	Group A	Group B
Number of induction cycles	116	117
Cycles with ovulation	110	113
Total number of dominant follicles	150	138
Cycles cancelled	9	4
Number of cycles of IUI given	107	113
Cancellation rate per induction cycle (Per cent)	7.75	3.41
Ovulation rate per cycle (Per cent)	94.82	96.58

**Table 3: Endometrial thickness.**

Endometrial thickness(mm)	Group A		Group B	
	Number	Per cent	Number	Per cent
<6 mm	10	33.33	12	40
6-10mm	14	46.66	17	56.66
>10 mm	6	20	1	3.33
Total	30	100	30	100

Mean: Group A: 7.71±2.1, Group B: 6.37±2.2 (p= .0185)

As shown in Table 2, 30 women were recruited in group A and underwent 116 cycles of controlled ovarian hyperstimulation followed by IUI. In group B, 30 women underwent 117 cycles of controlled ovarian stimulation and IUI. Nine cycles in group A and four cycles in Group B were cancelled due to refusal of patient or lost to follow up. Cancellation rate per induction cycle was 7.75 percent in Group A and 3.41 percent in group B.

Ovulation rate per cycle was 94.82 percent in group A and 96.58 percent in Group B. Pregnancy rate was 10 percent in each group.

The mean endometrial thickness was 7.71±2.1 mm in Group A and 6.37±2.2 mm in Group B and the difference was statistically significant (p=.0185) as shown in Table 3.

**Table 4: Comparison of result for pregnancy rate per cycle, mean E.T, mean number of follicles per cycle and mean size of follicles.**

Outcomes	Group A	Group B	T test	P value
Pregnancy rate per cycle (Per cent)	2.80	2.67		0.5
Mean ET (mm)	7.71	6.37	2.1352	0.0185
Average number of follicles per cycle	1.36	1.22	1.4918	0.0706
Average follicle size (mm)	18.57	18.97	-1.0045	0.1597

**Table 5: Life table analysis.**

Cycle	No. of couples in different cycles		Pregnancy during cycles		Drop out cancellation		Pregnancy rate per cycle of IUI (Per cent)	
	Group A	Group B	Group A	Group B	Group A	Group B	Group A	Group B
1	30	30	-	-	2	-	-	-
2	30	30	2	1	4	--	7.6	3.3
3	28	29	-	1	3	1	-	3.5
4	28	28	1	1	-	3	3.5	4
Total	116	117	3	3	9	4	2.8	2.65

As shown in Table 4, pregnancy rate per cycle were 2.8 percent and 2.67 percent in Group A and B respectively and were similar. The average number of follicles obtained per cycle in Group A was 1.36 and in Group B it was 1.22 (p=.07) while the average size of follicle in Group A was 18.57 mm and in Group B was 18.97 mm and was not significant (p=0.15).

None of the regimes resulted in higher order gestation. Mild ovarian hyperstimulation (OHSS) was reported in one woman (3.3%) in Group B while none developed OHSS in Group A.

Life table analysis is shown in Table 5. Total number of induction cycles given in group A were 116 and in group B were 117. Out of these 107 IUI cycles were done in group A whereas 113 were done in group B. Pregnancy rate of 2.8% (n=3) per IUI cycle was observed in group A whereas a pregnancy rate of 2.65% (n=3) per IUI cycle was observed in group B.

**DISCUSSION**

The use of ovulation induction combined with IUI as a treatment for sub fertility in women with patent fallopian tubes has increased in recent years and in fact remains a

mainstay of fertility therapy. The reported pregnancy rates per cycle have usually varied between 8% and 22%, but very low (4%) and high (40%) pregnancy rates have also been reported.<sup>9</sup>

However, ovulation induction and IUI facility is not available to most of the population in rural areas like ours in low resource settings. In one year period we could study only 60 couples with unexplained infertility. In the present study, 60 percent of women were from urban area, even though the hospital is in rural area suggesting that people from urban area have better access to avail hospital facilities like IUI that involve financial burden including drugs and transport cost. There were no statistically significant differences between the two groups in age, duration of infertility, BMI and endocrine status.

In the present study we have achieved a fairly good rate of ovulation i.e., 94.62 and 96.58 percent in group A and group B respectively. Pregnancy rate was 2.8% per cycle in group A and 2.65% per cycle in group B. In a similar study conducted by Romeu A et al, consisting of 364 patients and 416 ovulation induction cycles, 98.28% showed ovulation.<sup>7</sup> Pregnancy rate per cycle was 17.31% and cancellation rate of 8.9%. Further, Christin S et al

made a study comprising of two groups: Group A (rFSH step-up) and Group B (rFSH step-down) having 44 and 39 patients in each group who were given 85 and 72 OI cycles and observed the ovulation rate of 70% and 61% in group A and group B respectively.<sup>10</sup> In a study by Homberg R where clomiphene citrate and FSH were used for ovulation induction, an ovulation rate of 56.95% and a pregnancy rate of 14.35% were observed.<sup>11</sup> Peripheral anti-estrogenic effects of CC might explain low pregnancy rates in our study and other similar studies.

In the present study, we have observed that the mean endometrial thickness was 7.71mm in group A and 6.37mm in group B and was statistically different. Average number of follicles in group A and group B stood at 1.36 and 1.22 respectively. Further, it was observed that the mean size of follicle was 18.57mm and 18.97mm in group A and group B respectively.

Turhan N et al, reported in their study that the mean ET was 8.2mm to 8.3mm while dominant follicle count was 1.4 to 1.5 in group A and group B when ovulation induction was done by clomiphene citrate.<sup>12</sup> Similarly, ET was observed to be 8.1mm and average number of follicle 2.2 in group treated with CC in a study conducted by Akbari S et al.<sup>13</sup> Similar results were reported by Chaudhary K, and Gupta K on the women treated with CC + Gonadotropin and are in conformity with the results of our study.<sup>14,15</sup>

In the present study, 10% pregnancy rates were observed in both the groups where the ET was 6-10mm. In a study conducted by Nuojuia S et al, on 683 women, pregnancy rate per cycle was 12.7% when the ET was 6-10mm. Shoham et al, and Moradan S, demonstrated that no pregnancy occurs, if endometrium is <7mm in thickness. Endometrial thickness of 7-8mm indicates endometrial maturity.<sup>16-18</sup> The studies suggest that a triple line endometrium with a thickness >7-8mm is conducive to pregnancy.

Intrauterine insemination is a relatively simpler and less expensive. The pregnancy rate was 10% in each group in our study. Mukherjee S et al, reported that group A (uFSH +CC) had PR of 11% compared to 6.3% of group B (CC alone) in couples with unexplained infertility.<sup>19</sup> Gupta K et al, in their study observed higher pregnancy rate of 20% in CC+HMG group as compared to pregnancy rate of 15% in letrozole group.<sup>15</sup> In a similar study to the present study Chung MT et al, reported pregnancy rate of 14.8% in group 1(150U rFSH+CC) as compared to 20.4% in group 2(100U rFSH +CC).<sup>20</sup> In another study, Goverde AJ et al, observed pregnancy rates of 7.4% and 8.7% in IUI alone and COH+IUI groups respectively.<sup>21</sup>

In the present study only one case of mild OHSS in group B was observed which was managed as per protocol guidelines while none was present in group A. Van Santbrink EJ et al, Christin S et al, Balasch et al and

Hamilton et al have observed that OHSS ranged from 0-11% in their studies.<sup>22-25</sup>

In the present study, all the pregnancies occurred only in age group <35years in group A as well as group B.

In a retrospective analysis of the outcomes of 9, 963 consecutive IUI cycles, Stone BA et al, showed that the pregnancy rates were 18.9%, 13.9%, 12.4%, 11.4%, 4.7% and 0.5% in the age groups of <26, 26-30, 31-35, 36-40, 41-45 and >45, respectively.<sup>26</sup> In older couples, there may be a further compromise in fertility due to a higher rate of sperm aneuploidies.<sup>26</sup> Brzechffa P et al, in a similar study reported 23.1% pregnancies in women below 35 years age.<sup>27</sup> Age has a negative impact on ovarian reserve, oocyte quality, and a higher probability of fibroids, tubal pathology and pelvic inflammatory disease.

## CONCLUSION

The controlled ovarian stimulation regimes used in this study are equally effective, easy to administer, require less intensive monitoring and fewer medications, with little risk of OHSS and multiple gestation.

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