ORIGINAL ARTICLE

Comparison of Low-dose Human Menopausal Gonadotropins with Clomiphene Citrate for Ovarian Stimulation in Intrauterine Insemination: A Randomized Clinical Trial

Chitra Thyagaraju[1], Archana Naidu[2], Latha Chaturvedula[3]

Abstract

Introduction: Intrauterine insemination (IUI) is the treatment of choice for unexplained and mild male factor infertile couples not responding to ovulation induction (OI). Clomiphene citrate (CC) is the most common OI used but the success of pregnancy is very low due to its antiestrogenic effects. Gonadotropins are the second line of treatment in CC-resistant cases but they had the disadvantage of being costly with the risk of multiple pregnancies and ovarian hyperstimulation. However, low-dose human menopausal gonadotropins (hMG) have been found to be effective in these conditions with less risk of side effects.

Objectives: To assess the efficacy of ovarian stimulation of low-dose hMG and CC with IUI on pregnancy rate in unexplained infertility.

Materials and methods: The study was randomized control clinical trial conducted at a tertiary care hospital in South India. A total of 224 patients were randomized to two groups: the low-dose hMG group (75 IU) and CC group (100 mg). Women aged between 25 and 30 years with either unexplained or mild male factor infertility were included. All women were monitored for a follicular response, endometrial thickness, and ovulation. IUI procedure was done after 36–42 hours after HCG trigger. Statistical analysis was done using SPSS version 22 with Chi-square test and student *t*-test as statistical tests.

Results: The demography characteristics like age, duration of infertility, cause of infertility were almost similar in both groups. Compared to ovarian stimulation with CC, hMG stimulation was associated with more number of dominant follicles (2.2 ± 0.5 vs 1.9 ± 0.4) ($p = 0.001$), increased endometrial thickness (10 ± 1.3 mm vs 7.8 ± 0.15 mm and better pregnancy rate (31.2% vs 16.9%).

Conclusion: Low-dose human menopausal gonadotropins have a better pregnancy rate (31.2%) in comparison to clomiphene citrate (16.9%) when used for ovulation induction with IUI in patients with unexplained infertility and mild male factor infertility. Low-dose hMG was associated with more dominant follicles and better endometrial thickness which may lead to favorable reproductive outcomes.

Clinical significance: Low-dose gonadotropins can be considered for ovarian stimulation in IUI for better pregnancy rate and without any side effects, especially in low-resource settings.

Keywords: Clomiphene citrate, Human menopausal gonadotropins, Intrauterine insemination, Ovarian stimulation.

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Introduction

Infertile couples treated with intrauterine insemination (IUI) have a greater chance of conception than timed coitus following ovarian stimulation. Evidence supports that IUI has a clear-cut advantage over natural cycles following ovarian stimulation. The pregnancy rate is between 8% and 22% following ovulation induction and IUI.[1] Clomiphene citrate is the most commonly used OI, which is cheaper and has a lower incidence of multiple pregnancies. Although the ovulation rate with CC ranges from 40–80%, the conception rate averages up to 9–13 % only per cycle. This gap is attributed to the antiestrogenic effects of the drug-thinning of the endometrium, increased cervical mucus, and luteal phase defect.[2.] Controlled ovarian hyperstimulation with human menopausal gonadotropins along with IUI has a higher incidence of pregnancy rates in cases of unexplained infertility and mild male factor infertility.[3] However, gonadotropins are costly and have an increased risk of ovarian hyperstimulation syndrome (OHSS) and multiple pregnancies. Studies have shown that Low-dose gonadotropins are as effective as high-dose gonadotropins with a lesser risk of multiple pregnancies and OHSS.[4,5] Our study has been planned to see the ovulation and pregnancy outcome between the two groups using Clomiphene citrate or low-dose gonadotropin injections with IUI. It also contributes to elaborating some of the factors that contribute to a successful outcome in unexplained infertility and mild male factor infertility patients.

Aim

To compare the efficacy of ovarian stimulation of low-dose hMG/CC with IUI on pregnancy rate.

[1–3]Department of Obstetrics and Gynaecology, JIPMER, Puducherry, India

Corresponding Author: Chitra Thyagaraju, Department of Obstetrics and Gynecology, JIPMER, Puducherry, India, Phone: +91 9488818644, e-mail: drchitra@yahoo.com

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Materials and Methods

This study was a randomized controlled clinical trial conducted from January 2015 to June 2018. Women in the age-group 25–35 years with at least one tube patent were included. Semen analysis was done and parameters were reported using the World Health Organization (2010) criteria. Women with advanced-stage endometriosis, bilateral tubal pathology, pelvic inflammatory disease, or hypersensitivity to any drugs used were excluded from the study. The study was approved by the Institutional Review Board and was ethically conducted in accordance with the Declaration of Helsinki. Detailed history and physical examination were done for all women who were recruited. On the second day of the menstrual cycle, baseline transvaginal ultrasound, and baseline hormonal investigations were done. The patients were then randomized into two groups based on computer-generated randomization numbers and one of the drug protocols was allocated to them: group A: Ovarian stimulation was done by giving Injection Human menopausal Gonadotropins 75 IU (HUMOG, Bharat Serum Institute) intramuscular daily from Day 2 to Day 6 of the menstrual cycle. Group B: A dose of 100 mg/d Clomiphene Citrate (Clomid 100 mg, Sanofi) was administered on days 2–6 of the menstrual cycle for 5 days.The patients were monitored by transvaginal sonography (TVS) starting from Day 9 of ovarian stimulation. Follicular dynamics like the total number of follicles, their size, endometrial thickness at HCG trigger were noted. When the mean diameter of the leading follicle reached 16–18 mm, an injection of 5000 IU of urinary human chorionic gonadotropin was administered intramuscularly. After confirming ovulation, the IUI procedure was performed usually 36–41 hours after ovulation trigger. If there were more than three dominant follicles the cycle was canceled. Semen samples for IUI were prepared by the Swim-up Method and 0.4 mL of processed semen was instilled into the uterine cavity using a soft catheter. After insemination, luteal phase support was given with oral micronized progesterone 200 mg daily for 2 weeks. The main primary outcome measured was the pregnancy rate. The secondary outcome measure was the total number of follicles, number, and size of the leading follicle, the thickness of endometrium on the day of hCG trigger. The urine pregnancy test was if the patient missed periods and if there was the presence of intrauterine gestational sac with fetal pole and cardiac activity, clinical pregnancy was confirmed.

The sample size estimated in each group is 102 with a 95% confidence interval and 80% power using OpenEpi software (11). With an attrition rate of 10%, the estimated sample in each group is 112. Randomization was done using a computer-generated random sampling technique.

Statistical Analysis

Statistical analysis was done by using the SPSS software package, version 22.0. For categorical variables, Fisher's exact test and the Chi-square test were used. Student *t*-test and one-way ANOVA were used to compare means for normally distributed continuous variables. A *p*-value <0.05 was considered statistically significant.

Results

A total of 224 women were randomized to two groups on the second day of menstruation. After randomization, all women have subjected to three consecutive cycles of controlled ovarian stimulation (COS) either with low-dose gonadotropins or clomiphene citrate. Two patients in the hMG group and three patients in the CC group did not participate in the 3rd cycle of IUI. The demographic and fertility backgrounds were comparable between the two groups of patients. Unexplained infertility comprised 77% in the hMG group and 72.3% in the CC group while mild male factor infertility in both groups comprised 77% and 72.3%, respectively. Primary infertility comprised more than 70% in both the groups and the mean duration of infertility was 4.6 ± 2.1 years in the hMG group and 5.7 ± 3.7 years in the CC group (Table 1). A total of 224 patients attending infertility outpatient clinic of JIPMER for infertility treatment from January 2015 to June 2018 wererecruited in the study.

Table 1: Demography profile and hormonal values between two groups

Variable	*hMG group (N = 112)*	*CC group (N = 112)*
Mean age (±SD)	29.3 ± 3.8 years	29.0 ± 3.8 years
Mean infertility (±SD)	Primary- 4.6 ± 2.1 years Secondary-7.1 ± 2.6 years	Primary- 5.7 ± 3.7 years Secondary- 7.9 ± 2.6 years
Mean LH levels (±SD)	6.2 ±2 IU/L	6.0 ± 2.0 IU/L
Mean FSH levels (±SD)	6.2 ± 1.5 IU/L	5.6 ± 1.1 IU/L
Mean testosterone levels (±SD)	39.2 ± 22.1 ng/dL	42.9 ± 23 ng/dL
Mean prolactin levels (±SD)	11.9 ± 5.1 ng/dL	11.2 ± 4.4 ng/dL
Total sperm count (±SD)	71.7 ± 14.7 million/ml	86 ± 20.7 million/ml
Total motile count sperm (±SD)	52.7 ±15.6 million/ml	58 ± 28.1 million/ml
Progressive motile count (±SD)	36.5 ± 10.3 million/ml	42 ± 23.6 million/ml
Normal morphology (±SD)	83.8 ± 5.5%	86.4 ± 4.1%
Primary infertility	90 (80%)	94 (84%)
Unexplained infertility	86 patients (77%)	76 patients (72.3%)
Mild male factor infertility	26 patients (23%)	36 patients (27.7%)

Table 2: Comparison of number of dominant follicles and endometrial thickness between two groups

	Group				
	hMG (N = 112)		*CC (N = 112)*		
	Mean	*SD*	*Mean*	*SD*	*p-value*
No. of follicles	10.2	3.6	10.4	3.4	0.831
No. of DF	2.2	0.5	1.9	0.4	<0.001*
Endometrial thickness (mm)	10.148	1.365	7.812	0.158	<0.001*

**p*-value was calculated using Independent *t*-test

Table 3: Pregnancy rate between two groups hMG and CC

		Group				p-value**
		hMG (n = 112)		CC (n = 112)		
		Count	%	Count	%	
Pregnant	Yes	35	31.2%	19	16.9%	0.04*
	No	77	68.8%	93	83.1%	

$\chi^2 = 4.236$; df = 1; p = 0.04*; **p-value was calculated using Chi-square test

The total number of follicles was less in the hMG group compared to the CC group (10.2 vs 10.4) but the number of the dominant follicles (2.2 vs 1.9) and endometrial thickness were increased in the hMG cycle than CC group (10.1 vs 7.6 mm) at HCG trigger. This was statistically significant (Table 2).

In our study, the clinical pregnancy rates were significantly more in the hMG group (35/112; 31.2%) than in the CC group (19/112; 16.9%) ($p = 0.04$). Live birth rate (LBR) was also significantly higher in the hMG group (33/112; 29.4%) than in the CC group (16/112; 14.2%) ($p = 0.04$) (Table 3). Two patients in the hMG group and three patients in the CC group did not participate in the 3rd cycle of IUI. Pregnancy rate per total IUI cycles is (35/334; 10.5%) in hMG group and 19/333; 5.7%) ($p = 0.05$). Around 61.5% of women in the hMG group conceived in the third cycle of IUI compared to 40% women in the CC group. Multiple pregnancies were not noted in both groups. There were no adverse side-effects in both of the groups. Around 16.3% of patients in hMG group and 14% in the CC group had difficulty in instillation in the first IUI cycle.

None of the babies had congenital anomalies in both groups. Neonatal morbidity was similar in both groups. Three babies were admitted to NICU for mild respiratory distress syndrome, none of the babies had intubation. Our study did not record any perinatal morbidity or mortality in both groups.

Discussion

In our RCT study, we found that ovarian stimulation with low-dose hMG and IUI had a better pregnancy rate and live birth rate than stimulation with CC and IUI, without any incidence of multiple live birth rate or OHSS. In a study done by Azargoon et al.,[6] Sequential Ovulation induction using CC with gonadotropins resulted in the development of fewer medium- to large-sized follicles when compared to those using CC alone. In CC-treated cycles in PCOS women, although the ovulation rate is 80–90%, the conception rate is only 20–28% with a high abortion rate.[7] In our daily clinical practice, we have a lot of patients with subfertility/unexplained infertility who would have had OI failure/Resistant with CC. So in our practice, the type of ovarian stimulation is selected individually depending on the cycle, not on the patient level. Low-dose Gonadotropins (hMG) can be an alternative in women who are CC Resistant/failure with the advantage of less cost, less incidence of multiple birth and OHSS.

In our study, the follicles which started developing on D8 or D9 were more in the CC group than in the hMG group (10.4 vs 10.2), which was similar to the study by Azargoon et al., which may be due to the fact that CC secretes more gonadotropins leading to the growth of many follicles. This can be explained by the fact that during the follicular phase, gonadotropins act by recruiting more follicles for development.[8] On the contrary, Clomiphene citrate is known to act by depleting the central estrogen receptors thereby decreasing the negative feedback mechanism of estrogen on the hypothalamus and pituitary receptors resulting in an increase in gonadotropin secretion leading to the development of more follicles.[9] In a study conducted by Ecochard et al., to compare the pregnancy rates after Clomiphene citrate or gonadotropins with IUI it was observed that there was not much difference in the number of follicles developed in each group.[10]

Although the total number of follicles were more in CC, the mean number of dominant follicle was more in the hMG group than the CC group (2.2 vs 1.9), on the day of hCG administration. This may be due to the fact that er used low-dose stimulation which resulted in one or two dominant follicles. This is, in contrast, to a study done by Peeraer et al.,[11] which showed more dominant follicles in the CC group than in the hMG group (1.5 vs 1.2), this is due to usage of very low-dose gonadotropins (37.5 IU) in this study. During ovarian stimulation, the development of multiple follicles is dependent on starting dose of gonadotropins, this would have resulted in less dominant follicle development in the above study.

In a study by Nuojua-Huttunen et al.,[12] the hMG group had less dominant follicles than the CC group (1.5 vs 1.9). The low ovarian response in these patients is attributed to the advanced age of patients included in this study. In one study done by Ragni et al., patients had more dominant follicles in the hMG group compared to the CC group (hMG 4.1 ± 2.6 vs CC 2.5 ± 1.4), is because of the high dose of gonadotropins (300–400 IU/day) used in this study in comparison to other studies where low-dose gonadotropins were used.

The endometrial thickness at the time of HCG trigger was significantly higher in the hMG group than in the CC group ((10.1 mm vs 7.8 mm: $p = 0.0001$) which is similar to the study conducted by Rashidi et al.[13] However, in the studies performed by Al-Fozan et al.,[14] Jee et al.,[15] and Davar et al.[16] they did not find any significant relationship between these two groups. The thin endometrium may be due to anti estrogenic effects of CC, especially in CC-treated women, or due to inherent defective endometrium due to other causes. The success rate of IUI decreases when the endometrial thickness is less than 6 mm at HCG trigger[17] and none of the patients conceived in our study had ET <6 mm. Gerli et al.[18] in their randomized control study comparing endometrial thickness and pregnancy rate between CC with and without estrogen supplementation, found that CC with estrogen supplementation can countermand the detrimental effects of CC on the endometrial lining and that contribute to higher pregnancy rates. This was similar to a study done by Peeraer et al.[11] stated that the addition of estrogen supplementation can balance the deleterious effects of CC, but warranted future studies to evaluate the effects of estrogen supplementation in CC-treated Cycles.

The antiestrogenic effects of CC on the endometrium are usually seen with a higher dosage of the drug or when CC is given for a longer period and may be offset by high levels of estradiol seen with CC treatment. To counteract this negative impact of CC, ovulation induction with low-dose gonadotropins is a good option

that is as effective as high dose gonadotropins with lesser cost and fewer side effects.

In our study, most patients undergoing IUI demonstrated fertile type cervical mucus on the day of IUI (CC 55.7% vs hMG 81.1%), which was similar to a study conducted by Buyalos et al., who found that subjects receiving CC had lower cervical mucus scoring than patients receiving hMG for ovulation induction.[19–21] The existence of cervical mucus at the time of the IUI procedure does not increase the chances of conception but however, it is likely that cervical mucus itself facilitates fertilization during procreative intercourse.

In our study, it was observed that the hMG group has a higher pregnancy rate (23.2%) than the CC group (8.9%). This observation was in concordance with a study by Peeraer et al., in which pregnancy rates were higher in the hMG group than CC (14.4% vs 9%),[11] and in another study conducted by Manganiello et al. (hMG group 14.8% vs CC group 7.3%) 22, Karande et al. (hMG group 13% vs CC group 7%) 23, and Nuojua-Huttunen et al., (hMG group 18% vs CC group 5.3%).[12] This may be due to more number of dominant follicles in the hMG group than in the CC group. In another study conducted by Rashidi et al., it was found that pregnancy rate in Clomiphene citrate plus hMG followed by IUI had higher pregnancy rates (12.2%) than CC plus IUI alone (6.52%), which showed the addition of gonadotropins had higher chances of pregnancy rate than CC alone (Table 4). In a study conducted by Ecochard et al., the pregnancy results are contradictory to our study as well as to other literature with the CC group having a higher pregnancy rate than the hMG group (14% vs 7.14%). None of the patients in our both groups had multiple pregnancies, in contrast, to study done by Karande et al., the incidence of multiple pregnancies was high in the hMG group than CC group (30% vs 0%), which might be due to high dose of gonadotropins used in this study.

Table 4: Comparison of present study with literature on pregnancy rate and outcomes

Study (year)	*Total no. of patients*	*Age*	*Dose of hMG used*	*Dose of CC used*	*Pregnancy*	*Multiple pregnancy*
Karande et al. (1995)	NA	34	hMG dose NA	CC dose NA	hMG- 13% CC- 7%	hMG- 30% CC- 0%
Mangan-Iello et al. (1997)	83	33	hMG 150 IU day 3	CC 150 mg/day day 3–7	hMG-15% CC -7%	NA
Nuojua-Huttunen et al. (1999)	811	40	hMG 150 IU	CC 50–100 mg day 3–7	hMG- 18% CC- 5.7%	Overall 13.7%
Ecochard et al. (2000)	58	30	hMG 150 IU day 4,6,8,9	CC 50–100 mg day 3–7	hMG- 7% CC- 14%	Overall 10%
Ragni et al. (2012)[5]	249	38	High-dose FSH (300–400 IU/day)	100 mg day 2–7	rFSH- 6% CC-5%	NA
Peeraer et al. (2014)	306	32	hMG 37–75 IU/day 2–3	50 mg/day day 3–7	hMG- 12% CC- 7%	hMG- 8% CC- 5%
Present study (2018)	224	29 ± 3.8	hMG 75 1U day 2–6	CC 100 mg day 2–6	hMG- 23.2% CC- 8.9%	Nil

The abortion rate was more in the CC group than in the hMG group (15.7% vs 5.8%), respectively which was similar to the results of Al-Fozan and Davar et al., who found a higher incidence of abortion rate in the CC group.[14,16] Most of these abortions occurred in the early trimester which can be attributed to poor endometrial receptivity secondary to thin endometrium or due to some inherent genetic factor. Few studies have reported a high incidence of chromosomal aberrations,[22] luteinizing unruptured follicles,[23] or, subclinical pregnancy loss[24] in CC-treated cycles.

In the present study, a mean of 4.9 ± 1.6 additional doses of Injection hMG 75 IU/day intramuscular was needed to attain the dominant follicle size. These additional doses have been administered to allow for additional follicular growth and maturation. Further studies are needed to evaluate the role of additional doses needed for ovarian stimulation. However since monitoring with serum estradiol levels was not done in the present study, the values of serum estradiol levels combined with serial transvaginal ultrasound monitoring are the best predictor to assess the need for further doses for ovarian stimulation.

Our study has demonstrated that higher pregnancy rates can be achieved by IUI than natural cycles and low-dose human menopausal gonadotropins have a better reproductive outcome- number of follicles, size of the dominant follicles, and pregnancy rate as compared to Clomiphene citrate. Based on the results of our study that is in concordance with other several studies, ovulation induction with low-dose hMG plus IUI has a better outcome than CC alone plus IUI and can be recommended in patients with unexplained infertility.[25–27]

Conclusion

Our study showed that low-dose gonadotropins are a good alternative to clomiphene citrate in ovarian stimulation for IUI without any adverse effect on the endometrium and with better pregnancy rate and without any risk of multiple pregnancies and OHSS.

Clinical Significance

Low-dose gonadotrophins can be considered for ovarian stimulation in IUI with a better pregnancy rate without any side effects in low-resource settings.

Orcid

Chitra Thyagaraju https://orcid.org/0000-0002-3224-9180

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