

Comparison of pregnancy outcome between clomiphene citrate and sequential clomiphene citrate+human menopausal gonadotropin in intrauterine insemination

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ABSTRACT

Background: Intrauterine insemination (IUI) has been widely used as a common treatment for infertile couples. This study compares the sequential clomiphene citrate (CC) treatment with CC and human menopausal gonadotropin (hMG) treatment in women undergoing IUI. Therefore, this study was designed to determine the effects of addition of gonadotropin (CC+hMG) would improve the pregnancy rate in women undergoing IUI. And also compare the sequential CC+hMG treatment with CC treatment in women undergoing IUI.

Methods: A cross-sectional study design was conducted at D. Y. Patil Fertility Centre, D.Y Patil Hospital, Navi Mumbai from September 2018 to August 2019. Source populations were all patients who live in Mumbai, Maharashtra, India. A total of 67 patients were enrolled in this study. (It consisted of 67 sub fertile couples undergoing ovarian stimulation for IUI cycles).

Results: There was no significant difference between the two studied groups regarding endometrial thickness (8.3 ± 2.1 versus 9.7 ± 2.8 , respectively), number of mature follicles on the day of hCG injection (3.3 ± 1.2 versus 3.5 ± 1.1 , respectively) and, but there was significant difference between the CC+hMG group and CC group regarding the total dose of gonadotropins used in ovulation induction (305 ± 23.8 versus 655 ± 192 ; total IU, respectively) $p < 0.05$.

Conclusions: Women undergoing IUI, ovarian stimulation CC combined with hMG, significantly improved the pregnancy and live birth rates as compared to that of CC group. In women undergoing ovarian stimulation and IUI, there are no significant differences in pregnancy and live birth rates among the various stimulation protocols.

Keywords: Clomiphene citrate, Human menopausal gonadotropin, Intrauterine insemination

INTRODUCTION

Intrauterine Insemination (IUI) has been widely used as a common treatment for infertile couples. The reported clinical pregnancy rate varies considerably, ranging from 5 to 20%.¹⁻⁴ IUI technique is widely used to treat infertile couples with mild male factor infertility, anovulation, endometriosis, unexplained infertility, and other infertility causes, the limited IUI success rate can be affected by several factors with little consensus.^{5-8,9} The

potential beneficial effect of human menopausal gonadotropin (hMG) IUI cycles are associated with an increased rate of pregnancy clinically. Among them, the female's age, the male's sperm quality, the IUI attempt rank, the infertility type, and the used gonadotropin for controlled ovarian stimulation (COS) are considered the most predictive factors of IUI clinical outcomes.¹⁰⁻¹⁶ Despite its widespread use, the role and type of COS combined with IUI is controversial. Clomiphene citrate, an anti-estrogen, is mostly used as first choice for COS in

the context of IUI since clomiphene can be administered orally and is cheaper than gonadotrophin injections.¹⁷⁻¹⁹ IUI is considered a first-line procedure among assisted reproductive techniques due to its simplicity, ease of management, relatively low incidence of complications and low cost. Nevertheless, when IUI is used, should ovarian stimulation be used at the same time. Some investigators have advocated using the natural cycle.^{20,21} The IUI method is less expensive and less complicated compared with the other assisted reproductive technology, the in vitro fertilization (IVF) protocol. Since six clinical factors the female-age, endometrial thickness (ET), luteinizing hormone (LH), number and size (mm) of ovary follicles, and male factor, i.e., total motile fraction (million) controlled the success rate of an IUI protocol, it was intuitive to study the role of individual factors in the success. The sequential Clomiphene Citrate (CC) with hMG treatment improves response to CC, decreases hMG dose and finally reduces the treatment cost. During the sequential CC with hMG treatment, CC (100 mg/day) is started for 5 days, followed by hMG 75 IU for 4 days.^{22,23} Sequential CC With hMG treatment appears to be a cost-effective method in ovulation induction, requires less monitoring and leads to satisfactory pregnancy results.²⁴ Therefore, this study was designed to determine the effects of addition of gonadotropin (CC+hMG) would improve the pregnancy rate in women undergoing IUI. And also compare the sequential CC+hMG treatment with CC treatment in women undergoing IUI.

METHODS

A cross-sectional study design was conducted at D. Y. Patil Fertility Centre, D. Y. Patil Hospital, Navi Mumbai from September 2018 to August 2019. Source populations were all patients who live in Mumbai. A total of 67 patients were enrolled in this study. (It consisted of 67 sub fertile couples undergoing ovarian stimulation for IUI cycles.) All the recruited patients were explained about the study and written consent was taken from every patient dually signed by her.

Ethical approval and clearance were taken from institutional review of College of D. Y. Patil Fertility Centre and permission letter for data and sample collection has also been received from the department of obstetrics and gynecology. The cases were divided into two groups. The first group is the gonadotropin group (CC+hMG) (32 patients) and the second control (CC) (35 patients).

Inclusion criteria

- Women of good physical and mental health, 18-37 years old, with regular menstrual cycles, of 25-35 days, primary or secondary infertility for more than one-year, body mass index (BMI) less than 30 kg/m², no patient had received any hormone therapy for at least 60 days preceding the study. Normal prolactin

levels, normal thyroid function, normal uterine cavity and bilateral tubal patency assessed by hysterosalpingography and/or laparoscopy.

Exclusion criteria

- Women with hormone values outside the reference range by day 3-4 of their menstrual period (FSH levels >10 mIU/l) and with polycystic ovarian syndrome were excluded from this study.

Moreover, only patients with partners with normal seminal parameters according to World Health Organization (WHO) criteria and whose total motile sperm count (TMSC) after sperm washing by swim-up was equal to or greater than 10 million/ml were accepted.

Hormonal treatment

Gonadotropin group (CC+hMG)

A total 32 patients were subjected to a controlled ovarian stimulation (COS) protocol in which the use of CC with hMG IUI is associated with an increased rate of pregnancy (RP) clinically. On the 2 day of their menstrual period, the patients were examined by ultrasound to ensure ovarian quiescence. A fixed dose of 100 mg/per day of CC was then given to induce follicle recruitment for 5 days. At day 7 of COS, an ultrasound was performed to start injection hMG 75 IU and adjust the dose accordingly thereafter, if necessary. Subsequently, follicular development was monitored by ultrasound every 1 or 2 days. When adequate ovarian response was observed (follicles=18 mm), 10000 IU/i.m. hCG was administered, IUI was performed 36 hours later. IUI was cancelled if more than four follicles (16-20 mm) were present, in order to reduce the risk of multiple pregnancy. No severe ovarian hyperstimulation syndrome occurred. One cycle was converted to an IVF cycle due to excessive ovarian response (eight follicles ≥18 mm).

Control group (CC)

Total 35 patients were subjected, the hMG was not used and CC was administered from day 2 of menstrual cycle for 5 days. The dose was 100 mg once a day. Ultrasound was done every 1 or 2 days. When leading follicle reached ≥18 mm, hCG was given and IUI was performed 36 hrs later. As in the other group, IUI was cancelled if more than four follicles (16-20 mm) were present. One cycle was cancelled in order to avoid a multiple pregnancy since ultrasound had revealed seven follicles ≥18 mm.

Semen preparation

Semen analysis was collected after 2-3 days of abstinence. Concentration (number of sperm present per ml of the ejaculate): greater than 15 million/ml motility (percentage of sperm moving): 50% or more. It should

take 10 to 20 minutes before semen liquefies. While semen is initially thick, its ability to liquefy, or turn to a watery consistency, helps sperm to move. If semen does not liquefy in 10 to 20 minutes, fertility could be affected. The semen was incubated for 30 minutes at 37°C, and after liquefaction, the volume and viscosity were determined. The motility and initial concentration of the spermatozoa were calculated using a makler chamber. Swim-up technique was used to prepare the semen. Sperm preparation medium (60 ML; Medicult R) was used to wash the semen. The samples were incubated at 37°C in 5% CO₂ for 45 minutes on an inclined rack using the same culture medium. Finally, the concentration of motile spermatozoa in the preparation was determined using the makler chamber.

IUI procedure

The procedure itself involves transferring specially washed semen directly into the uterus via a thin catheter. Only single IUI was done at 36 h after Human chorionic gonadotropin (hCG) injection and the day of the IUI was recorded. β -hCG levels were measured on cycle day 22. If ovarian hyper stimulation syndrome (OHSS) developed, it was recorded and classified as mild, moderate or severe based on the combination of ovarian enlargement and the acute shift of the fluid to the extra vascular space. A diagnosis of clinical pregnancy was confirmed by serum β -hCG concentration and visualization of the gestational sac on subsequent ultrasound examination. The primary outcome measures were the pregnancy rate, number of mature follicles and total dose of gonadotropins used in ovulation induction,

while the secondary outcome measures were the number of cases that developed ovarian cyst and number of cases that developed OHSS after ovulation induction.

Statistical analysis

Data were expressed as the mean \pm SD. Continuous variables were compared with Student's t-test. The Chi-square test and Fisher test were used to compare clinical outcome between the two groups. The analysis was carried out using the statistical package for social sciences SPSS-20 (IBM). The p=0.05 was considered significant.

RESULTS

Total 67 patients were included in the study and were equally divided into two groups: one with gonadotropins (CC+hMG) and the other is the control (CC) group. There are no statistically significant differences between the two groups regarding age and BMI. There were also no statistically significant differences between the two groups in terms of duration of infertility (Table 1). In Table 1, were noted between the CC+hMG treated group and the control group. There was no significant difference between the two studied groups regarding endometrial thickness (8.3 \pm 2.1 versus 9.7 \pm 2.8, respectively), number of mature follicles on the day of hCG injection (3.3 \pm 1.2 versus 3.5 \pm 1.1, respectively) and, but there was significant difference between the CC+hMG group and CC group regarding the total dose of gonadotropins used in ovulation induction (305 \pm 23.8 versus 655 \pm 192; total IU, respectively) p<0.05; Table 2).

Table 1: Ovulation for intrauterine insemination gonadotropins.

| | CC+hMG Group (n=32) | CC Group (n=35) | p-value (X ²) |
|--------------------------------|---------------------|-----------------|---------------------------|
| Age (years) | 33.7 \pm 2.5 | 31.02 \pm 3.1 | 0.83 (NS) |
| BMI (kg/m ²) | 23.7 \pm 2.7 | 22.3 \pm 2.6 | 0.87 (NS) |
| Main causes of infertility (n) | | | |
| Unknown | 23 (71.8%) | 20 (57.1%) | 0.20 (NS) |
| Anovulation parity | 9 (28.1%) | 15 (42.9%) | |
| Parity (n) | | | |
| Primary infertility | 28 (87.5%) | 32 (91.4%) | 0.59 (NS) |
| Secondary infertility | 4 (12.5%) | 3 (8.6%) | |

CC: Clomiphene citrate, hMG: Human menopausal gonadotropins, BMI: Body mass index, *Values are (m \pm sd); NS: Not significant; X²: Chi square.

As expected, cycle length was extended to almost 1 day more (7.5 \pm 1.7 versus 6.5 \pm 1.6; days) in the CC+hMG treated group than in the control group, although this difference was not statistically significant. In CC+hMG group and in CC control group were the cases with of singletons and multiple [12 (85.7%) versus 8 (100%) and 1 (7.1%) versus 0 (0%), respectively], but the pregnancy rate was significantly high in the CC+hMG group compared to the CC group [14 (43.7%) versus 9 (25.7%), respectively] (p<0.05; Table 3).

There have been no miscarriages in both groups. Pregnancy rates were significantly increased in the group of patients receiving the gonadotropin (hMG) (43.7%) compared to the control group (25.7%). And number of cases with of singletons and multiple [12 (85.7%) versus 8 (100%) and 1 (7.1%) versus 0 (0%), respectively, to date, except for one ectopic pregnancy 7.1% in the CC+hMG and 11.1% in CC group. There have been no miscarriages and no live births occurred in the both groups (Table 3).

Table 2: Timing ovulation for intrauterine insemination with a gonadotropin.

| | CC+hMG Group (n=32) | CC Group (n=35) | p-value (X ²) |
|---|---------------------|-----------------|---------------------------|
| Day of IUI | 14.7±0.5 | 13.5±0.7 | 0.86 (NS) |
| Gonadotropins (total U) | 305±23.8 | 655±192 | <0.05 (S) |
| Stimulation (days) | 7.5±1.7 | 6.5±1.6 | 0.52 (NS) |
| Follicles (≥18mm) on the day of hCG injection | 3.3±1.2 | 3.5±1.1 | 0.84 (NS) |
| Swim-up sperm (×10 ⁶ /ml) | 22.9±9.0 | 19.7±18.2 | 0.75 (NS) |
| Endometrial thickness (mm) | 8.3 ± 2.1 | 9.7 ± 2.8 | 0.88 (NS) |

CC: Clomiphene citrate, hMG: Human menopausal gonadotropins, IUI: Intrauterine insemination, hCG: Human chorionic gonadotropin, *Values are (mean±sd), NS: Not significant; X²: Chi square.

Table 3: Timing ovulation for intrauterine insemination with a gonadotropin.

| | CC+hMG Group (n=32) | CC Group (n=35) | p-value (X ²) |
|----------------------------|---------------------|-----------------|---------------------------|
| Pregnancies total | 43.7% (14/32) | 25.7% (9/35) | <0.05 (S) |
| Miscarriages; % (n) | 0% (0) | 0% (0) | - |
| Multiple; % (n) | 7.1% (1/14) | 0% (0/9) | - |
| Ectopic pregnancies; % (n) | 7.1% (1/14) | 11.1% (1/9) | 0.741 |
| Live births; % (n) | 0% (0/14) | 0% (0/8) | - |
| Singletons; % (n) | 85.7% (12/14) | 100% (8/8) | |

CC: Clomiphene citrate, hMG: Human menopausal gonadotropins, OHSS: Ovarian hyperstimulation syndrome, *Values are (mean±sd), NS: Not significant; X²: Chi square.

DISCUSSION

Although CC is a successful ovulation-inducing agent, the number of pregnancies achieved after ovulation induction with CC is much lower than expected.^{22,25,26} The use of gonadotropins in ovulation induction is associated with increased risks of OHSS and multiple pregnancies and, therefore, intense monitoring of ovarian response is required.²⁷⁻²⁹ The sequential CC+hMG treatment appears to be cost effective in ovulation induction leading to satisfactory pregnancy results.^{22,24} In present study there was no significant difference between the two studied groups regarding endometrial thickness (8.3±2.1 versus 9.7±2.8, respectively), number of mature follicles on the day of hCG injection (3.3±1.2 versus 3.5±1.1, respectively) and, but there was significant difference between the CC+hMG group and CC group regarding the total dose of gonadotropins used in ovulation induction (305±23.8 versus 655±192; total IU, respectively) p<0.05.

But the pregnancy rate was significantly high in the CC+hMG group compared to the CC group [14 (43.7%) versus 9 (25.7%), respectively] (p<0.05). There are no statistically significant differences between the two groups regarding age and body mass index (BMI). There were also no statistically significant differences between the two groups in terms of duration of infertility. Higher pregnancy rates have been reported following IUI compared to expectant management (51 versus 33%, respectively).³⁰ Another 412 infertile women with unexplained infertility were randomized to receive either 100 mg of CC daily or 5 mg of letrozole daily for 5 days,

starting on day 3 of menses by Badawy et al. For ovulation induction in CC-resistant women with PCOS.

They found no statistically significant difference in pre-treatment endometrial thickness or endometrial thickness at the time of hCG administration between the two groups.³¹ Study is consistent with earlier reports with regard to the lack of benefit of CC.³² It has now been recognized that aggressive ovarian stimulation can increase the pregnancy rate, but at the expense of increasing the likelihood of higher-order pregnancy, and that an increasing number of follicles does not increase the pregnancy rate but only leads to a higher risk of multiple pregnancies.

CONCLUSION

Women undergoing IUI, ovarian stimulation CC combined with hMG, significantly improved the pregnancy and live birth rates as compared to that of CC group. In women undergoing ovarian stimulation and IUI, there are no significant differences in pregnancy and live birth rates among the various stimulation protocols. This study is in concordance with this work and demonstrates that there is no significant difference in clinical outcomes between different in IUI cycles, BMI and infertility types, including the age, and the Swim-up sperm, Primary infertility and Secondary infertility. The CC+hMG to COS-IUI cycles significantly increased pregnancy rates in study patients. Since this increase seems to be related to the number of follicles recruited, clinicians should balance this benefit against the risk of multiple gestation in IUI.

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