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Comparison of Different Clomiphene Citrate Regimens and their Outcome in Intrauterine Insemination Programme

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Summary

Clomiphene citrate has been utilized for ovarian stimulation in intrauterine insemination programmes quite successfully. The optimal time for initiation and amount of drug necessary for optimal development have not been identified. In this study 70 patients recruited for IUI were stimulated with CC in dose ranging from 50 to 250mg/day for 5 days starting from day 2 of the cycle. Maximum pregnancy rate occurred with 150mg group when started on day 2. therefore, it is concluded that if clomiphene citrate alone is utilized for multiple follicle development, a higher dose should be started early in the cycle to get a better outcome.

Introduction

Role of controlled ovarian hyperstimulation in intrauterine insemination programme has been proved in many controlled studies Kemmann et al (1987), Melis et al (1987) and Corson et al (1989). Almost all IUI programmes incorporate controlled ovarian hyperstimulation using agents like clomiphene citrate (CC), human menopausal gonadotropin (hmu) or a combination of CC+HMG. Considering the increased incidence of multiple gestation after HMG-IUI versus CC-IUI, higher risk of ovarian hyperstimulation after hMG Vs CC and higher cost of gonadotropin cycle, it is justified to use clomiphene citrate stimulation as a first step procedure in selected cases of human subfertility.

Traditionally, clomiphene citrate is used in step up fashion from day 5 of cycle for the purpose of induction of ovulation but for controlled ovarian hyperstimulation, no such regimen is followed. The dose of clomiphene citrate used as well as the time of initiation is very inconsistent and arbitrary (Corson et al, 1989). Anderson et al (1995). Published data regarding the impact of dose and time of initiation of clomiphene citrate on the number of follicles, ovulation rate, hyperstimulation and conception rate is limited. Moreover, the outcome of these studies are contradictory to each other [Corson et al (1989), Anderson et al (1995) and Ombelet et al (1997)].

This retrospective analysis was aimed to evaluate the influence of dose of clomiphene citrate and time of initiation on the outcome in the form of number of follicles, ovulation rate, and conception rate and to find out the optimum dose of clomiphene citrate and time of initiation in IUI programmes.

Materials and Methods

During a period of 12 months from March 1996 to February 1997, IUI homologous combined with clomiphene citrate superovulation was performed in 70 couples over 152 cycles at infertility division, department of Obst. & Gynae, UCMS & GTB Hospital, Delhi, India. The data was compiled and analysed retrospectively.

All patients had undergone a basic infertility work up including ESR, BBT charting, ultrasonography for follicular response, mid-cycle post coital test, hysterosalpingography and/or laparoscopy with chromotubation, to identify the etiological factor. In suspected cases of genital tuberculosis (high ESR, history of exposure) a premenstrual endometrial biopsy was performed. Male partners were subjected to at least two semen analyses 15 days apart. Couples with genital tuberculosis, female age more than 35 years, B/L tubal occlusion and subnormal semen parameters (WHO 1992) were excluded from the study.

Written informed consent was taken from all patients included in the study before starting the treatment protocol which was approved by the ethical committee of the College.

All patients were given clomiphene citrate 50-250mg/day starting from day 2 to 5 of the cycle for 5 days according to the response of individual patient and ovulatory status.

Follicular monitoring

Follicular maturation and endometrial response was monitored on P-700 USG system by 3.5 Mhz transabdominal sector/6.5 Mhz transvaginal probe from cycle day 9. When the follicular diameter of the largest follicle reached atleast 18mm, the ovulatory trigger with injection hCG 10,000 IU 1/M was given in all cases. A single insemination was planned 36 hours after ovulatory trigger or at ovulation whichever was earlier. All patients were given luteal support with dyhydrogestrone 20mg. A urine pregnancy test by ELISA was done once the patient missed the period for atleast 5 days. Further confirmation of pregnancy was done with USG.

Semen preparation

Semen preparation was done using swim up procedure. After liquifaction, semen samples were analysed following WHO guidelines. One ml aliquets of liquefied semen were diluted with 3ml of Hams-F-10 (Sigma laboratories) and centrifuged at 1000 rpm for 10 min. Pellet was resuspended and recentrifuged for 5 minutes. Supernatant was discarded and 0.3ml of Hams F10 was gently layered over each pellet and incubated at 37°C for 45 minutes. Supernatant containing most motile fraction was gently aspirated and finally analysed before insemination.

Statistical Analysis

Measures of central tendency were mean and measures of dispersion were SD. Statistical analysis of results was performed using either chi squares test or 2 tailed Fisher exact test. A $p<0.05$ was considered to be statistically significant.

Results

A total of 152 cycles were initiated. 21 cycles were cancelled either due to non-initiation of follicle (11 cycles) or due to ovarian hyperstimulation (10 cycles) leaving 131 cycles for insemination. Ovarian hyperstimulation was mild in 9 cases and moderate in one case.

The age of male partner ranged from 25-40 years with a mean of 29.60 ± 3.61 years while the age of female partner ranged from 20-35 years with a mean of 25.97 ± 3.32 years out of a total of 70 patients, 14 (20%) patients were diagnosed as cervical group, 48 (68.6%) belonged to unexplained infertility and 8 (11.4%) patients having anovulatory infertility.

Outcome in relation to different dosage schedule is shown in table-I. Mean number of follicles were statistically similar in all four groups (p=n). On comparing the total number of cycles initiated and cycles cancelled in different dose schedule, maximum percentage of cycle cancellation was observed in 50mg group.

Table 1 Outcome in relation to the dose of clomiphene citrate

Dose of CC in mg	Total No. of cycles	Cycles cancelled		Ovulatory cycles 18mm	mean no. of follicle	Conception
		OHSS	Nomination			
50	16	2 (12.5%)	2 (12.5%)	8 (50%)	1.25 ± 0.7	0
100	60	5 (8.3%)	2 (3.3%)	42 (70%)	1.66 ± 0.7	3 (5.6%)
150	64	2 (3.1%)	7 (10.9%)	48 (70%)	1.2 ± 1	7 (12.7%)
> 150	12	1 (8.3%)	0 (0)	8 (75%)	1.8 ± 1.2	1 (8.3%)

The ovulation in different dose schedules ranged between 50% (50mg group) to 75% (> 150mg group). On calculating the conception rate, after excluding the cancelled cycles, it was observed that maximum number of conception, i.e. 7 out of 11 occurred in 150mg group. ($p<0.001$ by chi squared test, although the expected frequency in > 20% cells was less than 5). An important observation was that conception rate increased with the increasing number of follicles. Highest conception rate (15.3%) was seen in the group where the number of follicles were ≥ 3 as compared to the lowest conception rate (7.2%) when there was only one follicle. But statistical significance could not be seen ($p > 0.930$ by Chi square test).

Another important observation was development of significantly higher number of follicles ($p<0.001$ by Turkey test) when the drug was started on second day of the cycle as compared to other days ($p<0.017$ by Turkey test) Table II. Irrespective of the day on which hCG was given, highest percentage of ovulation (74.6%) occurred between 24-48 hours. Only in 6.5% of cases, the ovulation took place before 24 hours. Incidence of LUF was as high as 50% when hCG was given at or before 10th menstrual day. Ten out of 11 conceptions were seen in those cycles when hCG was given on 11-14 day of cycle. Moreover, 10 out of 11 conceptions occurred when the hCG was administered at a follicular diameter of less than 20mm.

Table II: Outcome in relation to day on which CC started

Day on which CC started	Average no. of follicle	Mean ET	Conception
2 (n=3)	2.66 + 0.577	7.6 ± 2.08	1
3 (n=102)	1.34 + 0.81	7.3 ± 1.2	9
4 (n=27)	1.1 + 0.57	6.8 ± 1.2	1
5 (n=20)	1.2 + 0.716	7.3 + 1.0	0

Discussion

The present study focuses on an important aspect of controlled ovarian hyperstimulation with clomiphene citrate in IUI programmes. The results of this retrospective study suggests that though the number of follicles in different dosage schedule remains similar, but conception rates are significantly improved by using 150mg clomiphene. This finding is supported by the outcome of a study by Quigley et al (1983) which showed that inspite of similar follicular growth in 50 and 150mg group the follicular gonadotrophin level and luteal phase E_2 are much higher in 150mg group. The fact that higher FSH and E_2 production is observed in 150mg group also contradicts the hypothesis that higher dose of clomiphene exerts high antiestrogenic effect which in turn leads to defective implantation. The present study also showed that number of follicles and pregnancy rates were significantly more when the CC was started on day 2. This could be explained by the well known fact that dominant follicle selection starts early in the cycle and once the dominant follicle is selected secondary follicles began the process of atresia as has been showed in primate models Goodman et al (1977), Dizerega nd Hodgen (1981).

Contradicting this, Mars et al (1984) concluded that maximum number of oocytes were recovered when CC was started on day 5. The reasons as given by Mars for better outcome for day 5 was that there is no endogenous surge if stimulation is begun on day 5. Moreover the continued gonadotrophin stimulation was not present in a high enough concentration after CC was discontinued to allow follicle growth to continue and result in multiple dominant follicle development when CC was started earlier than day 5.

Later Wu and Winkel (1989) demonstrated that outcome in terms of ovulation rates, luteal phase defects or pregnancies was comparable when CC was started on day 2,3,4 and 5.

Another interesting finding was that irrespective of the day and diameter of follicle at which hCG was given most of the patients (80%) ovulated in 24-48 hours suggesting a single insemination around 36 hours should be optimal to give best outcome. Incidence of OHSS in the present study was 7.2%. However all cases were mild except one which was moderate.

Polishuk and Schenker (1969) reported a 2.5% incidence of hyperstimulation with CC administration alone. The use of hMG for COH is associated with a higher incidence of OHSS. Therefore, to conclude, at a time when one of the greatest hurdles for infertility treatment are limited resources it is often tempting to employ the simplest and least expensive therapy first.

COH with CC requires less monitoring and expense than the use of menotropins for IUI. A higher dose of CC should be started early in the cycle so as to increase the number of follicle recruited and to enhance the pregnancy rate.

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