A COMPARISON OF CLOMIPHENE CITRATE AND SEQUENTIAL CLOMIPHENE CITRATE PLUS HUMAN MENOPAUSAL GONADOTROPIN FOR USE IN CONJUNCTION WITH INTRAUTERINE INSEMINATION

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Abstract- There are currently many different protocols in use for controlled ovarian hyperstimulation (COH), but the optimal method has not yet been determined. To compare the outcome of COH using clomiphene citrate (CC) versus CC plus human menopausal gonadotropin (hMG) in conjunction with intrauterine insemination (IUI), we studied 117 infertile couples. IUI with CC was used in 92 cycles (group A) and IUI with CC plus hMG was used in 66 cycles (group B). Data analysis demonstrated no significant difference between the two groups with respect to patients' age, duration and type of infertility, prior COH and endometrial thickness and pattern. Group A had a little longer follicular phase length than group B. Pregnancy rate for group A and B were 6.52% and 12.12%, respectively (P= 0.22). Endometrial pattern and thickness had no impact on pregnancy rate. There were no multiple gestation and obvious hyperstimulation syndrome. For patients undergoing controlled ovarian hyperstimulation with IUI, CC plus hMG protocol yields higher pregnancy rate than one using CC, although this difference was not statistically significant because of limitation of number of cycles.

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Key words: Controlled ovarian hyperstimulation, clomiphene citrate, human menopausal gonadotropin, intrauterine insemination, pregnancy rate

INTRODUCTION

Many methods have been presented in management and treatment of infertility, including intrauterine insemination **(**IUI) with controlled ovarian hyperstimulation (COH). The precise mechanism of COH with IUI is unclear, and rather than acting via a single mechanism, its success likely represents a combination of actions, including correction of erratic LH pattern, augmentation of low mean LH surges, normalization of follicular growth, increasing the number of available oocytes ovulated per cycle with commensurate improvement in chance of ovum pick-up, fertilization, and implantation (1). The cycle fecundity rates for unstimulated cycles are extremely variable and mainly poor, ranging from 0% to 21% (2). The combination of IUI with COH has been shown to result in an increased pregnancy rate, ranging from 3% to 40% (3-6).

There are currently many different protocols in use for COH, but the optimal and the most cost-effective method has not yet been determined. This randomized study was performed to evaluate the efficacy of clomiphene citrate (CC) compared with CC plus human menopausal gonadotropin (hMG), for COH in conjunction with IUI. The goal of this study was to benefit patients by finding a more efficacious therapeutic protocol.

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MATERIALS AND METHODS

Patients

Two types of protocols were presented to the couples eligible for IUI, which were attending the Va1i-e-asr infertility treatment and research center of Tehran University of Medical Science from March 1999 to February 2001. A total of 131 patients with infertility of 2 to 8 years duration were included in the study. Etiologies of infertility included male factor, anovulation, unexplained infertility and mild endometriosis. Patients were randomized in 2 groups: patients in cycles stimulated with CC were named as group A and patients in cycles stimulated with sequential clomiphene plus hMG were named as group B.

All patients underwent a complete infertility evaluation that included a profound medical history, postcoital test (PCT), semen analysis, measurement of mid-luteal serum progesterone, prolactin and thyroid hormones, and tubal assessment (by laparoscopy or hysterosalpingography). In order to exclude ovarian follicles more than 1 cm in diameter a baseline transvaginal sonography was performed on cycle day 3 prior to initiating each treatment cycle in all patients.

Semen preparation

Semen was yielded with withdrawal or masturbation. Semen samples were brought to the laboratory and allowed to liquefy at room temperature. The semen sample was examined under a microscope to determine concentration and motility. A standard swim up was performed for 1 hour with a final specimen volume of 0.5 ml.

Clomiphene citrate group

In group A, ovarian stimulation was achieved by giving 100 mg CC (Iran Hormone, Iran) on cycle day 5 of either a spontaneous cycle or following progestin-induced withdrawal bleeding and continued daily for 3 days. Ovarian and endometrial response were monitored and repeated every other day using transvaginal ultrasonography (GERT 2800 7.5 MHS vaginal prob). When the lead follicle(s) attained a diameter of 20 mm, human chorionic gonadotropin (10000 IU) (Profasi, Serono laboratories) was administered at 9:00 PM. Insemination was performed 36 hours later at 9:00 AM.

Clomiphene citrate plus hMG group

For patient in group B, CC was administered for five consecutive days which was initiated on cycle day 3, followed by the administration of 150 IU of hMG (Humegon, Organon, Oss, the Netherlands) on cycle day 6. Repeated transvaginal ultrasonography determined further need to hMG which was administered 150 IU daily. When the lead follicle(s) attained a diameter of 18 mm, hCG (10000 IU) was administered at 9:00 PM to reduce the risk of multiple pregnancy and/or serious ovarian hyperstimulation. Ovulation was not induced and the IUI cycle was stopped if there were more than four follicles with a diameter of ≥ 15 mm at the time of induction and/or the plasma estradiol concentration of > 1500 pg/ml.

Intrauterine insemination and follow up

IUI (volume of 0.5 ml) was performed by using an intrauterine catheter (Wallace catheter SIMS Portex Ltd. UK) after 36 hours of administration of HCG.

The patient remained supine for 30 min thereafter. For all patient 50 mg/day progesterone, IM, was administered as the luteal phase support. Initial serum β HCG quantitation was performed 14-16 days after IUI. Positive pregnancy test was confirmed and followed by ultrasonography 2 and 4 weeks later.

Ethical consideration

This study was conducted in accordance with the guidelines described in the Declaration of Helsinki, and informed consent was obtained in all cases.

Statistical analysis

The data are presented as means ± SD. For the statistical analysis, proportions were compared via Chi square and Fisher's exact tests and *P* values were computed. Logistic regression procedures were used to assess trend in proportions. Two tailed *t* test was used for comparison of means. Statistical significance was considered as $P<0.05$.

RESULTS

During the 21-month study period, a total of 131 patients were enrolled in the study and assigned to receive CC or CC plus hMG. Fourteen couples dropped out from the study. Patients withdrew for a variety of reasons, including high expense of procedure (n=6), switching to IVF (n=3), moving away from the area (n=3), presence of ovarian cyst (n=1) and death of patient in car accident (n=1). The two groups did not differ significantly with respect to mean age ($P = 0.29$), duration of infertility ($P = 0.051$) and type of infertility ($P = 0.88$) (Table 1).

There were no significant difference in cycles' performance parameters for group A and group B with respect to pattern of endometrium ($P = 0.54$), mean endometrial thickness ($P = 0.37$) and previous COR ($P = 0.169$). There was a small difference in length of follicular phase between two groups ($P = 0.045$); group A had a little longer follicular phase length than group B (Table 2).

In group B, patients took 2 to 25 hMG ampoules (75 IU) with a mean of 9.8 ± 4.3 ampoules. In group B, 3 patients had more than four preovulatory follicles on the hCG administration day and the administration of hCG was held because of fear of threatened hyperstimulation. No cases of severe hyperstimulation syndrome developed in the study. There were 14 pregnancies documented by ultrasonography: 6 occurred in the group A and 8 occurred in group B (Table 3). This represents a pregnancy rate of 8.9% per cycle, with pregnancy rate of 6.52% in CC-treated cycles and 12.12% in CC plus hMG- treated cycles ($P = 0.22$).

The spontaneous miscarriage rate was 21.42% (3 of 14 pregnancies). Of these, 1 occurred in CC-treated cycles and 2 occurred in CC plus hMG-treated cycles. There was no multiple gestation in either group. The 6 pregnancies in group A included 5 term pregnancies and 1 spontaneous abortion. The 8 pregnancies in group B included 5 term pregnancies, 1 preterm pregnancy and 2 spontaneous abortions (Table 3).

Surprisingly in 12 months follow up, 5 spontaneous pregnancies occurred after the termination of IUI cycles, 2 after termination of CC-treated cycles and 3 after CC plus hMG-treated cycles. Logistic regression procedures were used to assess the effect of endometrial thickness and pattern on pregnancy rate. *P* values for effect of endometrial thickness on pregnancy rate were 0.97, 0.77 and 0.97 for group A, B and total cycles, respectively. *P* values for effect of endometrial pattern on pregnancy rate were 1.00, 0.30 and 0.10 for group A, B and total cycles, respectively.

Table 1. Comparison of characteristics of group A (clomiphene citrate) and group B (clomiphene citrate plus human menopausal gonadotropin)*

Parameter	Group A (n= 92)	Group B (n=66)	Probability
Age (year)	25.71 ± 4.03†	26.38 ± 3.85†	NS (0.29)
Duration of infertility (year)	3.98 ± 2.28†	4.82 ± 2.86†	NS (0.051)
Type of infertility			NS (0.88)
Primary	73 (79.4%)	53 (80.3%)	NS
Secondary	19 (20.6%)	13 (19.7%)	NS
Etiology of infertility			
Cervical factor	2 (2.17%)	1 (1.51%)	NS
Unexplained infertility	10 (10.88%)	18 (27.27%)	NS
Anovulation	38 (41.30%)	19 (28.79%)	NS
Mild endometriosis	4 (4.53%)	3 (4.50%)	NS
Male subfertility	19 (20.65%)	19 (28.79%)	NS
Multifactorial	19 (20.65%)	6 (9.10%)	NS

Abbreviation: NS, not significant.
* Data are given as number (percent) unless specified otherwise.
† means ±SD.

Table 2. Characteristics of cycles' performance parameters for group A and group B*

Parameter	Group A (n= 92)	Group B (n= 66)	Probability
Endometrial thickness	8.42±2.14†	8.78±1.92†	NS (0.37)
Endometrial pattern			
Trilaminar	70 (76.08%)	47 (71.21%)	NS (0.54)
Homogenous	22 (23.92%)	19 (28.79%)	NS
Previous COH	65 (70.70%)	53 (80.30%)	NS (0.169)
Follicular phase duration	14.25 ± 3.36†	13.52 ± 2.02†	S (0.0458)

Abbreviations: NS, not significant; S, significant; COH, controlled ovarian hyperstimulation.
* Data are given as number (percent) unless specified otherwise.
† means ±SD.

DISCUSSION

Controlled ovarian hyperstimulation (COR) with IUI has gained widespread acceptance as treatment for a variety of infertility-related diagnosis. Different hormonal treatment protocols have been used for COR, including CC or hMG alone or in combination. The reported cycle fecundity rates are controversial and vary greatly: those reported are 3% to 12% for CC (2, 5, 7), 7% to 30% for hMG (2, 4, 6, 8) and 2.5% to 22% for CC plus hMG (3, 7, 9).

In our study, CC or CC plus hMG was used for COR in IUI treatment. The pregnancy rate was 6.52% in CC group and 12.12% in CC plus hMG group. Our result, although not reaching statistical significance, depict a trend toward significance which suggests that CC plus hMG may be more efficacious than CC alone when used in combination with IUI. We detected less than a doubling in pregnancy rate in CC plus hMG group. Our pregnancy rate with CC (6.52%) was lower than previously reported by Ecochard *et al.* (14.44%) (10) but was higher than those reported by Manganiello *et al.* which was 4.1% (11). In the study by Manganiello *et al.* the dosage of CC used (150 mg/d for 5 days) was differed from that used in our protocols (100 mg/d for 5 days). Ecochard *et al.* used similar dosage to that used in our study, however, their success rate was more than a doubling pregnancy rate than our study; the reason of this difference is unclear. In contrast, our pregnancy rate per CC plus hMG cycle (12.12%) was higher than those reported by Ransom *et al.* (9.1%) (1) and was consistent with those reported by Noujua- Huttunen *et al.* (12.5%) (12).

Iatrogenic multiple gestation is one of the most serious risk factors associated with COR and IUI. In this study no case of multiple gestations was found. This may be due to the fact that cycles with excessive ovarian responsiveness were held and the hCG administration was not performed.

Table 3. Pregnancy rates and outcomes*

Parameter	Group A (n= 92)	Group B (n= 66)	Probability
Pregnancy/ cycle	6 (6.52%)	8 (12.12%)	NS (*P*= 0.22)
Term pregnancy/ cycle	5 (5.62%)	5 (7.57%)	NS (*P*= 0.30)
Abortion/ cycle	1 (1.09%)	2 (3.03%)	NS (*P*= 0.57)
Threatened hyperstimulation	0 (0%)	3 (4.54%)	NS (*P*= 0.71)
Multiple gestation/ cycle	0 (0%)	0 (0%)	NS
Preterm labor	0 (0%)	1 (1.50%)	NS

Abbreviation: NS, Not significant.
*Data are given as number (percent).

Follicular phase length has been demonstrated to have significant impact on cycle outcome. When the induction period extends 10 to 15 days, optimum results are obtained, whereas follicular phases shorter than 10 days are associated with higher rates of miscarriage (13). Surprisingly, in our study 5 women conceived spontaneously after the termination of IUI cycles in 12 month follow up. Collins *et al.* reported their experience with treatment-independent pregnancies among infertile couples (14). In their study, pregnancy occurred in 35% of untreated couples. When the patients were followed up longer, the percentage of treatment-independent pregnancies increased to 42% (14).

Dickey *et al.* reported that among their COR patients, the number of pregnancies was greater when endometrial pattern were trilaminar and when endometrial thickness was greater (15). Most of our patients had trilaminar pattern, but with respect to both endometrial pattern and thickness, there were no significance differences between two groups and endometrial pattern and thickness had no impact on pregnancy rate. CC acts as an anti estrogenic compound. This effect on the endometrium has been documented by the observance of relatively thinner sonographic stripes, a finding which can be reversed with high doses of estrogen (15, 16). Some researchers have noted a toxic effect of CC in rabbit embryo (17) and mouse embryo (18). Because we use CC in both groups, we could not assess the effect of CC in these aspects.

Cost-effectiveness plays an important role when choosing between different alternative treatment protocols. In our study, in CC plus hMG group the mean number of hMG ampoules required was 9.8 ± 4.3 and the mean medication expense was approximately 6 times the cost of CC-treated group. As cycle fecundity did not improve significantly and the cost per cycle was increased, the cost-effectiveness of the use of CC plus hMG for COR in conjunction with IUI remains questionable.

In conclusion, pregnancy rate was higher when using COR with CC plus hMG versus CC in combination with IUI. Although not statistically significant, the study does show a trend toward significance in the CC plus hMG-treated group compared with CC-treated group.

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