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ORIGINAL ARTICLE

Gonadotropin Alone is a Better Drug for Ovarian Stimulation than in Combination with Clomiphene in Intrauterine Insemination

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Abstract

Objective This study compares the efficacy of sequential clomiphene citrate (CC) + Gonadotropin to that of Gonadotropin alone with ultrasound monitoring.

Methods It is a retrospective analytic study done on a total of 100 couples to compare two groups receiving CC + Gonadotropin and Gonadotropin alone for ovarian stimulation followed by intrauterine Insemination (IUI). We studied the cycle performance parameters. Cumulative pregnancy rates and ovulation rates were the primary outcomes. Results were analyzed following the intention-to-treat principle.

Results There were no significant differences with respect to indications and the numbers of dominant follicles recruited. The endometrial thickness was significantly better in Gonadotropin-alone group ($P < 0.05$). Ovulation rate was better for CC + Gonadotropin at 95.91 %. Nine pregnancies were in the CC + Gonadotropin group (18.36 %) and 17 in Gonadotropin-alone group (33.3 %).

Conclusions Significant differences in pregnancy rates and endometrial thickness were seen. Gonadotropin alone thus appears to give better results, but CC + Gonadotropin seems to be a cost-effective drug.

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Keywords Intrauterine insemination · Clomiphene citrate · Gonadotropin · Sub fertility

Introduction

Intrauterine insemination (IUI) with or without ovarian stimulation is regarded as the first treatment option for couples with unexplained, moderate-to-mild male subfertility, and WHO type II anovulation. Compared with natural cycle IUI, IUI with ovarian stimulation improves the chances of conception in couples with subfertility [1]. In the current era, various drugs are available for ovarian stimulation and these drugs can be used in combination to give better results. Oral antiestrogenic clomiphene is well accepted first-line drug for ovarian stimulation because of its cost effectiveness and compliance [2]. In women who fail to ovulate or conceive with clomiphene citrate (CC), Gonadotropin ovulation induction combined with intrauterine insemination is used as the second-line therapy [3, 4]. To get better results with cost effectiveness, sequential CC and Gonadotropin is being used since a long time. Ransom et al., compared and found that menotropin alone is superior to clomiphene and menotropin combination for superovulation induction among CC failures [5]. Those authors suggested that COH with IUI represents a combination of actions, including correction of erratic LH pattern; augmentation of low mean LH surges, normalization of follicular growth, increase in the number of available oocytes ovulated per cycle with commensurate improvement in chances of ovum pick-up, fertilization, and implantation.

Whether sequential CC with Gonadotropin or Gonadotropin alone is better second-line therapy is still controversial. There is lack of data of good strength to prove that one is better than the other. Study related to the comparison of sequential CC + Gonadotropin to that of Gonadotropin only on Indian subpopulation is lacking. We made an attempt by retrospective analysis to compare in a parallel design the efficacy of sequential CC + Gonadotropin with Gonadotropin alone for ovarian hyperstimulation in an IUI cycle.

Materials and Methods

Patients

Two types of protocols were presented to the couples who were eligible for IUI and attending the Indraprastha Apollo Hospital infertility treatment and research center, New Delhi from January 2011 to December 2013.

Inclusion Criteria

A total of 100 patients with infertility of 1 year or more duration were included in the study. Each of them underwent a maximum of three cycles of ovarian hyperstimulation with IUI. Patients of at least 18 years of age and aged less than 40 years were selected. Etiologies of infertility included male factor, anovulation, and unexplained infertility. Various procedures, drugs used in them, and the total procedure's cost were explained to each couple in detail. Patients were divided into two groups after counseling and written consent. Patients in whom cycles were stimulated with sequential CC + Gonadotropin were assigned as group A and patients whose cycles were stimulated with Gonadotropin alone were assigned as group B depending on patient's choice and socioeconomic status.

All patients underwent a complete infertility evaluation scheme which included a profound medical history and physical examination of both husband and wife, anthropometry [weight, height, BMI, waist–hip ratio] for diagnosis of polycystic ovarian syndrome, Endocrinological parameters [prolactin, thyroid hormones, basal serum FSH, luteinizing hormone (LH)], uterine cavity, and tubal assessment (by laprohysteroscopy or hysterosalpingography) in female and semen analysis (as per WHO criteria 2010) in male. A baseline transvaginal sonography was performed on day 2, prior to initiating treatment in each cycle and if ovarian follicular size was found to be >30 mm, then that cycle was canceled.

Ovarian Stimulation

Clomiphene Citrate Plus Gonadotropin Group (Group A)

For the patients in group A, Clomiphene citrate (CC) (Siphene, Clomid, Fertil) 100 mg was administered for five consecutive days initiated between day 2 and day 6 of the cycle, followed by the administration of 75 IU of Gonadotropin FSH (Folliculin, Ovitrop, Gonal F) on day 7 of the cycle. Further need of administration of FSH (75 IU) daily/alternate day was assessed by repeated transvaginal ultrasonography. When the lead follicle(s) attained a diameter of 17 mm and endometrial thickness was >7 mm, hCG (10,000 IU) was administered between 9:00 PM and 1:00 AM. The cycle was canceled if there were more than three follicles with a diameter of $\geq$17 mm at the time of induction to avoid risk of multiple pregnancy and ovarian hyperstimulation.

Gonadotropin-Only Group

In group B, Gonadotropin FSH (Folliculin, Ovitrop, Gonal F) was started on day 3 with initial dose of 75 IU I/M daily till day 7. The dose was adjusted according to transvaginal ultrasonography, done on alternate day after day 7 of the cycle till the leading follicle(s) attained a diameter of 17 mm and endometrial thickness was >7 mm thick. hCG (10,000 IU) was administered around 9:00 PM–1:00 AM. The cycle was canceled if there were more than three follicles with a diameter of ≥17 mm at the time of induction to avoid risk of multiple pregnancy and ovarian hyperstimulation.

Semen Preparation

Semen samples were collected in semen collection room of the laboratory by masturbation or withdrawal and allowed to liquefy at room temperature. The semen sample was examined under a microscope to determine sperm concentration and motility. A standard swim up was performed, and 0.5 ml of final solution was used for IUI.

Intrauterine Insemination and Follow Up

IUI was performed by using an intrauterine catheter after 36 h of administration of hCG. The patient remained supine for 30 min thereafter. For all patients, luteal phase support was given by micronized progesterone (uterone, susten) 200 mg twice daily vaginally. Initial serum β hCG quantification was performed 14–16 days after IUI. Positive pregnancy test was confirmed (β HCG > 5 mIU/ml) and followed by ultrasonography 2 and 4 weeks later.

Statistical Analysis

The data are studied as mean ± SD. Proportions were compared via Chi square and Fisher's exact tests for the statistical analysis. To assess trend in proportions, logistic regression procedures were used. $P < 0.05$ was considered as statistically significant.

Results

A total of 49 couples were given CC with Gonadotropin and 51 were given Gonadotropin alone. The two groups did not differ significantly with respect to mean age (*P*—NS), duration of infertility (*P*—NS), and type of infertility (*P*—NS) (Table 1).

There were significant differences in the cycles' performance parameters for group A and group B in respect of mean endometrial thickness ($P < 0.05$) that was better in Group B, while the number of follicles ruptured ($P < 0.05$) was more in group A. There was no difference in the length of follicular phase between two groups ($P = \text{NS}$) (Table 2). In both the groups, one patient each had more than three preovulatory follicles on the hCG administration day, and the administration of hCG was held because of fear of threatened stimulation. No case of severe ovarian stimulation syndrome developed in the study. One cycle in Group A was canceled as no follicle growth was seen.

There were 26 pregnancies documented by ultrasonography and serum β hCG: nine were in the group A and 17 in group B (Table 3). This represents a total pregnancy rate of 26 % per couple, with pregnancy rate of 18.36 % in CC + Gonadotropin-treated cycles and 33.33 % in Gonadotropin-treated cycles ($P < 0.05$). The spontaneous miscarriage rate was 19.23 % (5 of 26 pregnancies). Of these, two occurred in CC + Gonadotropin-treated cycles, and three occurred in Gonadotropin-treated cycles. There were two multiple gestations in group B.

Discussion

Main Findings

There was total pregnancy rate of 26 % per couple, with pregnancy rate of 18.36 % in CC + Gonadotropin-treated cycles and 33.33 % in Gonadotropin-treated cycles ($P < 0.05$). The ovulation rate was higher in sequential clomiphene + Gonadotropin 95.91 % (47), while it was 90.16 % (46) in Gonadotropin-alone group (*P*—NS). There was significant difference in cycles' performance parameters for group A and group B in respect to mean endometrial thickness ($P < 0.05$) that was better in Group B while no. of follicles ruptured ($P < 0.05$) were better in group A.

Strengths and Limitations

This study was carried out in infertility department of multi disciplinary hospital of India. There are only few studies comparing these two widely used protocols for infertility. Still today large randomized studies are lacking.

The limitation in our study was sample small size. We suppose further randomized controlled trials with larger sample size to help in a better judgment.

Interpretation

Controlled ovarian stimulation (COS) prior to IUI is now widely used as a treatment modality for various cases of infertility. Different hormonal treatment protocols include CC, letrozole, or various Gonadotropins alone or in combination. The reported cycle pregnancy rates are

Table 1 Comparison of characteristics of group A (CC + Gonadotropin) and group B (Gonadotropin)

Parameter	Group A ($n = 49$)	Group B ($n = 51$)	P value
Age (patient)†	29.89 ± 4.32	30.68 ± 4.45	NS
Age (husband)†	33.24 ± 4.25	34.72 ± 5.37	NS
Duration of infertility (year)†	4.33 ± 3.42	4.82 ± 3.64	NS
Type of infertility			
Primary	45 (91.8 %)	46 (88.2 %)	NS
Secondary	04 (07.2 %)	05 (11.8 %)	NS
Etiology of infertility			
Anovulation/PCOS	16 (32.65 %)	17 (33.33 %)	NS
Male factor	17 (34.69 %)	16 (31.37 %)	NS
Unexplained	16 (32.65 %)	18 (35.29 %)	NS

Data are given as number (%) unless specified otherwise

NS not significant, *S* significant

† Mean ± SD

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

Parameter	Group A ($n = 49$)	Group B ($n = 51$)	P value
Endometrial thickness†	9.1 ± 1.78	12.4 ± 0.82	$P < 0.05$
Follicular phase duration†	13.52 ± 2.34	13.22 ± 2.16	NS
No. of follicles > 17 mm†	2.07 ± 0.74	1.55 ± 0.75	NS
No. of follicles ruptured†	2.06 ± 0.68	1.3 ± 0.58	$P < 0.05$

Data are given as number (%) unless specified otherwise

NS not significant, *S* significant

† Mean ± SD

Table 3 Characteristics of cycles' outcome parameters for group A and group B

Parameter	Group A ($n = 49$)	Group B ($n = 51$)	P value
Ovulation rate	47 (95.91 %)	46 (90.16 %)	NS
Pregnancy rate	9 (18.36 %)	17 (33 %)	$P < 0.05$
Abortions	2 (4.08 %)	3 (5.88 %)	NS
Multiple pregnancy	0	2 (3.92 %)	$P < 0.05$
Canceled cycles	2 (4.08 %)	1 (1.96 %)	NS

Data are given as number (%) unless specified otherwise

NS not significant, *S* significant

controversial and vary greatly: those reported are 3–12 % for CC, 7–30 % for gonadotropin and 2.5–22 % for CC + Gonadotropin [6].

In our study, pregnancy rates of 18.36 % in CC + Gonadotropin-treated cycles and 33.33 % in Gonadotropin-treated cycles were found, which are statistically significant ($P < 0.05$). Raslan also found better pregnancy rate in Gonadotropin group, but in this study, it was not statically significant [7]. Our results are contradictory to a few previous studies. In the study of Ibrahim et al., CC + Gonadotropin group had 26.7 % pregnancy rates versus 6.7 % in Gonadotropin alone [8], while Akbary et al. and Ganesh and colleagues reported acceptable pregnancy rates without any statistically significant differences between the two groups [9–11]. Study of Ransom et al. had results much similar to those of our study, with pregnancy rates for Gonadotropin alone and sequential being 0.192 and 0.09, respectively [5].

The two groups in our study did not differ significantly with respect to mean age, duration of infertility, and type of infertility. Koli et al. also found the same results in their study [12].

An important outcome of ovarian hyperstimulation is multiple gestations which is statistically significant in

Gonadotropin group in our study (3.92 vs. 0 %), which warned us for cautious use of Gonadotropin. Van Rumuste et al. and Ransom et al. also found higher multiple pregnancy rates in hMG-alone group [8, 13].

It is important to study the effects of drug on the number of follicles, endometrial thickness, and the duration of follicular phase. Clomiphene being antiestrogenic shows poor endometrial thickness in spite of a good number of matured follicles [13]. It is noteworthy that our study also gave the same results. There were significant differences in cycles' performance parameters for group A and group B with respect to mean endometrial thickness ($P < 0.05$) which was better in group B, while the number of follicles ruptured ($P < 0.05$) was more in group A. There was no difference in the length of follicular phase between these two groups ($P =$ NS).

Several studies revealed that CC reduces endometrial receptivity, as it impairs endometrial development and uterine blood flow, resulting in endometrial thinning in 15–50 % of patients with subsequent implantation failure and induces early pregnancy loss due to luteal phase defect [14]. Raslan, Walid, and Elkatan found poor endometrial thickness, trilaminar pattern, and endometrial blood flow in clomiphene cycles due to its antiestrogenic effect [7, 15, 16]. Seddigeh and Mehbobeh (2006) identified a statistically significant difference in the mean endometrial thicknesses between cycles that resulted in pregnancy and those that did not [17]. The comparison of a novel minimal stimulation protocol with CC + recombinant follicle-stimulating hormone to the recombinant follicle-stimulating hormone alone for ovulation induction in non-IVF cycle done by Altay et al. concluded that both groups were similar in respect to the number of follicles matured and duration of follicular phase. They also had significantly larger endometrial thickness on the day of hCG injection similar to that found in our study [9]. Akbary and colleagues in their 1-year study performed to compare three different groups—CC + hMG, letrozole + hMG, and hMG alone—also observed that between the group of CC + hMG and the group of hMG, this thickness was thinner in the group of CC + hMG [10]. While Ibrahim et al., in their study designed to compare CC/hMG versus hMG, found no significant difference in the groups regarding the above parameters [8]. Thus, it can be safely concluded that clomiphene has antiestrogenic effect on endometrial thickness which might affect the pregnancy rates.

A Cochrane review for evaluating different ovarian stimulation protocols (antiestrogens, aromatase inhibitors, and Gonadotropins with or without GnRH agonists/antagonists) was conducted by Cantineau and Cohlen (2007) suggested that there are limited studies regarding the comparison of Gonadotropin alone to sequential anti-estrogen and Gonadotropin [18]. Although Gonadotropin alone was found to be a better drug, more studies were advised to improve strength of the study. In summary, the results of this study suggest that Gonadotropin alone is a better choice as second-line drug for ovarian stimulation in IUI because it gives better endometrial thickness and desirable pregnancy rate. On the other side, it lags behind CC + Gonadotropin with respect to cost in poor resource set-ups and has greater multiple pregnancy rates.

Conclusion

Significant differences in pregnancy rates and endometrial thicknesses were seen between CC + Gonadotropin and Gonadotropin only. Gonadotropin alone thus appears to produce better results, but CC + Gonadotropin being less expensive, seems to be cost effective drug.

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Compliance with ethical requirements and Conflict of interest Our study is retrospective data analysis as per ethics with consent of using stored data from treating doctor and hospital authority. The study is designed with an intension to treat patient and to find out which method is better for ovarian stimulation. There are no conflicts of interests that I should disclose, having read the instructions of submission and policies of journal.

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