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Taiwanese Journal of Obstetrics & Gynecology 50 (2011) 58–61
www.tjog-online.com

Original Article

Comparison of the effect of two different doses of recombinant gonadotropin for ovarian stimulation on the outcome of intrauterine insemination

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Accepted 19 January 2010

Abstract

Objective: The aim of this study was to identify an optimal stimulation protocol for intrauterine insemination (IUI) to obtain an acceptable pregnancy rate and low frequency of multiple pregnancies.
Materials and Methods: In total, 340 patients, who received intrauterine insemination because of ovulation dysfunction, were enrolled in this study. Group I consisted of 203 patients who received recombinant FSH (r-FSH) 150 U every other day as an ovulation induction agent. Group II consisted of 137 patients who received r-FSH 100 U every other day as an ovulation induction agent. All patients in both groups also received clomiphene citrate 100 mg/day for consecutive five days from the fifth day of the cycle. Only patients with at least two follicles >18 mm on the human chorionic gonadotropin injection days were included in this study.
Results: The clinical pregnancy rate was 14.8% (30/203) in Group I compared with 20.4% (28/137) in Group II, $p > 0.05$. The incidence of multiple pregnancy was 41.7% (10/24) in Group I compared with 12.5% (3/24) in Group II, $p < 0.05$.
Conclusions: The concurrent use of low-dose r-FSH and clomiphene citrate would seem not only to be cost-effective but also highly satisfactory in that it prevents high-order multiple pregnancies.

Keywords: High-order multiple pregnancy; Insemination; Multiple pregnancy; Ovarian hyperstimulation syndrome; Ovulation induction

Introduction

Intrauterine insemination (IUI) is a common therapeutic approach for couples who are suffering from a wide variety of types of infertility. IUI can be accomplished in a natural cycle or with ovulation stimulation. To increase the number of oocytes and achieve a better pregnancy rate, controlled ovarian hyperstimulation is usually performed in the majority of IUIs [1,2]. However, significant variation in IUI clinical outcome has been reported with different protocols of ovulation induction. For example, when clomiphene citrate alone was used for ovulation induction, the average pregnancy rate has been reported to be below 10% per cycle in some studies [3,4]. When controlled ovarian hyperstimulation was performed with gonadotropin, the average pregnancy rate has been reported to be about 15% per cycle [5–7]. Although ovarian

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1028-4559/$ - see front matter
doi:10.1016/j.tjog.2010.01.001

stimulation with gonadotropin results in a better pregnancy rate, it also carries the risk of the subject developing ovarian hyperstimulation syndrome and/or having a high-order multiple pregnancy [8–10]. To our knowledge, as yet, no consensus exists about the drug of first choice to be used for hyperstimulation.

Ideally, an IUI should be accomplished with a satisfactory pregnancy rate per initiated cycle and a low risk of high-order multiple pregnancies. To determine an optimal stimulation dosage for IUI, a comparison of the clinical outcome in IUI using two different protocols of gonadotropin for ovarian stimulation was studied by retrospectively analysis.

Materials and methods

Under the approval of institutional review board in Chi Mei Medical Center, we analyzed retrospectively IUI cycles using husband's sperm from January 2005 to November 2007. The inclusion criteria were female subjects younger than 38 years of age with a normal body mass index; furthermore, the indication for IUI was anovulation. The couples with other indications for IUI such as male factor, tube factor, and unknown factor were excluded. Hysterosalpingography was routinely used to evaluate the openness of the fallopian tubes. Only patients with patent bilateral fallopian tubes were included in this study. In total, we enrolled 340 patients for the analysis. Patients were randomly enrolled into two groups. Group I included 203 patients who received recombinant FSH (r-FSH, Gonal-F; Serono, Geneva, Switzerland) 150 U every other day from the 4^{th} day to the 10^{th} of the cycle as an ovulation induction agent. Group II included 137 patients who received r-FSH 100 U every other day from the 4^{th} day to the 10^{th} of the cycle as an ovulation induction agent. All patients in both groups also received clomiphene citrate (CC; Clomiphene, Shinogi, Taiwan) 100 mg/day for five consecutive days from the fifth day of the cycle as adjuvant stimulation. A single IUI was then performed 36 hours after human chorionic gonadotropin (Pregnyl, Organo, Oss, Holland) administration. The primary outcomes were the clinical pregnancy rate per cycle, the ongoing pregnancy rate (the pregnancy with gestational age more than 12 weeks) per cycle, and the multiple pregnancy rate per cycle. The outcomes are presented as mean ± SEM. χ^2 tests were used for statistics analysis. Differences were considered statistically significant at $p < 0.05$.

Semen preparation

Semen was prepared as previously described. Briefly, after the semen was collected it was allowed to liquefy at 37°C and a small drop was placed in a Makler sperm counting chamber (Sefi Medical Inc., Haifa, Israel) for evaluation. The remaining of the specimen was suspended in 5 mL of a discontinuous two-layer (40% and 80%) PureSperm solution gradient (NidaCon International AB., Gothenburg, Sweden) and centrifuged at 300*g* for 20 minutes. Sperm cells present in the 80% PureSperm layer were collected and washed twice in synthetic human tubal fluid. The final pellet was resuspended in 0.5 mL of fresh human tubal fluid and was ready for IUI with a Genitor catheter (Laboratory C.C.D., Paris, France). A speculum was used to visualize the cervix, mucus was removed with a cotton swab, the catheter was gently introduced into the endometrial cavity, and the sample was slowly injected. Patients were allowed to rest for 15 minutes after the procedure. Each patient was prescribed 10 mg of oral dydrogesterone (Dyphastone, Duphar, Taiwan) three times a day after the insemination. A urinary pregnancy test was used for initial assessment of success 14 days later. Clinical pregnancy was confirmed by identification of a positive fetal heartbeat 2 weeks later by transvaginal ultrasound examination.

Results

Across the 340 patients enrolled, the two treatment groups, 203 patients in Group I and 137 patients in Group II, were similar with respect to mean age (31.9 ± 3.0, Group I, compared with 31.3 ± 3.1, Group II). The total sperm count, sperm motility, and percentage of sperm with progressive motility were also similar between the treatment groups (Table 1). As expected, there was a slight, but not significant, difference in the number of follicle >18 mm in Group I compared with Group II (5.1 ± 3.6 *vs.* 4.3 ± 1.9, $p > 0.05$).

Surprisingly, although statistically non-significant, the clinical pregnancy rate and ongoing pregnancy rate were higher in patients who received the lower dosage of ovulation stimulation. The clinical pregnancy rate was 20.4% (24/137) in the 100 IU Group compared with 14.8% (30/203) in the 150 IU Group ($p > 0.05$). The ongoing pregnancy rate was 17.5% (24/137) in the 100 IU Group compared with 11.8% (24/203) in the 150 IU Group, $p > 0.05$. As expected, the incidence of multiple pregnancy was statistically significant higher in the 150 IU Group than that in the 100 IU Group [41.7% (10/24) *vs.* 12.5% (3/24), $p < 0.05$, respectively]. Furthermore, there were two triplet pregnancies and one quadruplet pregnancy in the 150 IU Group compared with no high-order multiple pregnancies in the 100 IU Group (Table 2).

Discussion

IUI is a common therapeutic approach for couples with a wide variety of types of infertility. The overall pregnancy rates for IUI vary greatly from as low as 5% to as high as 66% [1]. IUI combined with ovarian hyperstimulation has long

Table 1
Comparison of age and semen quality between the two study groups

	Group I	Group II	*p*
Age	31.9 ± 3.0	31.3 ± 3.1	>0.05
Total sperm count ($\times 10^6$)	32.5 ± 32.4	31.5 ± 30.4	>0.05
Motility (%)	91.9 ± 10.4	93.3 ± 8.9	>0.05
Progressive motility (%)	51.3 ± 21.1	53.9 ± 22.5	>0.05

Group I: r-FSH 150 U; Group II: r-FSH 100 U.
Data are presented as mean ± standard error of the mean.

Table 2
Comparison of the clinical outcomes between the two study groups

	Group I	Group II	*p*
Follicle number	5.1 ± 3.6	4.3 ± 1.9	>0.05
Body mass index (kg/m^2)	21.2 ± 2.6	20.9 ± 2.3	>0.05
Dose of gonadotrophins (IU)	533 ± 242	513 ± 184	>0.05
Clinical pregnancy rate	14.8% (30/203)	20.4% (28/137)	>0.05
Ongoing pregnancy rate	11.8% (24/203)	17.5% (24/137)	>0.05
Multiple pregnancy rate	41.7% (10/24) 7 Twins, 2 triplets, 1 quadruplets	12.5% (3/24) 3 Twins	<0.05

Group I: r-FSH 150 IU; Group II: r-FSH 100 IU.
Data are presented as mean ± standard error of the mean.

been demonstrated to be an effective form of treatment for subfertile couples [2]. Although IUI can be performed using the natural cycle without any ovarian stimulation, previous studies have suggested that there are higher pregnancy rates per cycle when the patients are subjected to ovarian hyperstimulation [3,4,7]. CC, a traditional first-line oral ovulation agent, can be used alone for ovulation induction in IUI. However, many studies have shown that there is a higher pregnancy rate in IUI cycles, compared with CC alone, when gonadotropin stimulation is also used [11–13].

Human menopausal gonadotropin (HMG), a pharmaceutical preparation from postmenopausal urine extracts, was most popular for ovarian stimulation in the first few years. It was not until 1996 that r-FSH preparations became available. These preparations are completely lacking in any luteinizing hormone activity or extraneous human protein and began to replace HMG for ovulation stimulation [14]. Since then, many comparisons of different ovarian stimulation protocols for IUI have been described; nonetheless, there is no universal consensus in terms of an optimal stimulation protocol [14–18]. Demirol and Gurgan [19] have suggested r-FSH would seem to result in a better clinical pregnancy rate per IUI cycle than urinary FSH and HMG. In their study, they found the r-FSH group used a lower follicle-stimulating hormone dose and produces more mature oocyte per cycle when compared with the urinary FSH and HMG groups. On the other hand, Dankert et al [20] declared that there was no significant difference in live birth rates per IUI cycle between CC and r-FSH. However, in their study, cycles with more than three follicles were canceled. Despite all these conflicting results, r-FSH, which greatly improved the clinical outcome in *in vitro* fertilization and embryo transfer (IVF-ET) after it began to be used, indeed attracted attention for use in IUI [21,22].

The major drawbacks of gonadotropin stimulation in IUI are multiple gestation, ovarian hyperstimulation, and greater expense of the treatment. Reducing the stimulation dosage to a mild hyperstimulation protocol is obviously an option. However, the cost-effectiveness of a mild stimulation protocol needs to be carefully evaluated. For example, Goverde et al [23] used 75 IU of follicle-stimulating hormone daily for ovulation stimulation and found this mild stimulation protocol did not result in a higher pregnancy rate than IUI using the natural cycle, whereas at the same time multiple pregnancies could not be avoided. Meanwhile, Ryan et al suggested that combining an oral ovulation induction agent with low-dose gonadotropin injections might be an ideal treatment for IUI [24]. In his study, he gave oral medication followed by gonadotropins before human chorionic gonadotropin and IUI and found this combined protocol was less costly and equally effective; furthermore, it potentially gave rise to fewer multiple births than with gonadotropin alone.

In the past decade, scientists had tried many different protocols to attempts to obtain an acceptable pregnancy rate, a tolerable expense level for the treatment, and minimal risk of a multiple pregnancy. In this context, it would seem that our 100 IU protocol fulfills the above requirements. In our study, we simplified the combined protocol to consist of the concurrent use of clomiphene citrate and r-FSH. The patients were randomized into two groups, one of which received clomiphene citrate with 100 IU of r-FSH stimulation for 4 days, whereas the other received clomiphene citrate with 150 IU of r-FSH stimulation for 4 days. The pregnancy rates were 20.4% and 14.8%, respectively. Thus, we found that no benefit was gained from the higher gonadotropin stimulation dose during IUI, since the clinical pregnancy rate and ongoing pregnancy rate were comparable between the two groups. We also found when the gonadotropin stimulation dosage was increased from 100 IU to 150 IU daily, this caused more multiple pregnancies and more high-order multiple pregnancies. The incidence of multiple pregnancies was 41.7% (10/24) in the 150 IU Group compared with 12.5% (3/24) in 100 IU Group ($p < 0.05$). Altogether, there were seven twin pregnancies, two triplet pregnancies, and one quadruplet pregnancy in the 150 IU Group compared with three twin pregnancies and no high-order multiple pregnancy in the 100 IU Group. We attributed this result to the greater number of mature follicles in 150 IU r-FSH group, although this was statistically non-significant. Although this is a retrospective study and therefore there are a number of pitfalls associated with the approach, these results still give us some important hints and broaden experience in this area.

An ideal stimulation protocol should be able to achieve a satisfactory pregnancy rate with an acceptable multiple pregnancy rate and without any high-order multiple pregnancies if at all possible. From our experience, the combined use of a low dose of r-FSH and clomiphene citrate is able to achieve such a satisfactory pregnancy rate without any high-order multiple pregnancies per initiated cycle. Accordingly, we suggest this protocol be considered for IUI of infertile couples with female ovulation dysfunction.

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