Effectiveness of Soft Stimulation Protocol, Compared with Conventional GnRH Antagonist Multiple dose Protocol in Patients Undergoing Controlled Ovarian Stimulation with Intrauterine Insemination

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과배란유도하 자궁강내 인공수정시술을 받는 환자에서 연성자극요법과 성선자극호르몬 길항제 다회투여법의 효과 비교

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목 적: 과배란유도하 자궁강내 인공수정시술을 받는 불임 환자들을 대상으로 연성자극요법의 효과를 성선자극호르몬분비호르몬 길항제 다회투여법과 비교, 평가하고자 본 연구가 시행되었다.

연구방법: 불임 환자 80명을 연성자극요법군 (n=40)과 성선자극호르몬분비호르몬 길항제 다회투여법군 (n=40)으로 무작위로 1:1로 배정하였다. 두 군 모두에서 질식초음파상 평균 직경이 18 mm에 도달한 난포가 1개, 또는 17 mm에 도달한 난포가 2개 이상 관찰될 때, 재조합 사람융모성성선자극호르몬 250 μg을 1회 투여했으며, 이 후 36~40시간째에 자궁강내 인공수정이 시행되었다.

결 과:. 과배란유도를 위해 사용된 재조합 사람난포자극호르몬의 총용량과 투여일수는 연성자극요법군에서 유의하게 적었다 (p<0.001, p<0.001). 두 군 모두에서 조기 황체화호르몬 급상승은 관찰되지 않았다. 시술 주기당 임상적 임신율, 자연유산율, 다태임신율, 중증 난소과자극증후군의 발생빈도는 두 군간에 차이를 보이지 않았다.

결 론: 연성자극요법은 성선자극호르몬분비호르몬 길항제 다회투여법에 비하여 재조합 사람난포자극호르몬을 적은 용량, 짧은 기간 사용하면서도 유사한 임신율을 나타내므로, 과배란유도하 자궁강내 인공수정을 시행 받는 환자를 위한 환자 친화적이고 효과적인 과배란유도법이 될 수 있을 것이다.

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중심단어: 성선자극호르몬분비호르몬 길항제, 연성자극요법, 과배란유도, 자궁강내 인공수정

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Controlled ovarian stimulation (COS) is extensively used to increase oocyte numbers and pregnancy rates in assisted reproductive technology (ART) program such as in vitro fertilization (IVF) and intrauterine insemination (IUI). COS has evolved since late 1970s to a highly specialized practice. Stimulatory drugs have also evolved from clomiphene citrate (CC) and gonadotropins to pure recombinant forms of both follicle stimulating hormone (FSH) and luteinizing hormone (LH). In the mid 1980s, the introduction of gonadotropin releasing hormone (GnRH) agonists lowered cancellation rates by the prevention of premature LH surge and increased the number of oocytes retrieved. These results of COS by GnRH agonists has been shown to improve follicular development and pregnancy outcome especially in intermediate and high responders.[1,2] Since their introduction, the use of CC for IVF and even for COS with IUI (COS/IUI) was mostly abandoned because of a high cancellation rate due to premature LH surge and low pregnancy rate. However, a recently introduced GnRH antagonists can make treatment more comfortable and more patient-friendly, using CC in ART cycles. GnRH antagonists offer possibilities to create innovative ovarian stimulation regimens with lower chances of side effects. GnRH antagonists bind to GnRH receptors and induce a fall in FSH and LH levels within hours. Their administration in the late follicular phase can effectively prevent or interrupt the LH surge without compromising fertilization, cleavage and pregnancy rates.[3~5] They do not cause a 'flare-up' as found with GnRH agonists, so prior desensitization for a period of some weeks is not necessary.[6] Craft et al.[7] used GnRH antagonist with CC/FSH for 18 poor responders undergoing IVF and reported that this protocol produced favourable results. Thereafter, several studies on soft stimulation protocol using GnRH antagonist with CC/gonadotropins have been performed in patients undergoing IVF treatment.[8,9] However, prospective randomized trials to evaluate the effects of this protocol in COS/IUI cycles have not been reported. Therefore, this study was performed to investigate the effectiveness of soft stimulation protocol using GnRH antagonists with CC/ recombinant FSH (rFSH), compared with standard GnRH antagonist multiple dose protocol (MDP) in infertile patients undergoing COS/IUI.

MATERIALS AND METHODS

1. Patients

Our prospective randomized study was performed at a university-based infertility clinic at the Asan Medical Center, Seoul, South Korea. The study population consisted of 80 infertile women who had undergone 80 COS/IUI cycles. The institutional review board of the University of Ulsan College of Medicine, Asan Medical Center, approved the study, and all patients provided the written informed consent. Inclusion criteria were as follows: women aged 20~39 years, a body mass index (BMI) of 18~29 kg/m^2, a normal menstrual cycle (24~35 days), at least one normal fallopian tube, a basal serum FSH below 10 mIU/mL at cycle day 2~3, and an indication for COS/IUI (endometriosis stage I or II, unexplained infertility). In addition, patients were recruited only for their first COS/IUI cycle during the study period. Patients who had any ovarian abnormality that would interfere with adequate stimulation, a history of hospitalization due to severe ovarian hyperstimulation syndrome (OHSS), a history of previous (within 12 months) or current abuse of alcohol or drugs, a history that may influence on this study results and a history of any other hormone drugs within the preceding 3 months were excluded.

Patients were randomly allocated into soft stimulation protocol group using GnRH antagonist/CC/rFSH (n=40) or GnRH antagonist MDP group (n=40) by the use of sealed envelopes and a computer-generated list. The

sequence of allocation to the two groups was provided to the investigating physicians and randomization was performed as planned according to the randomization list order.

2. Ovarian stimulation protocols

Patients included in soft stimulation protocol group received CC 100 mg daily for 5 days from day 3 of the cycle and got injected 150 IU/day rhFSH (Puregon pen®, Schering-Plough Organon, Oss, The Netherlands) from day 5 of the cycle (stimulation day 3) to the day of hCG administration. Subcutaneous injections of 0.25 mg GnRH antagonist cetrorelix (Cetrotide, Merck Serono SA, Geneva, Switzerland) was started when the leading follicle reached 13 mm in a mean diameter, and was continued daily until the day of hCG injection. For GnRH antagonist MDP group, rhFSH (Puregon pen®) at a dose of 150 IU/day was administered daily from the day 3 of the cycle. When the leading follicle reached 13 mm, cetrorelix at a dose of 0.25 mg/day was started and continued daily up to the day of hCG administration. From stimulation day 5 onwards, transvaginal ultrasonography (Aloka SSD-1700, Aloka Co., Tokyo, Japan) was performed for monitoring of follicular growth in both groups. After stimulation day 5, the rhFSH dose was adjusted according to the clinical response to COS. When one leading follicle reached 18 mm in diameter or 2 or more follicles reached 17 mm, 250 μg recombinant hCG (rhCG, Ovidrel, Merck Serono SA) was administered for triggering of oocyte maturation. On the day of hCG injection, blood was drawn for measurement of serum LH and progesterone levels. A single IUI was performed 36~40 hours after hCG injection. For IUI, semen was obtained by masturbation and liquefied at room temperature and then its amount, sperm concentration, and sperm motility were evaluated. Two-step silane-coated silica (PureSperm, Nidacon Laboratories, AB, Gothenburg, Sweden) gradient method was used for sperm preparation. Luteal support was provided by administering 90 mg of vaginal progesterone gel (Crinone gel 8%, Merck Serono SA) once daily from the day of IUI. Pregnancies were confirmed by rising serum β-hCG concentrations and transvaginal ultrasonographic evidence of a gestational sac. If pregnancy was diagnosed, vaginal progesterone administration was continued for another 5 to 7 weeks. Clinical pregnancy was defined as the presence of a gestational sac by ultrasonography, while miscarriage rate per clinical pregnancy was defined as the proportion of patients who failed to continue development before 20 weeks of gestation in all clinical pregnancies.

3. Hormone assays

Serum LH was measured by immunoradiometric assay (IRMA) with BioSource LHsp-IRMA kit (BioSource Europe S.A., Nivelles, Belgium). Its interassay and intraassay variances were less than 8.0% and 3.9%, respectively. Serum progesterone was measured by radio-immunoassay (RIA) with Coat-A-Count Progesterone kit (Siemens Healthcare Diagnostics Inc., Los Angeles, CA, USA). Its interassay and intraassay variances were less than 9.7% and 8.8%, respectively. Serum β-hCG was measured 11 or 12 days after IUI by IRMA method with hCG MAIACLONE kit (Serono Diagnostics, Woking, UK); interassay and intraassay variances were less than 10% and 5%, respectively.

4. Statistical analysis

The mean value was expressed as the mean ± standard deviation (SD). A Student's t-test was used to compare the mean values. Chi-square test and Fisher's exact test were used for the comparisons of fraction. Statistical significance was defined as $p<0.05$. All analyses were performed using the SPSS statistical package for Windows, ver. 11.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

All 80 women finished the trial; no patient was lost to follow-up or abandoned the study because of side-effects. There were no differences in the age of patients, duration of infertility, body mass index (BMI) and the proportion of nullipara between soft stimulation protocol and GnRH antagonist MDP groups. There were also no statistical differences in the antral follicle count (AFC) and basal endocrine profile between the two groups (Table 1).

The number of follicles ≥11 mm on the day of hCG administration was significantly lower in soft stimulation protocol group than in GnRH antagonist MDP group (p=0.002). On the day of hCG injection, serum LH levels were significantly higher in soft stimulation protocol group than in GnRH antagonist MDP group (p=0.001). Serum progesterone levels were also higher in soft stimulation protocol group, but the difference did not achieve a statistical significance (p=0.079). However, a premature LH surge (defined as measurement of LH >10 IU/L and progesterone >1 ng/mL) did not occur in any patients included in soft stimulation protocol group as well as GnRH antagonist MDP group (Table 2). Total dose and days of rFSH required for COS were significantly fewer in soft stimulation protocol group than in GnRH antagonist MDP group (p<0.001, p<

Table 1. Patient characteristcs

	Soft stimulation protocol	GnRH antagonist MDP	p-value
No. of patients	40	40	
Age of patients (yr)	32.0±2.7	32.0±2.5	NS
Age of husbands (yr)	35.7±3.2	35.3±3.0	NS
Infertility duration (yr)	2.7±1.5	2.8±1.5	NS
BMI (kg/m^2)	20.1±2.0	20.4±2.2	NS
No. of nullipara	35 (87.5)	35 (87.5)	NS
AFC	12.8±3.2	13.1±3.6	NS
Basal serum FSH (IU/L)	5.8±2.1	6.1±2.0	NS
Basal serum LH (IU/L)	5.6±2.1	5.8±2.1	NS
Basal serum E_2 (pg/mL)	47.4±19.6	45.6±11.8	NS
Serum total T (ng/mL)	0.5±0.4	0.4±0.3	NS
Indications			
Endometriosis stage I or II	7 (17.5)	6 (15.0)	NS
Unexplained infertility	33 (82.5)	34 (85.0)	NS

Values are presented as mean ± SD or number (%).
GnRH, gonadotropin releasing hormone; MDP, multiple-dose protocol; NS, not significant; BMI, body mass index; AFC, antral follicle count; FSH, follicle stimulating hormone; LH, luteinizing hormone; E_2, estradiol; T, testosterone. SD, standard deviation.

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0.001). Duration of GnRH antagonist cetrorelix was also significantly shorter in soft stimulation protocol group (p<0.001) (Table 2). Despite fewer total dose and days of rFSH, clinical pregnancy rate per cycle was similar between the two groups (30.0% vs. 35.0%, respectively). Miscarriage rate, multiple pregnancy rate and the incidence of severe OHSS were also comparable between the two groups (Table 2).

DISCUSSION

CC in conjunction with gonadotropins has been used for COS since 1980's. This stimulation protocol reduces the amount of gonadotropins required and the costs due to the synergistic effect of these compounds. In addition, the gonadotropins counteract the detrimental effects of the CC to the endometrium. Therefore this stimulation protocol has been a standard protocol for COS in the past therapy.[10,11] However, this protocol was abandoned because of a high cancellation rate due to premature LH surge when GnRH agonists were introduced in ARTs including IVF. Recently, GnRH antagonists have revived these types of treatment, because premature LH surge can be eliminated by using a GnRH antagonist. Actually, soft stimulation protocol using GnRH antagonists with CC/gonadotropins has been adopted for COS in patients undergoing IVF.[7~9]

Soft stimulation protocol is also likely to become one

Table 2. Comparison of controlled ovarian stimulation results and IUI outcome

	Soft stimulation protocol	GnRH antagonist MDP	p-value
No. of cycles initiated	40	40	
No. of IUI cycles	40	40	
Days of rhFSH	7.3±1.2	9.8±1.6	< 0.001
Total dose of rhFSH (IU)	971.9±194.0	1445.6±465.9	< 0.001
Days of GnRH antagonist	3.8±1.0	5.5±1.3	< 0.001
On hCG day			
No. of follicles ≥ 11 mm	8.6±3.4	11.1±3.4	0.002
Endometrial thickness (mm)	10.0±1.5	10.4±1.2	NS
Serum LH (IU/L)	3.3±1.5	2.3±0.9	0.001
Serum progesterone (ng/mL)	0.9±0.6	0.7±0.4	0.079
Clinical PR per cycle	30.0% (12/40)	35.0% (14/40)	NS
Miscarriage rate per clinical pregnancy	16.7% (2/12)	14.3% (2/14)	NS
Ongoing or delivered PR per cycle	25.0% (10/40)	30.0% (12/40)	NS
Twin PR per clinical pregnancy	25.0% (3/12)	28.6% (4/14)	NS
Severe OHSS	2.5% (1/40)	5.0% (2/40)	NS

Values are mean ± SD unless otherwise indicated.
MDP, multiple-dose protocol; IUI, intrauterine insemination; rhFSH, recombinant human follicle stimulating hormone; NS, not significant; PR, pregnancy rate; OHSS, ovarian hyperstimulation syndrome. SD, standard deviation.

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of COS options for COS/IUI program, but prospective studies on this protocol for patients undergoing COS/IUI have not been reported yet. To the best of our knowledge, this is the first prospective and randomized study investigating the effectiveness of soft stimulation protocol using GnRH antagonist/CC/rhFSH compared with GnRH antagonist MDP group in infertile patients undergoing COS/IUI. This study demonstrates that soft stimulation protocol is advantageous to patients undergoing COS/IUI because of the shortened time required for follicular maturation and the diminished amount of rhFSH required to provide adequate ovarian stimulation.

It is well known that COS/IUI should be attempted before IVF in couples with cervical infertility, ovulatory disorder, mild male factor infertility, endometriosis in absence of anatomic distortion or unexplained infertility, because COS/IUI is less expensive, stressful and invasive than IVF with similar fecundity rates. COS is one of the crucial factors for the success of COS/IUI treatment. It has been demonstrated that GnRH antagonists can effectively prevent premature LH surge,[3~5] and therefore these may theoretically allow better timing of IUI and improve the pregnancy rates. More recently, GnRH antagonists with gonadotropins have been administered to infertile women undergoing COS/IUI, but there are limited data with conflicting results.[12~14] In the present study, clinical pregnancy rate in soft stimulation protocol group was comparable to that in GnRH antagonist MDP group (30.0% vs. 35.0%, respectively). These pregnancy rates in both groups are encouraging. Pregnancy rate in GnRH antagonist MDP group from the present study is similar to that reported by Gomez-Palomares et al.[13]

In CC cycles, CC increases the amplitude of LH and FSH pulses in the midfollicular phase by increasing the hypothalamic GnRH pulse frequency and sensitivity of the pituitary for GnRH, and these effects were not influenced by FSH administration.[15] Therefore, LH levels are more likely to be higher during the follicular phase in CC cycles than in non-CC cycles. In this study, we documented a significantly higher concentrations of serum LH on the day of hCG in soft stimulation protocol group, compared with GnRH antagonist MDP group. A retrospective study by Tavaniotou et al showed a similar result in IVF cycles.[8] Engel et al[9] reported that the overall rate of premature LH surge was 21.5% in IVF cycles using soft stimulation protocols with CC. These results suggest that LH concentrations during follicular phase are higher in COS cycles using CC than in non-CC cycles, despite GnRH antagonists administration and soft stimulation protocols can increase the risk of premature LH surge. Therefore, soft stimulation protocol using CC should be applied with caution for prevention of premature LH surge. For overcoming the problem of premature LH surge, we did not wait to start the GnRH antagonist until day 7 of stimulation. GnRH antagonist administration was started on day 5 or 6 of stimulation. Also we did not wait until the leading follicle reached 14 mm. These measures can contribute to prevent the premature LH surge in this study. Engel et al. commented that increasing the daily dose of cetrorelix from 0.25 to 0.5 mg could decrease the incidence of premature LH surge.[9] Increasing the daily dose of GnRH antagonist for obese women might be beneficial in the prevention of premature LH surge. However, in non-obese women, increasing the daily dose of GnRH antagonist might be unnecessary. Although cetrorelix at a daily dose of 0.25 mg was administered in this study, a premature LH surge did not occur in any patients of soft stimulation protocol group as well as GnRH antagonist MDP group. Further study is needed to determine the minimal effective dose of GnRH antagonist to prevent the premature LH surge in soft stimulation protocol.

In conclusion, soft stimulation protocol using GnRH antagonist in combination with CC/rhFSH can prevent a premature LH surge and provide similar pregnancy rates to GnRH antagonist MDP with a fewer dose and days

of rhFSH in patients undergoing COS/IUI. Therefore, soft stimulation protocol can be considered as a first-line therapeutic option in patient-friendly COS/IUI program.

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= **Abstract** =

Objective: To evaluate the effectiveness of soft stimulation protocol using GnRH antagonist/clomiphene citrate (CC)/recombinant FSH (rFSH) in patients undergoing controlled ovarian stimulation (COS) with intrauterine insemination (IUI), compared with GnRH antagonist multiple dose protocol (MDP) using GnRH antagonist/rFSH.

Methods: Eighty infertile women were randomized to soft stimulation protocol group (n=40) or GnRH antagonist MDP group (n=40). In both groups, IUI was performed 36~40 hours after hCG injection. Statistical analysis was performed using Student's *t*-test, χ^2 test or Fisher's exact test as appropriate.

Results: Total dose and days of rFSH required for COS were significantly fewer in soft stimulation protocol group ($p<0.001$, $p<0.001$). A premature LH surge did not occur in any patients of both groups. Clinical pregnancy rate per cycle was similar between the two groups.

Conclusion: Soft stimulation protocol provides comparable pregnancy rates to GnRH antagonist MDP despite fewer total dose and days of rFSH, and so can become one of the patient-friendly, cost-effective alternatives for infertile patients undergoing COS with IUI.

Key Words: GnRH antagonist, Soft stimulation protocol, Controlled ovarian stimulation, Intrauterine insemination