Impact of controlled ovarian hyperstimulation protocols on the outcomes of assisted reproductıon cycles

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Abstract

Objective:
The objective of the present study is to determine the possible differences of controlled ovarian hyperstimulation (COH) regimens in assisted reproduction cycles. A total of 790 patients undergoing COH for assisted reproduction.
Materials and methods: The study is designed as a retrospective study in an assisted conception unit of a university hospital. The patient information including COH regimens, serum estradiol measurement, transvaginal sonographic scanning for ovarian follicles, oocyte retreival, and embryo transfer were recorded from the patient files retrospectively. The main outcome measure was clinical pregnancy rate.

Results:
Of the cycles with embryo transfer, the clinical pregnancy rates were 17.6%, 20.3% and 12.2% in urinary FSH and hMG, urinary FSH and recombinant FSH groups, respectively. This difference is not statistically significant ($p>0.05$). In the subgroup of short-course of treatment with a gonadotropin-releasing hormone agonist of urinary FSH only group, number of developing oocytes were found to be significantly higher and total dose of gonadotropin administered found to be lower. No significant differences were found with regard to other parameters.

Conclusion(s):
In terms of the clinical pregnancy rate, no significant differences between the stimulation regimens can be stated.

Key words:
IVF/ICSI, hMG, recombinant FSH

Introduction

Folliculogenesis and oocyte maturation are extremely complex processes that are dependent on an integration of cellular and endocrine mechanisms. The gonadotropic hormones, follicle stimulating hormone (FSH) and luteinizing hormone (LH), play a critical role in the growth of ovarian follicles. The final maturation of ovarian follicles begins approximately 85 days before ovulation (1,2). The follicles start to grow more rapidly in the luteal phase of the cycle preceding ovulation, the so-called gonadotropin-regulated growth phase. The selective rise in FSH levels that occurs during the luteal-follicular transition is a potent stimulus for follicle recruitment, and several early antral follicles begin to enlarge in this phase of the cycle. Further, FSH also stimulates estrogen production from granulosa cells through the induction of the aromatase system that catalyzes androgen conversion into estrogens. The role of LH in folliculogenesis is more complex. Theca cells constitutionally contain LH receptors; LH is capable of stimulating androgen substrate production from theca cells since fetal life. In addition to acting as a substrate for granulosa cell estrogen production, androgen may be involved in the development of follicle atresia (3).

Whereas human menopausal gonadotropin (hMG) was the only urinary-derived gonadotropin available until the late 1970s, purified FSH (with <1% LH contamination) and highly purified FSH (with <0.1% LH contamination) later became the other therapeutic options for controlled ovarian hyperstimulation. The most recent addition to this group of gonadotropins has been recombinant human FSH, which is completely devoid of LH activity. Controlled ovarian hyperstimulation regimens for assisted reproduction have been complicated further since the mid-1980s by the introduction of gonadotropin releasing hormone (GnRH) analogs. The key rationale for the use of GnRH agonists is the prevention of the untimely LH surge

that causes premature ovulation and follicle luteinization (4). In addition, it was found that long GnRH agonist regimens (ie, those started in the midluteal phase of the cycle preceding ovulation induction, or before) are associated with easier patient scheduling, greater follicle yield, and overall better clinical results. Long GnRH agonist regimens generally are characterized by low follicular phase LH levels, although the degree of pituitary suppression also is related to the dose and the route of administration.
The aim of the present study is to determine the possible differences of controlled ovarian hyperstimulation protocols in assisted reproduction cycles.

Materials and Methods

In this study, a total of 790 patients attending the assisted reproduction program at the Family Planning and Infertility Research and Treatment Center, Ege University, Izmir, Turkey were recruited retrospectively. Treatment with urinary FSH and hMG were used for 363 patients (363 cycles), urinary FSH only for 256 patients (256 cycles) and recombinant FSH for 171 patients (171 cycles). The groups were further divided into subgroups of short- or long-course treatment with a gonadotropin-releasing hormone agonist.

In long protocol, pituitary desensitization was started in the previous luteal phase with daily administration of triptorelin (Decapaptyl®, Ferring, Kiel, Germany). In short protocol, pituitary desensitization was started just before or simultaneously with the initiation of gonadotropin stimulation in the follicular phase with daily administration of triptorelin (Decapaptyl®, Ferring, Kiel, Germany). If the serum estradiol concentrations were <70 pg/mL and transvaginal sonography revealed no ovarian cyst >15 mm in diameter, controlled ovulation hyperstimulation with hMG (Pergonal®, Serono, Aubonne, Switzerland; Humegon®, Organon, Oss, Netherlands), urinary FSH (Metrodin®, Serono, Aubonne, Switzerland), recombinant FSH (Puregon®, Organon, Oss, Netherland or Gonal F®, Serono, Aubonne, Switzerland) was commenced. Meanwhile, triptorelin 0.1 mg/day s.c. was continued until the day of hCG administration.

The dose of gonadotropin hormone was individualized according to patient's age, baseline hormone concentrations, and previous stimulation history or response to stimulation. Cycles were monitored by transvaginal sonography (Kretz, Combison 310, 5 MHz transvaginal probe, Zipf, Austria) and serum estradiol levels. Follicular maturation was completed by the administration of 10.000 IU hCG (Pregnyl® 5000 IU, Organon; Profasi® 2000 IU, Serono, Bari, Italy). Endometrial thickness was measured at the uterine fundus in longitudinal axis by transvaginal sonography. Oocyte retrieval was performed using transvaginal sonographic guidance 36 hour after hCG administration. IVF/ICSI procedure was accomplished as described previously (5).

Luteal phase support was provided by administering progesterone vaginal suppositories (Utrogestan®, Iscovesco, Paris, France) and hCG (1500-2000 IU) administration on days +1, +4, +7 and +9 after embryo transfer. A clinical pregnancy was defined when serum hCG concentrations reached >1000 IU/mL and intrauterine gestational sac with fetal heartbeat was detected by transvaginal sonography.

Clinical pregnancy rate, total dose of gonadotropin administered, number of developing oocytes, number of oocytes retrieved, number of metaphase II oocytes, endometrial thickness and maximum estradiol levels at the day of (human chorionic gonadotropin) hCG administration were compared between the groups and subgroups.

Commercially available software (Statistical package for Social Sciences for Windows, release 10.0) was used for the analysis of data. The groups were compared with one-way analysis of variance using the post hoc test of Scheffe. Kruskal-Wallis test was used to compare the means when the Levene's test was found to be significant. A p value <0.05 was considered significant. The percentages were compared with chi-square test.

Results

Of the cycles with embryo transfer, the clinical pregnancy rates were 17.6%, 20.3% and 12.2% in urinary FSH and hMG, urinary FSH and recombinant FSH groups, respectively. This difference is not statistically significant (p>0.05). In the subgroup of short-course of treatment with a gonadotropin-releasing hormone agonist of urinary FSH only group, number of developing oocytes were found to be significantly higher and total dose of gonadotropin administered found to be lower. No significant differences were found with regard to other parameters (Table 1-4).

Discussion

Most of the gonadotropin regimens used in assisted reproduction are administered to women with normal ovulation with the goal of producing multiple follicles. Most patients undergoing IVF/ICSI also receive concomitant GnRH analogs. The low endogenous LH levels achieved with GnRH analogs in some cases may amplify the differences

in treatment outcome seen with the use of hMG and FSH preparations (6). Most studies (7-9) did not identify any substantial differences in the use of different types of exogenous gonadotropins in patients undergoing assisted reproduction. Although there appeared to be a trend toward the attainment of more oocytes and embryos with purified FSH, and more immature oocytes were aspirated with hMG, pregnancy rates did not differ.

Devroey et al (10) found no significant differences in drug doses, follicle and oocyte numbers, preovulatory estradiol levels, or pregnancy rates in 158 women who were given hMG or purified FSH without GnRH agonist suppression. Balasch et al (11) treated two groups of leuprorelin-suppressed women: in 188 patients, purified FSH alone was compared with purified FSH supplemented with hMG, whereas in 252 patients, higly purified FSH alone was compared with highly purified FSH supplemented with hMG. No differences in the number of gonadotropin ampules, the duration of stimulation, preovulatory estradiol levels, follicle and oocyte numbers, or pregnancy rates were identified. Imthurn et al (12) compared highly purified FSH with hMG in 76 patients undergoing a short GnRH agonist regimen and found comparable duration of stimulation, number and maturity of oocytes, and fertilization, cleavage and pregnancy rates.

Daya et al (13) treated 232 patients with a short GnRH agonist regimen and different menotropins. They found that fertilization rates were better with purified FSH but pregnancy rates were similar to those obtained with hMG. The same group (14) also reported the results of a meta-analysis that assessed differences between the use of hMG and purified FSH in eight studies in which they found that the use of purified FSH was associated with higher pregnancy rates.

Mercan et al (15) treated 357 patients with purified FSH either alone or in combination with hMG and found a significantly higher pregnancy rate per transfer in the purified FSH-only group. Nevertheless, the numbers of drug ampules and days of stimulation required, preovulatory estradiol levels, numbers and maturity levels of oocytes retrieved, and pregnancy rates per attempt and per retrieval were not different in the two treatment groups. Westergaard et al (16) compared stimulation with hMG to stimulation with highly purified FSH in 218 patients who underwent a long GnRH agonist protocol. The drug doses, duration of treatment, numbers of oocytes, and pregnancy, implantation, and abortion rates were comparable in the treatment groups, but the hMG group had a higher fertilizaiton rate. Strehler et al (17) investigated the differences between recombinant FSH and hMG for ovarian stimulation in IVF/ICSI cycles. Of the cycles with embryo transfer, the pregnancy rates were 30.1% and 32.3% in the recombinant FSH and the hMG groups, respectively ($p=0.798$). Treatment with recombinant FSH resulted in a significantly higher number of recovered oocytes compared with the hMG group but also associated with a higher number of ampules needed to reach the criterion for hCG administration.

In the present study, of the cycles with embryo transfer, the clinical pregnancy rates were 17.6%, 20.3% and 12.2% in urinary FSH and hMG, urinary FSH and recombinant FSH groups, respectively. This difference is not statistically significant ($p>0.05$). In the subgroup of short-course of treatment with a gonadotropin-releasing hormone agonist of urinary FSH only group, number of developing oocytes were found to be significantly higher and total dose of gonadotropin administered found to be lower. No significant differences were found with regard to other parameters.

In conclusion, in terms of the clinical pregnancy rate, no significant differences between the stimulation regimens can be stated

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Table 1
IVF/ICSI outcomes in cycles with embryo transfer

Groups	Age	Maximum estradiol level (pg/mL)	Endometrial Thickness (mm)	Number of developing follicles	Number of oocytes retrieved	Number of metaphase II oocytes	Number of ampules used
uFSH and hMG	33.6±4.5 (n=363)	1611±1144 (n=363)	13.5±2.3 (n=363)	6.3±2.9 (n=363)	6.8±5.7 (n=357)	4.9±3.7 (n=357)	40.7±14.3 (n=363)
uFSH	32.5±4.5 (n=256)	1748±1232 (n=256)	12.8±2.3 (n=256)	6.9±2.8 (n=256)	8.7±6.2 (n=255)	6.3±4.3 (n=255)	37.0±38.4 (n=256)
rFSH	35.5±4.3 (n=171)	1332±1085 (n=171)	12.8±7.1 (n=171)	5.2±2.8 (n=171)	6.2±5.7 (n=168)	4.5±4.1 (n=168)	46.5±19.7 (n=171)
P value	0.001	0.001	0.001*	0.01	0.001*	0.001*	0,001

*Kruskal-Wallis test was used to compare the means because the Levene's test was found to be significant ($p<0.05$).
uFSH: Urinary FSH, rFSH: Recombinant FSH

Table 2
IVF/ICSI outcomes in cycles with embryo transfer in short-protocol group

Groups	Age	Maximum estradiol level (pg/mL)	Endometrial Thickness (mm)	Number of developing follicles	Number of oocytes retrieved	Number of metaphase II oocytes	Number of ampules used
uFSH and hMG	35.8±3.5 (n=226)	1534±119 (n=226)	13.1±2.3 (n=226)	5.6±3.0 (n=226)[a]	5.0±4.1 (n=221)	3.9±3.1 (n=221)	42.7±15.7 (n=221)[a]
uFSH	36±3.1 (n=107)	1787±1396 (n=107)[a]	12.6±2.3 (n=107)	5.6±2.7 (n=107)	6.2±5.2 (n=106)	4.7±3.7 (n=105)	39.1±16.2 (n=107)[a]
rFSH	36.4±3.8 (n=145)	1281±1092 (n=145)"	12.8±7.6 (n=145)	4.9±2.7 (n=145)[a]	5.5±5.3 (n=142)	4.0±3.8 (n=142)	47.7±19.6 (n=145)[a]
P value	0.37	0.003*	0.62	0.03	0.26*	0.13	

*Kruskal-Wallis test was used to compare the means because the Levene's test was found to be significant ($p<0.05$).
[a]The two groups were significantly different with post hoc comparasion.
uFSH: Urinary FSH, rFSH: Recombinant FSH

Table 3
IVF/ICSI outcomes in cycles with embryo transfer in long-protocol group

Groups	Age	Maximum estradiol level (pg/mL)	Endometrial Thickness (mm)	Number of developing follicles	Number of oocytes retrieved	Number of metaphase II oocytes	Number of ampules used
uFSH and hMG	30.0±3.7 (n=137)	1738±1048 (n=137)	14.1±2.2 (n=137)[a]	7.4±2.6 (n=137)	9.7±6.6 (n=136)	6.5±4.1 (n=136)	37.2±10.8 (n=137)
uFSH	30.0±3.6 (n=149)	1721±1104 (n=149)	13.0±2.4 (n=149)[a]	7.8±2.5 (n=149)	10.4±6.3 (n=149)	7.5±4.4 (n=149)	35.5±48.5 (n=149)
rFSH	30.9±4.3 (n=26)	1618±1016 (n=26)	13.1±2.3 (n=26)	7.1±2.5 (n=26)	10.3±6.4 (n=26)	7.0±4.8 (n=26)	39.8±19.5 (n=26)
P value	0.51	0.87	0.001	0.35	0.63	0.16	0.82

*Kruskal-Wallis test was used to compare the means because the Levene's test was found to be significant ($p<0.05$).
uFSH: Urinary FSH, rFSH: Recombinant FSH

Table 4
Clinical pregnancy rates in short and long-protocol groups

Groups	Clinical pregnancy rates		
	Total group (%)	Short-protocol group (%)	Long-protocol group (%)
uFSH and hMG	17.6	12.3	26.2
uFSH	20.3	8.4	28.8
rFSH	12.2	11.7	15.3

uFSH: Urinary FSH, rFSH: Recombinant FSH