Comparision of reproductive outcome of the women with hypogonadotropic hypogonadism and tubal factor infertility

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Summary

Objective: To evaluate the outcome of women with hypogonadotropic hypogonadism (HH) undergoing in-vitro fertilization (IVF). *Materials and Methods:* Data from 13 cycles of ten hypogonadotropic patients treated with in vitro fertilization from the period January 2006 to January 2008 were analyzed and compared with treatment results from 20 patients with tubal factor infertility (TI). All patients underwent ovarian hyperstimulation for IVF/ICSI at the same center. HH patients initiated the treatment by receiving daily injections of hMG. The patients in the control group were given the same dosage of recombinant FSH. *Results:* Demographic characteristics of the patients were comparable. Mean duration of stimulation was 13 days in the HH group and nine days in the TI group; the difference was significant ($p < 0.001$). Significantly more gonadotropins were used for the stimulation of HH patients ($p < 0.05$). Peak serum E2 concentration was found to be higher in the TI group. We evaluated the proportion of metaphase II (MII) oocytes to total oocytes retrieved in HH patients and found the number was similar to the TI group. Despite that fertilization and implantation rates were similar in both groups, the cancellation rate was higher in the HH group (23.1% vs 0). However pregnancy and live birth rates were similar. *Conclusions:* The present study showed that HH women undergoing IVF/ICSI are good responders. The treatment of HH women with IVF/ICSI did not increase multiple pregnancies and OHSS rates over the TI group.

Key words: Hypogonadotropic hypogonadism; In vitro fertilization; Treatment outcome; Tubal factor infertility.

Introduction

There are four groups of patients with suspected anovulatory disorders. These groups are classified as hypogonadotrophic, normogonadotrophic, hypergonadotrophic and hyperprolactinemic anovulation. Hypogonadotropic anovulation is called as Class I by the World Health Organization (WHO) [1].

Because of the complexity and patient intolerance of pulsatile GnRH, gonadotrophin therapy is primarily a substitute treatment. Both FSH and LH are required to achieve full maturation of the follicles in women with anovulatory disorders. In spite of recent developments in recombinant technology, a urinary extract containing a fixed combination of LH and FSH, human menopausal gonadotrophin (hMG) has been the most efficient drug for ovulation induction in patients with hypogonagotrophic hypogonadism (HH) [2].

In this study, cycle characteristics and assisted reproductive outcomes of HH patients were assessed and compared with women who had undergone IVF/ICSI (in vitro fertilization/intacytoplasmic sperm injection) because of tubal factor infertility.

Materials and Methods

Data from 13 cycles of ten HH patients treated with in vitro fertilization in the period from January 2006 to January 2008 were analyzed and compared with treatment results of 20 patients with tubal factor infertility (TI).

Seven of ten HH patients were referred to us with their confirmed diagnoses elsewhere, but three were diagnosed in our center. All of the HH patients had a history of primary/secondary amenorrhea and no withdrawal bleeding after a progesterone challenge. FSH and LH levels of all the HH patients were under 2 mIU/ml and estradiol was under 20 pg/ml. Their serum thyroid-stimulating hormone (TSH) and prolactin levels were normal. All of the HH patients presented with atrophic endometium (endometrial thickness < 5 mm). A normal hypophyseal appearance excluded empty sella syndrome.

A control group treated at the same center was comprised of 20 infertile patients who were diagnosed as having tubal factor infertility (TI). Their current hysterosalpingography or latest laparoscopic procedure revealed blocked tubal patency, otherwise their hormonal status and menstrual cycles were normal.

In both groups the patient husband's sperm parameters were within normal limits (concentration ≥ /20 million/ml, ≥ /50% total motility, and ≥ 30% normal forms (WHO). Patients who had pathological results were eliminated and not included in the study analysis.

hMG (75 IU FSH + 75 IU LH, Menogon-Ferring, Switzerland) was started in all HH patients (225-450 IU/day) and response was assessed with the findings of transvaginal ultrasonography (TVS) and estradiol level. The patients were not given any antagonist medication because a premature LH surge is not usual in these patients. When leading follicles reached 18-20 mm in diameter, 10,000 IU hCG (Pregnyl- Schering Plough/Organon) was administered and TVS-guided oocyte retrieval was performed 36 hours later. ICSI was performed in all oocytes. On days 2-5 after oocyte retrieval, depending on the number of good quality embryos and patient age, two to three embryos were transferred.

Recombinant FSH (Gonal F- Serono/Merck Laboratories) was given to TI patients. The dosage was adjusted according to the patient status (225-450 IU/day) and response was assessed with TVS and estradiol level. When at least one leading follicle

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reached 14 mm in size, a GnRH antagonist of 0.25 mg daily injection (cetrotide- Serono/Merck Laboratories) was added to the treatment and continued up to the day of hCG administration. When leading follicles reached 18-20 mm in diameter, 10,000 IU hCG (Pregnyl-Organon/Shering Plough) was given and TVS-guided oocyte retrieval was performed 36 hours later. ICSI was performed on all oocytes. On days 2-5 after oocyte retrieval, depending on the number of good quality embryos and patient age, two to three embryos were transferred.

The luteal phase was supplemented with 50 mg of progesterone in oil IM (Progynex- Kocak) daily starting on the day after oocyte retrieval, and was continued until a negative pregnancy test was obtained, or if pregnancy occurred, with 8% vaginal progesterone (Crinone- Serono/Merck Laboratories) daily until week 12 of gestation in both groups. Pregnancy was confirmed by a positive blood test for β-hCG 12 days after the transfer procedure. Ongoing pregnancy was determined if the pregnancy continued after 12 weeks.

Data were analyzed using the SPSS version 11.5 for Windows (SPSS Inc., USA). The Mann-Whitney U and chi-square tests were used for statistical analysis, where appropriate; $p \leq 0.05$ was considered significant.

Results

The IVF/ICSI cyle outcomes of 13 HH patients were compared to 20 TI patients. All patients underwent treatment cycles for IVF/ICSI at the same center. Demograpic characteristics of the patients were comparable (Table 1). In spite of no differences between estradiol levels of the two groups, FSH and LH levels of the HH patients were statistically lower than the others.

Table 1. — *Demograhic characteristics of the HH and TI patients*.

	HH n = 10 Mean ± SD	TI n = 20 Mean ± SD	*p*
Age (years)	31.3 ± 5.6	31.5 ± 4.7	NS
Duration of infertility (years)	6.8 ± 3.6	6.8 ± 3.2	NS
Weight (kg)	61.6 ± 9.6	65.8 ± 8.7	NS
BMI (kg/m^2)	25.3 ± 3.1	25.8 ± 3.1	NS
FSH (mIU/ml)	0.7 ± 0.6	6.7 ± 1.3	< 0.001
LH (mIU/ml)	1.4 ± 2.2	6.7 ± 1.3	< 0.001
E2 (pg/dl)	30.4 ± 8.6	33.4 ± 9.4	NS

BMI: Body mass index; E_2: estradiol.

Mean duration of stimulation was 13 days in the HH group and nine days in the TI group and the difference was significant ($p < 0.001$). Total gonadotropin consumption in the HH group was significantly larger than for TI (3630 IU vs 2500 IU). Peak serum estradiol level was significantly lower in the HH group (1044 vs 2500). There were no significant differences from the stand-point of totally retrieved oocyte number and total MII oocyte count (Table 2).

The fertilization rates were 81.9% and 72.9% in the HH and TI groups, respectively, and the difference was not statistically significant. Cleavage and grade 1 embryo rates were not different. Totally transferred embryo numbers were 2.6 and 2.8, respectively. Implantation rate was higher in the TI group but the difference was not significant (52.5% vs 38.3%). Only three cycles were cancelled. All of them belonged to the HH group and two were cancelled due to impaired follicular response, while the other one was cancelled because of failure to achieve an oocyte.

Table 2. — *Comparision of the ART cycle characteristics of the two groups*.

	HH n = 13 Mean ± SD	TI n = 20 Mean ± SD	*p*
Duration of stimulation (day)	13.0 ± 2.4	9.2 ± 0.8	< 0.001
Total gonadotropins used (IU)	3630 ± 1685	2501 ± 536	< 0.05
Peak E2 (pg/ml)	1044 ± 613	2500 ± 245	< 0.001
Total Oocyte (n)	6.5 ± 3.1	7.7 ± 3.6	NS
MII Oocyte (n)	5.9 ± 2.0	5.4 ± 2.7	NS
FR (%)	81.9 ± 14.3	72.9 ± 19.5	NS
Transfered embryo number (n)	2.6 ± 0.8	2.8 ± 0.5	NS
IR (%)	38.3 (24.8)	52.5 (25.3)	NS
CR (%)	3 (23.1)	0	0.05
PR (%)	8 (80)	14 (70)	NS
Ongoing pregnancy (%)	2 (25)	2 (14.3)	NS
Missed abortion rate (%)	2 (25)	3 (21.4)	NS
Ectopic pregnancy (%)	0	1 (7.1)	NS
LBR (%)	4 (50)	8 (57.1)	NS

E_2: Estradiol. MII: Metaphase II. FR: Fertilization rate. IR: Implantation rate. CR: Cancellation rate. PR: Pregnancy rate. LBR: Live birth rate.

Eight of 13 hypogonadotropic patients (80%) and 14 of 20 tubal factor patients (70%) became pregnant with no significant difference. At the time of this study two pregnancies from the HH group and two pregnancies from the TI group were continuing without any complications. The abortion rate was 25% and 21.4% in the HH and TI groups, respectively. Live birth rate was 50% and 57.1% in the HH and TI groups, respectively.

Discussion

This study has confirmed that HH patients undergoing ICSI cycles have comparable outcomes and usually are good responders. We had a small number of HH women and although we are a tertiary center only 13 patients were admitted to our center during two years. Thus, we believe that the cycle outcomes of these women deserved a comparision with other good responders (group TI), considering the rareness.

In spite of a good adjustment between the two groups – according to the general demographic factors – the duration of stimulation was longer and the consumption of gonadotropins was higher in HH patients. It is known that a large amount of gonadotropin usage has a detrimental effect on oocyte and embryo quality. Kumbak *et al*. pointed out that this high gonadotropin usage did not adversely affect the oocyte yield in HH patients [3]. They compared 27 HH patient cycles with 39 unexplained infertility cases. MII oocyte numbers were the same but the fertilization rate was higher in the HH group. They found no significant difference between the groups with regard to the ratio of grade 1 embryos. High fertilization and implantation rates were found in the HH group. They concluded that the extreme dosages of gonadotropins

used in the HH patients were not detrimental to the oocytes and embryos. "The need of higher gonadotropin usage in regard to silent ovaries, which need to be activated before follicular response is achieved" was their explanation. We agree with their point of view – the need of large doses may be due to the long duration of the hypoestrogenic state.

hMG was used for the stimulation of the HH patients in this study. Ovulation induction for HH patients requires concomitant administration of both FSH and LH to achieve optimal therapeutic results. According to current concepts of the roles of FSH and LH in folliculogenesis, follicular responsiveness to FSH and LH is developmentally regulated [4]. LH is necessary for theca cell androgen synthesis which serves as a substrate for the aromatase enzyme to be converted into estrogen by granulosa cells. Once ovarian follicles reach a diameter of 10-12 mm, their granulosa cells begin to express LH receptors and become receptive to LH stimulation. In other words, while granulosa cells from early antral follicles are only responsive to FSH, granulosa cells from FSH-stimulated follicles are responsive to either FSH or LH. In assisted reproductive therapy (ART) cycles, usually endogenous LH activity is enough for follicular development and only FSH can provide an adequate response. HH patients need both FSH and LH for ovulation induction. The treatment with urinary FSH or recombinant FSH alone may induce follicular development but presents low fertilization rates [5].

The ovulation induction of hypogonadotropic women with urinary FSH or recombinant FSH alone induces follicular development but it causes low oocyte and embryo yield. Because of that we used hMG. In contrast to our treatment, Burgues and the Spanish Collaborative Group on female hypogonadotrophic hypogonadism concluded that combined rFSH and rLH treatment induce follicular growth, ovulation and pregnancy in a good proportion of hypogonadotrophic hypogonadal patients [6]. hMG was the only source of LH at one time, however today many case reports and case series have suggested that rLH is effective and safe for the treatment of HH patients. We used hMG because of its cost effectiveness. Using rFSH with rLH is more expensive for patients when compared to hMG. The main disadvantage of hMG is its administration route. Unlike recombinant preparations, hMG unfortunately can be used only intramuscularly.

The major drawback to our study was that we compared two different stimulation protocols for two groups. TI women are considered to be ideal controls in an IVF/ICSI setting. We used analogues for these patients but there is no need to add analogues in the treatment of HH patients.

There has been some controversy about pregnancy loss rate in HH patients after ART treatment. Previously some studies showed pregnancy losses of 22% and 27% in HH patients undergoing ovulation induction [7, 8]. Our pregnancy loss rate was 25% in the HH group. In contrast to our results, Ulug *et al*. reported an 8% pregnancy loss in their series [9].

Multiple pregnancy and ovarian hyperstimulation syndrome (OHSS) are the most common serious complications of ART. None of our patients showed severe or moderate OHSS in either group. Only one triple pregnancy was achieved in TI patients. The twin pregnancy rate was 37.5% and 25% in the HH and TI groups, respectively. Based on our small number of cases we can easily say that multiple pregnancy and OHSS were not major concerns in the treatment of HH. Moreover, the transferred embryo number should not exceed three in HH patients.

In conclusion, the outcomes of ART treatments in HH patients were comparable to women with TI. Ovulation induction for HH patients requires concomitant administration of both FSH and LH to achieve optimal therapeutic results. Multiple pregnancy and OHSS rates were lower than the general population of infertile patients. Optimization of the treatment of infertility in HH patients still needs a large case series and well-randomized controlled trials.

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