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Assisted reproductive technique outcomes in hypogonadotropic hypogonadism women

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BACKGROUND AND OBJECTIVES: To evaluate the outcomes of using in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI cycle) techniques in hypogonadotropic hypogonadism (HH) women and comparing them to women with tubal factor infertility.

DESIGN AND SETTINGS: Retrospective cohort study in Royan Institute, Iran.

PATIENTS AND METHODS: Data from 81 HH patients treated with IVF/ICSI in the period from early 2009 until the end of 2010 were analyzed and compared with treatment results from 89 patients with tubal factor infertility. Moreover, data from the HH patients were analyzed with respect to the age factor. P value <.05 was considered statistically significant. The main outcome measures were implantation, fertilization, pregnancy, and live birth rates.

RESULTS: Despite a higher fertilization rate and higher number of grade A/B embryos transferred in the tubal factor group, the implantation, pregnancy, and live birth rates were found to be similar between the 2 groups (P=.3, P=.1, P=.1, respectively). When the HH patients were evaluated according to the age factor, no significant difference was found regarding outcome parameters (P=.2).

CONCLUSIONS: HH women that were treated with IVF/ICSI cycles seem to have a sound potential for pregnancy, even in advanced age patients.

Hypogonadotropic hypogonadism (HH) is the group I of ovulation disorders according to the World Health Organization (WHO) classification system.[1] This disorder is manifested by primary or secondary amenorrhea, and low or normal serum gonadotropins.[2,3] HH occurs most frequently in idiopathic form, but it can also occur as part of congenital syndromes.[4] This disorder usually is associated with extreme physical, nutritional, or emotional stress, regardless of the cause, the patients suffer from delayed puberty, osteopenia, and infertility. In the case of infertility, ovarian stimulation with gonadotropins or pulsatile gonadotropin-releasing hormone (GnRH) analogues is widely used.[4] A few articles have studied the characteristics of induction of ovulation by gonadotropins or pulsatile GnRH analogue cycles.[1,5-7] HH is a rare cause of infertility only affecting a small number of patients. Furthermore, there is a little data on the cycle characteristics. This study reports a retrospective analysis performed on the HH patients conducted in the Royan Institute and compares the results of this group with those of the patients having tubal factor infertility (TF) during the same time period.

PATIENTS AND METHODS

This retrospective cohort study was performed in the infertility department of the Royan Institute Research Center between January 2009 and December 2010. The data of 81 HH patients and 84 patients with TF, who had undertaken in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI), were evaluated. All the 81 patients with HH suffered from primary amenorrhea. The diagnosis of HH was based on the primary or secondary amenorrhea, absence of withdrawal bleeding following a progesterone challenge test, and normal or low level of gonadotropin. Pituitary magnetic resonance imaging (MRI) was undertaken for 78 patients, sella X ray imaging was done for 1 patient, and the rest had no imaging of the pituitary area. The MRI results demonstrated the following: 5 patients (6.2%) with empty sella, 6 patients with hypophyseal microadenoma, and the rest were normal. The hypophyseal axis was checked by measuring TSH, cortisol, and prolactin (PRL), which showed no other abnormalities. All patients experienced previous multiple ovulation induction with or without intrauterine insemination (IUI) or assisted reproductive techniques (ART) cycles. The HH patients did not have any other infertility factors. As the control group, we included all the women with TF who had undergone IVF/ICSI during the same period. All patients with TF had both tubes occluded in hysterosalpingography (HSG) with regular cycles; however, the patients with hydrosalpinges, endometrioma, or tuberculosis were excluded from this study. Both groups had a normal uterine cavity with HSG or hysteroscopy. The ethics committee of Royan Institute approved the collection of data. A written informed consent was obtained from all patients for using the data for scientific research at the first visit. The HH patients received at least 2 months hormonal replacement therapy (HRT) and then initiated the super ovulation on the second or third day of menstruation after receiving the HRT. They received the daily human menopausal gonadotropin (HMG) preparation: Menopur (75 IU Ferring, the Netherlands) or Menogon (75 IU Ferring, Copenhagen, Denmark), or Merional (75 IU IBSA, Switzerland) with or without Gonal F (75 IU Serono Laboratories Ltd, Geneva, Switzerland). The mean number of gonadotropin ampoules for starting the superovulation was 4.2 (1.4). The monitoring was performed using ultrasound, and the gonadotropin dose was adjusted according to the ovarian response. The mean of the maximum number of gonadotropin per day was 5.4 (1.9). In the TF group, a standard long protocol was performed as described in other studies.[8] Ovulation was triggered with 10 000 IU human chorionic gonadotropin (hCG; choriomon; IBSA, Switzerland), when at least 2 follicles reached 18 mm, in both groups, 34 to 36 hours later the oocyte retrieval was performed. IVF or ICSI procedures accomplished as described in other studies.[9] The embryos were classified on the basis of morphological criteria as described previously in the study conducted by Hill et al.[10] A total of 2 to 3 days after the ovum pick up, the embryo transfer was performed. In the TF group, the uteal phase was supported with 400 mg of vaginal progesterone (Aburaihan Co., Tehran, Iran) twice a day. In the HH group, the luteal phase was supported with 400 mg of vaginal progesterone and 2 mg oral of estradiol valerate (Aburaihan co., Tehran, Iran) twice a day in all the patients. Beta hCG was measured 15 days later, and the luteal phase support was continued for 12 weeks of gestation if conception had occurred. Clinical pregnancy was defined as a positive pregnancy test followed by the presence of gestational sac on transvaginal ultrasound 4 weeks after the embryo transfer. A statistical analysis was performed using SPSS, version 16, (SPSS Inc., Chicago, Illinois) and Stata/SE 11.0 package. Chi-square test and *t*-test were performed to evaluate the statistical differences between the variables. Ordinal logistic regression was used to examine the independent variables affecting clinical pregnancy rate (PR). $P<.05$ was considered statistically significant.

RESULTS

Table 1 shows demographic characteristics of patients in the 2 groups. The differences between the means of the 2 groups regarding age, body mass index (BMI), infertility duration, PRL level, esteradiol level, and thyrotropin (TSH) level were not significant; however, the HH patients had significantly lower follicle-stimulating hormone (FSH) and luteinizing hormone levels than the TF patients. In addition, they had more previous treatment cycles and primary infertility cases in comparison to the TF group patients. In the HH group, the cycles of 3 patients (3.7%) were canceled due to no ovarian response; 2 patients (2.5%) had no oocytes and 2 patients (2.5%) had no embryos for transfer after the oocyte retrieval. In 9 patients (11.1%), all embryos were frozen; these patients were elected for embryo freeze transfer later. This decision was made for 8 cases due to the following two reasons: (1) the risk of ovarian hyperstimulation syndrome (OHSS) and (2) a thin endometrium (endometrial thickness ≤ 7 mm), therefore the embryo transfer was undertaken for 65 patients. The duration of ovulation induction in the HH group was significantly longer than in the TF patients. Moreover, a significantly larger amount of gonadotropin was needed to stimulate the ovaries of these patients ($P<.001$). No significant differences were found between the 2 groups in terms of the total number of oocytes retrieved, metaphase II (MII) oocytes, and total number of embryos transferred. While the number of grade A and B embryos transferred between the 2 groups was significantly different, the number of grade A and B embryos transferred to patients in the TF group was significantly higher. The endometrial thickness was measured on the day of hCG administration using transvaginal ultrasonography, and no significant difference was found between the 2 groups in this regard. (**Table 1**). ICSI or

Table 1. Demographic characteristics and cycle outcomes of 2 groups.

Variables	HH (n=81)	Tubal factor (n=84)	*P* value
Age (y)	33.5 (5.3)	32.8 (4.0)	.3
BMI (kg/m2) mean (SD)	26.1 (4.0)	26.2 (3.3)	.8
FSH level at second day of cycle mean (SD)	1.9 (0.9)	5.1 (3.3)	<.001
LH level at second day of cycle mean (SD)	1.0 (0.5)	5.4 (3.4)	<.001
TSH mean (SD)	2.6 (2.7)	4.5 (11.9)	.15
Esteradiol (pg/mL) mean (SD)	30.7 (24.8)	24.9 (29.3)	.17
Prolactin (ng/mL) mean (SD)	91 (143)	87 (141)	.86
Duration of infertility mean (SD)	8.9 (5.4)	7.5 (5.2)	.09
Type of infertility (N[%]) primary secondary	80 (98.8) 1 (1.2)	49 (58.2) 35 (41.8)	<.001
No. previous cycles	1.7 (1.9)	0.5 (0.6)	<.001
No. of total gonadotropins (75IU/amp)	64.6 (28.5)	30.2 (12.8)	<.001
Duration of gonadotropins (d)	13.8 (2.6)	10.4 (1.9)	<.001
No. of oocytes retrieved mean (SD)	8.3 (6)	9.5 (4.8)	.1
No. of MII oocytes mean (SD)	6.3 (4.7)	7.1 (4.3)	.2
No. of embryo transferred mean (SD)	2.2 (0.8)	2.4 (0.7)	.2
No. of grade A embryo transferred	1.1 (1.0)	1.6 (1.1)	.01
No. of grade B embryo transferred	1.0 (0.9)	2.0 (1.1)	<.001
Endometrial thickness at ET day mean (SD)	9.6 (2)	9.2 (1.6)	.1
No. of cycles with no embryo (%)	2 (2.5)	0	.06
No. of cycles with no oocyte (%)	2 (2.5)	0	.06
No. of cycles with no response to gonadotropins (%)	3 (3.7)	0	.05
No. of all freeze embryos cases (%)	9 (11.1)	2 (2.3)	.02
Fertilization rate mean (SD)	61.2(27.8)	77 (21.8)	.001
Implantation rate mean (SD)	40 (27.4)	48 (20)	.3
Clinical pregnancy rate/started cycle (fresh embryo transfer) (%)	14/72 (19.4)	24/82 (29.2)	.1
Twin pregnancy rate n (%)	4 (5.5)	6 (7.3)	.5
Live birth rate n (%)	11 (15.2)	20 (24.3)	.1

HH: Hypogonadotropic hypogonadism, FSH: follicle-stimulating hormone, LH: leuteinizing hormone, TSH: thyrotropin.

ICSI + IVF were performed in the HH and TF group patients and a fertilization rate (FR) of 61.2 (27.8) was achieved in the HH group, which was significantly lower than the rate obtained in the other group (P=.001). Despite FR being higher in the TF group patients (77% vs. 61%), the implantation, clinical pregnancy per transfer, multiple pregnancy, and ongoing PRs were similar in both groups. All multiple pregnancies in both groups were twins (**Table 1**).

The IVF/ICSI cycle characteristics were compared in 2 age ranges (≥35 years and <35). In the HH group the infertility duration, total number of gonadotropin ampoules, total retrieved oocytes, and number of MII oocytes were significantly different between 2 age

Table 2. Cycle characteristics of women in 2 groups according to the existence of advanced. Reproductive age (≥35 yr).

Variables	HH (n=81)		*P* value	Tubal factor (n=84)		*P* value
	≥35 y (n=37)	<35 y (n=44)		≥35 y (n=26)	<35 y (n=58)	
Age mean (SD)	38.2 (2.7)	29.5 (3.2)	<.001[a]	37.6 (2.1)	30.6 (2.4)	<.001
BMI mean (SD)	26.2 (4.3)	26.0 (3.7)	.8	26.9 (3.5)	26.0 (3.2)	.3
Infertility duration mean (SD)	12.1 (5.8)	6.2 (3.1)	<.001[a]	9.3 (6.0)	6.7 (4.6)	.05
No. previous cycles mean (SD)	2.1 (2.1)	1.4 (1.6)	.07	0.5 (0.7)	0.4 (0.6)	.8
No. of total gonadotropins (75IU/amp)	78.1 (27.7)	53.2 (24.0)	<.001[a]	39.5 (12.6)	26.0 (10.7)	<.001
Duration of gonadotropins (d)	13.6 (2)	13.6 (3.0)	.9	10.3 (1.8)	10.5 (1.9)	.5
No. of oocytes retrieved mean (SD)	6.4 (4.7)	9.8 (6.5)	.01[a]	8.8 (5.0)	9.8 (4.5)	.3
No. of MII oocytes mean (SD)	4.8 (4.3)	7.6 (4.8)	.007[a]	6.5 (47)	7.3 (4.0)	.4
No. of embryo transferred mean (SD)	2.3 (0.9)	2.2 (1.0)	.6	2.5 (0.9)	2.3 (0.6)	.2
ET day mean (SD)	2.4 (0.5)	2.3 (0.5)	.4	2.4 (0.4)	2.5 (0.5)	.2
No. of grade A embryo transferred mean (SD)	1.0 (0.9)	1.2 (1.0)	.4	1.6 (1.1)	1.5 (1.1)	.6
No. of grade B embryo transferred mean (SD)	1.1 (0.9)	0.9 (0.9)	.5	1.7 (1.3)	2.2 (1.0)	.1
Endometrial thickness at ET day mean (SD)	9.7 (2.0)	9.6 (2.0)	.8	8.9 (1.8)	9.4 (1.5)	.1
Cancellation rate n (%)[a]	4 (10.8)	12 (27.2)	.07	1 (3.8)	1 (1.7)	.6
No. of cycles with no response to gonadotropins n (%)	1 (2.7)	2 (4.5)	.6	0 (0)	0 (0)	-
Fertilization rate mean (SD)	56.8 (24.5)	68.2 (27)	.1	73.4 (23)	79.5 (21)	.2
Implantation rate mean (SD)	38.3 (33.3)	43 (15.2)	.7	44 (10)	49 (22)	.5
PR/ET n (%)	5/33 (15.1)	9/32 (28.1)	.2	2/25 (8)	22/57 (38.5)	.008
Live birth rate/ET (%)	5/33 (15.1)	6/32(18.7)	.9	2/25 (8)	18/57 (31.5)	.02[a]

BMI: body mass index, ET: embryo transferred, PR: pregnancy rate.

[a]The number of patients in which the embryo transfer was not performed in the present cycle

ranges; nevertheless, other characteristics and outcomes were similar (**Table 2**). The cycle characteristic in the TF group showed that the total gonadotropin consumption was significantly higher in aged woman. Also, older women had a significantly lower pregnancy rate per embryo transfer (PR/ET) compared to younger patients (P=.01) (**Table 2**).

Logistic regression was performed and all risk factors such as age, BMI, total number of gonadotropin ampoule, number of retrieved oocytes, number and grade of embryo transferred (ET) , endometrial thickness (mm), infertility duration, and type of gonadotropin consumption were included in the initial model. A stepwise backward elimination was used to choose the final model in which the number of ET was the only variable significantly associated with pregnancy (odds ratio: 2.6 and 95% confidence interval: 1.2- 5.7).

DISCUSSION

HH is one of uncommon etiologies for female infertility.[1] Gonadotropins and pulsatile GnRH are alternative therapies for replacing the absent endogenous hormones. However, HMG preparations were widely used and led in most cases to ovulation. The PR was reported as 25% to 30% after an average of 3 treatment cycles.[5,11]

There are only a few studies on ART characteristics in this rare condition. This study is one of the largest series of infertile women with HH (81 patients). In another study by Kumbak and Kahraman that compared the cycle characteristics of 27 patients with HH and 39 patients with unexplained infertility, a longer stimulation duration and higher gonadotropin consumption was observed, and despite transferring better embryos to an unexplained group, the implantation rate was better in HH, while the PR/ET was similar in both groups.[6] In a study by Yildirim et al, which was consistent with our results, 13 cycles with the HH patients were compared with 20 TF patients, and it was concluded that despite similar implantation., pregnancy, and live birth rates, the cancellation rate was higher in the HH group.[7] As expected, in agreement with previous studies the numbers of ampoules used in the HH patients were higher than in the control group. This may be due to the ovaries being dormant and needing to be woken up before the follicular response is achieved.[1,6] Because the usual predictors of the ovarian reserve (cycle day 3 FSH or the number of antral follicles) were not applicable in women with HH, we could not predict the response to treatment. Therefore, we started the ovarian stimulation with larger amounts of gonadotropins; therefore, the patients in the HH group were at a higher risk of OHSS. In the study conducted by Ulug et al, the mean number of retrieved oocytes, implantation, fertilization, pregnancy, and multiple PRs were not significantly different in comparison to the tubal group patients.[1] In the present study, the fertilization rate was lower in the HH group, and when the embryo quality was compared, a significant difference was found between the 2 groups in the ratio of grade A and B embryos transferred. The high dosage of gonadotropin used in the HH women might be having an adverse effect on the oocytes and embryos.[12,13] However, the implantation, clinical pregnancy, multiple pregnancy, and live birth rates did not show significant differences between the two groups. Higher numbers of previous cycles for HH patients probably indicated that these women had greater difficulty of achieving pregnancy, although most of the previous treatment cycles were IUI and had been done in other infertility centers. We compared the cycle characteristics in the existence of the advanced reproductive age. As the results indicate, the difference between the 2 age ranges in terms of PR was not significant in the HH group, but the number of oocytes retrieved and MII oocytes were significantly higher in the younger ones. Despite the PR almost doubled in the younger ones, the ratio (5 pregnant per 34 embryos transfer) versus (9 pregnant per 38 embryos transfer) was not significantly different. It could be due to the high rate of embryo freeze cases in younger ones. However, in the TF group, the pregnancy rate decreased in women with advanced age. These findings show that the HH patients with advanced age have a similar chance of pregnancy compared with younger women. This is in accordance with the study conducted by Kumbak and Kahraman suggesting that ovarian response and pregnancy may not be affected by age.[6]

The multivariate logistic regression analysis revealed that the number of embryos transferred was the strongest predictor of the treatment success in the HH group. Clinical PRs did not show any independent relation to other variables such as patient age, infertility duration, type of gonadotropin, or gonadotropin dosage used to start the stimulation. Also different types of the luteal phase support had no effect on the pregnancy success. The most important limitation of our study was its retrospective nature and inhomogeneous luteal phase support in the study population.

In conclusion, the HH women that were treated with IVF/ICSI cycles were found to have a sound potential for pregnancy, even with the coexistence of age factor.

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