Assisted reproductive technique outcomes in hypogonadotrophic 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.
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.9 Ovulation was triggered with 10000 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 utal 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
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

| 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       |
| Estriadiol (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 (88.8)  | 49 (58.2)           | <.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     |
| No. of cycles with no embryo (%)              | 13.8 (2.6) | 10.4 (1.9)          | <.001     |
| No. of oocytes retrieved (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 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.
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*             | 37.6 (2.1) | .8                      |
| BMI mean (SD)                          | 26.2 (4.3) | 26.0 (3.7) | .8                 | 26.9 (3.5) | 26.0 (3.2)              |
| Infertility duration mean (SD)         | 12.1 (5.8) | 6.2 (3.1) | <.001*             | 9.3 (6.0)  | .07                     |
| No. previous cycles mean (SD)          | 2.1 (2.1)  | 1.4 (1.6)  | .07                | 0.5 (0.7)  | 0.4 (0.6)               |
| No. of total gonadotropins (75IU/amp)  | 78.1 (27.7)| 53.2 (24.0)| <.001*             | 39.5 (12.6)| 26.0 (10.7)             |
| Duration of gonadotropins (d)          | 13.6 (2)   | 13.6 (3.0)| .9                 | 10.3 (1.8) | 10.5 (1.9)              |
| No. of oocytes retrieved mean (SD)     | 6.4 (4.7)  | 9.8 (6.5)  | .01*               | 8.8 (5.0)  | 9.8 (4.5)               |
| No. of MII oocytes mean (SD)           | 4.8 (4.3)  | 7.6 (4.8)  | .007*              | 6.5 (47)   | 7.3 (4.0)               |
| No. of embryo transferred mean (SD)    | 2.3 (0.9)  | 2.2 (1.0)  | .6                 | 2.5 (0.9)  | 2.3 (0.6)               |
| ET day mean (SD)                       | 2.4 (0.5)  | 2.3 (0.5)  | .4                 | 2.4 (0.4)  | 2.5 (0.5)               |
| 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)               |
| 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)               |
| Endometrial thickness at ET day mean (SD) | 9.7 (2.0) | 9.6 (2.0)  | .8                 | 8.9 (1.8)  | 9.4 (1.5)               |
| Cancellation rate n (%)a              | 4 (10.8)  | 12 (27.2) | .07                | 1 (3.8)    | 1 (1.7)                 |
| 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)               |
| Implantation rate mean (SD)            | 38.3 (33.3)| 43 (15.2)| .7                 | 44 (10)    | 49 (22)                 |
| PR/ET n (%)                            | 5/33 (15.1) | 9/32 (28.1)| .2                | 2/25 (8)   | 22/57 (38.5)            |
| Live birth rate/ET (%)                 | 5/33 (15.1) | 6/32 (18.7)| .9                | 2/25 (8)   | 18/57 (31.5)            |

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

*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

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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 an- 
other study by Kumbak and Kahraman that compared 
the cycle characteristics of 27 patients with HH and 39 
patients with unexplained infertility, a longer stimula-
tion 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 consist-
ent with our results, 13 cycles with the HH patients 
were compared with 20 TF patients, and it was con-
cluded that despite similar implantation, pregnancy, 
and live birth rates, the cancellation rate was higher 
in the HH group.7 As expected, in agreement with previ-
ous 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 need-
ing 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 folli-
cles) 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.7 In the present study, the fer-
tilization rate was lower in the HH group, and when 
the embryo quality was compared, a significant differ-
ence 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 hav-
ing 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 re-
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 find-
ings 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 re-
response and pregnancy may not be affected by age.6 
The multivariate logistic regression analysis re-
vealed 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 re-
lation to other variables such as patient age, infertility 
duration, type of gonadotropin, or gonadotropin dos-
age 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 po-
tential for pregnancy, even with the coexistence of age 
factor.

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