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SHORT COMMUNICATION

ISTANBUL, TURKEY

The reproductive performance of women with hypogonadotropic hypogonadism in an in vitro fertilization and embryo transfer program

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***Purpose*:** To evaluate the outcome of women with hypogonadotropic hypogonadism undergoing in-vitro fertilization (IVF).
***Methods*:** We retrospectively assessed outcomes in 58 women with hypogonadotropic hypogonadism (HH) and, as matched controls, in 116 women with tubal factor (TF) infertility who underwent assisted reproduction treatment (ART). For ovulation induction, human menopausal gonadotropin (hMG) was used in HH patients and a combination of hMG and gonadotropin releasing hormone (GnRH) agonist was used in TF patients. Conception and implantation rates, as well as duration of stimulation and number of oocytes retrieved, were the main outcome measures.
***Results*:** Of the 58 HH patients, 53 (91.3%) responded adequately to ovulation induction and underwent ET. A larger amount of gonadotropins and a longer duration of ovarian stimulation were needed in HH patients than in TF patients. The mean number of retrieved oocytes and implantation rates did not differ between the groups. In addition, there were no differences between the HH and TF groups in pregnancy (53.8 vs. 48.6%) and multiple pregnancy (63.4 vs. 48.4%) rates. In the HH group, the miscarriage rate was 3.4%, and none of these patients developed severe OHSS.
***Conclusion*:** IVF in HH patients, in which there was a background of previous failed ovulation induction, was as successful as in women with TF infertility.

KEY WORDS: IVF; hypogonadotropism; hypogonadism; ovulation; induction; pregnancy.

INTRODUCTION

Hypogonadotropic hypogonadism (HH) has been classified as a World Health Organization (WHO) group I anovulation disorder (1). HH is usually idiopathic, with no anatomical lesions in the hypothalamo-pituitary tract (2), and is characterized by amenorrhea, hypoestrogenism, low serum gonadotropins, and a broad spectrum of abnormal secretion patterns of hypothalamic gonadotropin-releasing hormone (GnRH) (3,4). Women with this condition have normal central nervous system imaging and normal parameters in the remainder of the hypothalamic-pituitary axes (5).

Several etiologic factors have been described for idiopathic HH, including intense or frequent exercise, weight loss, psychological stress, and psychological disturbances (6–9). In addition to being infertile, women with HH suffer from conditions associated with a low estrogenic milieu, including osteopenia, requiring hormone replacement therapy. Several studies have demonstrated that women with HH who received exogenous gonadotropins or pulsatile GnRH analogue achieved favorable pregnancy rates. Due to the small numbers of women reported in these studies, the most efficient method to achieve pregnancy in women with HH has not been established. The data on results in women with HH undergoing in vitro fertilization (IVF) and embryo transfer (ET) who previously failed ovulation induction courses is thus also scanty. Here we report a retrospective analysis of our experience with women with HH in an IVF program and compare their results to a group of women with tubal factor (TF) infertility.

MATERIALS AND METHODS

Patients

The files of patients who underwent assisted conception treatments in the German Hospital Assisted Reproduction Center between January 1999 and January 2003 were retrospectively evaluated. Of a total of 7194 women, 64 (0.8%) were diagnosed as having HH, and these women have undergone 74 treatment cycles. In 59 patients primary amenorrhea and in 5 patients secondary amenorrhea (absence of spontaneous menstruation for $\geq$6 months) was present. The diagnosis of HH was based on the absence of withdrawal bleeding following progesterone challenge, and serum levels of FSH <2.0 IU/L and LH <1.0 IU/L. Each All HH patient had a normal uterus with thin endometrium (<5 mm) and small sized ovaries, with mean (+SD) longitudinal and transverse diameters of 2.7 ± 1.1 cm and 2.1 ± 0.9 cm, respectively, on transvaginal ultrasonography. None

had hypophyseal findings on MRI or karyotype abnormalities. None of the HH patients had conceived previously, or had a serious medical disorder. Among the women with HH, 6 (9.3%) of them also had coexisting male factor infertility and underwent to intracytoplasmic sperm injection (ICSI). In the remaining 58 patients, none of them had any coexisting infertility factor and all experienced previous multiple ovulation induction (between four and eight), alone or in combination with intrauterine insemination (IUI) cycles performed outside our clinic. Those 58 women had undergone 58 IVF cycles and were recruited for the study.

As a control group, we used 116 women, matched with background characteristics, diagnosed with tubal factor (TF) infertility, who underwent ART during the same period. The diagnosis of TF infertility was based on a demonstration of bilateral tubal obstruction on hysterosalpingogram or during laparoscopy. None of the TF patients had any coexisting infertility factor. Women with TF who had hydrosalpinges were excluded.

Participating couples were thoroughly informed about the infertility treatment options for HH, and all of these couples voluntarily chose ART at our center as first line treatment. The ethics committee of the German Hospital at Istanbul approved the collection of data, and written informed consent was obtained from all patients for the use of data for scientific report purposes.

Ovulation Induction Protocol for HH Patients

All women received daily human menopausal gonadotropin (hMG, Pergonal, 75 IU, Serono Laboratories) 450–600 IU for 4 days and were then evaluated for serum E_2 level by pelvic sonography. The hMG dose was adjusted with a step-down regimen according to the individual patient's ovarian response. When at least two follicles reached 18 mm in diameter, ovulation was triggered with 10,000 IU hCG (Pregnyl, Organon, Oss, The Netherlands).

Ovulation Induction Protocol for TF and MF Patients

Pituitary desensitization was initiated by daily treatment with 0.5 mg GnRH agonist (Lucrin, Abbott, France), starting from the midluteal phase of the preceding menstrual cycle, as described previously (10). Administration of 225–300 IU hMG/day was initiated on the third day of the menstrual bleeding that followed, when the daily dose of GnRH agonist was reduced to 0.25 mg per day. Following 4 days of hMG, its dose was adjusted according to the individual patient's response. When at least two follicles reached 18 mm in diameter, 10,000 IU hCG was administered as above.

Oocyte Retrieval and IVF

Oocytes were retrieved 32–38 h following hCG injection and inseminated with sperm as previously described (11). Three days after oocyte retrieval, the embryos were transferred transcervically under ultrasonographic guidance. Selective laser used assisted hatching were performed to transferred embryos having thickened zonae. Luteal phase was supported by 100 mg/day progesterone in oil i.m. and if conception occurred, it was continued for 10 weeks of gestation. Pregnancy was diagnosed by the ultrasonographic demonstration of an intrauterine gestational sac with heartbeat.

Statistical Analyses

We utilized the Chi-square test and Student's *t*-test for normally distributed continuous parameters and the Mann–Whitney-*U* test for continuous parameters of uncertain distribution. A probability value of less than 0.05 was considered statistically significant.

RESULTS

Of the 58 HH women who underwent ovulation induction, 53 (91.3%) reached embryo transfer. The remaining five patients (8.6%) did not undergo oocyte retrieval because of poor ovarian response, and the couples elected to cancel.

Age, body mass index (BMI) and baseline hormonal assays of both the HH and TF groups are listed in Table I. The groups did not differ in age, prolactin or TSH levels, but HH patients were significantly leaner and had lower FSH and LH levels than TF patients.

The cycle characteristics and outcomes of both groups are detailed in Table II. The duration of ovulation induction in HH patients was significantly longer than in TF patients. Although larger amounts of hMG were needed to stimulate ovaries of HH patients, the serum E_2 levels at the time of hCG injection was significantly lower in HH than in TF patients.

Endometrial thickness at the time of embryo transfer, measured by transvaginal ultrasonography, did not differ between the two groups. The total

Table I. Characteristics of Women with Hypogonadotropic Hypogonadism and Women with Tubal Factor Infertility Undergoing IVF-ET

	Hypogonadotropic hypogonadism patients ($n = 58$)		Tubal factor patients ($n = 116$)		
	Mean ± *SD*	Range	Mean ± SD	Range	*p*
Age (years)	32.21 ± 5.2	*21 – 41*	31.08 ± 4.0	*22 – 42*	NS
BMI (kg/m$^{2)}$	21.09 ± 1.3	*19.3 – 23.8*	25.04 ± 0.8	*23.7 – 31.0*	0.0001
FSH (mIU/L)	0.88 ± 0.7	*0.09 – 1.9*	6.01 ± 1.8	*2.1 – 10*	0.0001
LH (mIU/L)	0.58 ± 0.3	*0.01 – 1.0*	5.48 ± 3.0	*2.4 – 16.1*	0.0001
TSH (mIU/L)	0.98 ± 0.4	*0.4 – 1.9*	1.12 ± 0.2	*0.4 – 2.1*	NS
Prolactin (μg/L)	17.15 ± 2.7	*12 – 21*	16.80 ± 1.8	*14 – 22*	NS

Note. Numbers are means with standard deviations. Numbers given in italics indicate range.

number of oocytes retrieved in women with HH was significantly lower than in women with TF infertility, but the percentage of metaphase II oocytes did not differ between the two groups. Both groups had comparable numbers of embryo transfer. Fertilization and implantation rates, as well as pregnancy rates per embryo transferred and multiple pregnancy rates also did not differ between the groups. Severe ovarian hyperstimulation syndrome (OHSS) was not detected in either group of patients. Two patients in each group aborted prior to 20 weeks of gestation.

DISCUSSION

Pulsatile GnRH treatment, alone or in combination with exogenous gonadotropin, has been utilized for the management of women with HH suffering from infertility. These methods yield pregnancy rates per cycle of 25–45% (12–18). In contrast, treatment with gonadotropins alone was proposed that did not result in adequate follicular growth (19). However, pulsatile GnRH requires near perfect compliance and close monitoring. In addition, use of a portable pump injection device and the need to inject subcutaneously or intramuscularly has been regarded as a disadvantage (20).

To our knowledge, this study is the first to report the outcome of IVF in a group of HH patients. Although the starting dose of menotropins may be somewhat high, we have found it appropriate due to the very long duration of gonadotropin administration used to stimulate these ovaries. Although stimulation of ovaries with small doses of exogenous

Table II. Results in Women with Idiopathic Hypogonadotropic Hypogonadism Who Underwent Ovarian Stimulation and IVF-ET, Compared with Women with Tubal Factor Infertility Who Underwent to Controlled Ovarian Hyperstimulation and IVF-ET

	Hypogonadotropic hypogonadism patients ($n = 58$)	Tubal factor patients ($n = 116$)	*p*
Duration of stimulation (days)	13.61 ± 2.1	11.69 ± 1.5	0.0001
Gonadotropin ampoules consumed (75 IU each)	80.92 ± 21.8	47.8 ± 16.2	0.0001
E_2 at the time of hCG (pg/mL)	1649.7 ± 1040.6	2886.6 ± 1169.5	0.0001
Endometrial thickness (mm)	10.2 ± 2.3	10.5 ± 2.0	NS
Total oocytes retrieved	12.35 ± 9.6	16.69 ± 6.3	0.001
MII/total oocyte ratio (%)	75.8	76.3	NS
Fertilization rate (%)	73.9	73.0	NS
Embryos transferred	3.01 ± 1.3 (1 – 5)	3.17 ± 0.4 (2 – 4)	NS
Grade I–II/ embryos transferred (%)	80.5	81.1	NS
Implantation rate (%)	32.4	27.4	NS
Pregnancy	30	60	
ET cycles	53	116	
Pregnancy rate/ET (%)	56.6	51.7	NS
Multiple pregnancy (%)	46.6	48.3	NS

gonadotropins in patients with hypothalamic amenorrhea (e.g. PCOS) requires a long duration (21), we initiated induction with high dosages. Thus, the peak E_2 level of 3000 pg/mL was exceeded in only four patients, and no severe OHSS was detected. The need for this large dose may have been due to these women having begun to be hypoestrogenic and their hypophysis may not have been primed. In addition to this, our practice routinely uses basal antral follicle count to test ovarian reserve and accordingly those individuals eventually clinically demonstrated diminished ovarian reserve (22). However, precycle priming with estrogens or oral contraceptives to induce gonadotropin receptor formation in granulosa cells may benefit women with HH, reducing the number of gonadotropins. Treating patients with a course of estrogen prior to commencement of gonadotropin administration may have improved their response to COH. While we did not attempt to verify this, future studies should address this issue. Similarly our results also can be best tested if ovarian stimulation be performed with low doses of gonadotropins in a prospective controlled study.

Although TF patients can be regarded as ideal controls in an ART setting, the major drawback to this study was that we compared two different ovarian stimulation protocols in two groups of patients. The GnRH analogue had not been employed in stimulation protocols for women with HH. In our opinion, this is justified, due to the lack of expected hypophyseal premature LH-surge. Despite this, ovarian stimulation required a longer period of time and a higher gonadotropin dose in HH than in TF patients. Nevertheless, the number of harvested oocytes and their quality did not differ between these two groups, and their chance to conceive was comparable.

In contrast to earlier studies, which showed pregnancy losses of 22.9 and 27% in HH patients undergoing ovulation induction (19,23), we observed a pregnancy loss rate of less than 8%.

While multiple pregnancy is a common and serious complication in ART, we found that treatment of HH women with ART did not increase the multiple pregnancy rates over that observed in a general population of women undergoing ART in our facility. We found that high order pregnancies constituted 13% of all pregnancies in HH group, which can be compared with the 30% multiple pregnancy rate observed during ovulation induction (21). Our practice, however, did not underestimate the necessity for multiple outcome measures in evaluating ART success. Perinatal as well as maternal mortality and morbidity are increased in multiple pregnancies. In this regard, our practices have changed during recent years, as have those in other infertility centers around the world. Twin and singletonbirths should thus be counted as successful outcomes in ART. The essential aimof infertility treatment should be a healthy low order (singletonor twin) birth (24). From another point of view, transferring limited number of embryos in IVF treatment would also prevent high order multiple pregnancy rate in patients undergoing only ovulation induction.

The addition of intrauterine insemination to exogenous gonadotropin treatment has been shown to increase the efficacy of infertility treatment in patients with unexplained and male factor infertility (25–27). Conceivably, following gonadotropin administration, IUI can be considered for women with HH. Since pregnancy is considered the principle outcome in HH women receiving infertility treatment, the stimulation of ovaries with greater amounts of exogenous gonadotropins followed by IUI can be questioned in terms of cost-effectiveness. One of the limitations of our study was the lack of evaluation of previous ovulation induction outcomes of HH women. Due to the inappropriate documentation of previous treatments, we could not evaluate the characteristics of previous ovulation induction courses among our group of HH women. Our results, however, have shown that IVF can be successfully employed in women with IHH and that reproductive response to ART treatment in those individuals did not differ from that in other ovulatory patients.

Since this procedure entails medical risks and is quite expensive, each case should be evaluated individually. Our results also showed that HH women constitute fewer than 1% of patients requiring infertility treatment. It is therefore important not to make clear cut statements about the management of treatment based on such a small group of infertile patients. Other factors, including previous infertility treatment history, the age of the couple, coexistence of male factor infertility and financial burden should all be considered regarding each patient.

In conclusion, we found that the results of ART in HH patients, even on a background of previous by failed ovulation induction, were comparable to those in women with TF infertility.

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