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Original Article

Management of ovulation induction and intrauterine insemination in infertile patients with hypogonadotropic hypogonadism

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ABSTRACT

Aim: To investigate the effectiveness of ovulation induction and intrauterine insemination (OI + IUI) in female patients with hypogonadotropic hypogonadism (HH), and to compare the outcomes of different stimulation protocols and cycle characteristics.
Material and methods: The outcomes of OI + IUI treatments in patients with HH diagnosed between 2010 and 2018 were retrospectively evaluated. Cycles using recombinant (rec) luteinizing hormone (LH) or human menopausal gonadotropin (hMG) as LH sources were compared with each other. The cycle characteristics and pregnancy rates of the first cycles were compared with those of the second cycles in patients who underwent 2 or more cycles.
Results: Of 104 patients diagnosed with World Health Organization type 1 anovulation, 99 were treated with hMG or rec LH + rec follicle-stimulating hormone (FSH) in a total of 220 cycles. The mean age of the study patients was 27.8 ± 4.6 years (range, 19–39 years). Rec FSH + rec LH was given in 37 cycles, and hMG was used in 183 cycles. The hormone values were as follows: FSH, 1.4 ± 1.6 mIU/mL; LH, 0.7 ± 1.2 mIU/mL; oestradiol, 13 (15.8 ± 12.0) pg/mL; and anti-Müllerian hormone, 2.1 (2.6 ± 1.2) ng/mL. A dominant follicle was observed in 85.7% of the first cycles and in 86.2% of the second cycles. The treatment lasted 17.2 ± 5.0 and 15.5 ± 3.8 days until the human chorionic gonadotropin (hCG) administration day in the first and second cycles, respectively, and the difference was statistically significant ($p < 0.05$). The cycle cancellation rate was 8.1% (n = 3) in cycles done using rec gonadotropins and 29% (n = 53) in patients stimulated with hMG, and the difference was statistically significant ($p < 0.05$). The pregnancy rates were 12.7% and 28.3% per cycle and per patient, respectively. The pregnancy rate in hCG-triggered patients (successful stimulation) was 17.1% per cycle in all patients.
Conclusion: OI with gonadotropins and IUI is a safe, efficient, and relatively cost-effective treatment option in patients with HH, yielding reasonable pregnancy rates per cycle and per patient. The use of rec FSH + rec LH facilitates cycle management but does not positively contribute to pregnancy rates and is more expensive than some other feasible options.

Introduction

Hypogonadotropic hypogonadism (HH) is diagnosed in approximately 10% of anovulatory women, and this condition is classified as World Health Organization (WHO) type 1 anovulation [1]. Both hypothalamic amenorrhoea (HA) and idiopathic HH (IHH) have hypothalamic causes, and together with hypopituitarism (HP), a diffuse pathology of the pituitary gland, these conditions form a wide clinical spectrum.

Infertility due to anovulation is a major problem in women of childbearing age who desire to conceive. FSH and LH are required for ovulation induction (OI). Gonadotropin-releasing hormone (GnRH) pulsatile injections or pumps are effective in patients with HA and IHH, but they are not used in the treatment of HP. The pulsatile release of GnRH provides monofollicular development, physiologic oestradiol (E2) levels, and luteal phase conditions that restore normal ovarian function [2,3]. Although gonadotropins provide higher pregnancy rates, their administration is more cumbersome for patients, which decreases treatment compliance. In patients with HP, growth hormone, ACTH, and TSH might also be

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affected besides FSH and LH. Therefore, all other hormones that are deficient should be replaced, including FSH and LH [2].

Despite causing more non-physiologic hyperstimulation, multifollicular development, and risks of ovarian hyperstimulation syndrome and multiple pregnancy than GnRH therapies, OI with gonadotropins can be used effectively in all clinical conditions (HA, IHH, and HP) representing HH [4]. In OI, treatment with FSH alone is sufficient to achieve pregnancy in most women with infertility. Women with HH have very low LH levels, inadequate oocyte maturation, inadequate follicular growth, low oestrogen levels, low endometrial scores, and increased amount of FSH use, thus decreasing their pregnancy rates [2,5]. The addition of LH or preparations containing

LH improves this problem and increases the pregnancy rates [6]. When the LH source is problematic, the counterpart of human menopausal gonadotropin (hMG) as an LH active agent is rec LH. A combination of rec LH and rec FSH can be safely and effectively used for OI in patients with HH [7].

The aim of this study was to investigate the cycle characteristics and pregnancy outcomes in successive intrauterine insemination (IUI) with OI cycles in patients with HH, as well as with respect to the LH source.

Material and methods

This multicentre retrospective cohort study was conducted in the infertility units of Istanbul University of Health Sciences, Kanuni Sultan Suleyman Training and Research Hospital, Bagcilar Training and Research Hospital, and Medipol University Hospital Gynecology and Obstetrics Clinic. Institutional review board approval (decision no. 21/02/2018-5) was obtained. The outcomes of OI + IUI treatments in patients with HH diagnosed between 2010 and 2018 were retrospectively evaluated. Cycles using rec LH or hMG as LH sources were compared with each other. In patients who underwent 2 or more cycles, the cycle characteristics and pregnancy rates of the first cycles were compared with those of the second cycles.

The criteria for the diagnosis of HA include amenorrhoea, anovulation, and negative progesterone challenge tests, as well as low oestrogen and gonadotropin levels and menstrual bleeding with combined use of oral contraceptives. In the hormone profile between 2 and 4 days of menstruation, TSH and prolactin should be normal, FSH and LH should be <5 mIU/mL, and E2 should be <10 pg/mL.

The inclusion criteria for this study were a diagnosis of WHO type 1 amenorrhoea, a desire for childbearing, no other cause of infertility, and a normal genital anatomy. The exclusion criteria were any other cause of infertility, abnormal TSH and/or prolactin levels, and a prediagnosed hypothalamic or pituitary lesion on magnetic resonance imaging. Patients with chronic systemic diseases were also excluded from the study. Patients with HP (in whom other deficient hormones are replaced besides FSH and LH) were excluded because additive hormones might have adverse effects on the pregnancy rates. Patients with HH received E2 + P (progesterone) pretreatment for at least 3 months.

Ovulation induction

The treatment was started on day 2 or 3 of the first menstrual bleeding after the end of the E2 + P treatment (Cyclo-Progynova® 1 mg, Schering AG, Berlin, Germany). hMG (Menogon®, Ferring, Brazil) or rec FSH (Gonal-F®, Merck Serono SA, Kiel, Germany) or purified urinary FSH (Puregon®, MSD, Ireland) with rec LH (Luveris®, Merck Serono SA, Kiel, Germany) at 75 IU was started at day or 3, and the durations and doses of treatments were adjusted according to the ovarian response. The starting gonadotropin doses varied according to the patient's weight, age, and anticipated response to treatment. Follicle growth was monitored using transvaginal ultrasound and serum E2 level measurements. Ovulation, defined as the presence of a leading follicle >18 mm in mean diameter, was triggered by administering 5000–10,000 U human chorionic gonadotropin (hCG) (Choriomon®; IBSA, Switzerland) or 250 μg choriogonadotropin alpha (Ovitrelle®; Merck, Germany). We cancelled the IUI treatment cycle when there were >3 mature follicles [8].

Sperm preparation and IUI

Semen specimens were collected via masturbation after a minimum of 2–3 days of sexual abstinence. Semen analyses were performed for liquefaction time, volume, sperm count, concentration, pH, white blood cell count, and Kruger morphologic criteria. Semen pellets were reconstituted in 0.4 mL human tubal fluid medium for IUI.

The IUI sample was injected using a simple catheter with the patient in the dorsal lithotomy position. IUI was performed 36–40 h after ovulation triggering. After IUI, the women had a bed rest for 20 min.

Luteal phase support was used routinely in all patients, commencing the day after IUI. It consisted of progesterone vaginal gel administration (Crinone 8%; Merck Serono SA, UK) until week 7 of pregnancy. Oestrogen was also administered to the patients either in the form of a transdermal patch or as oral tablets until 7 weeks of pregnancy.

Clinical pregnancy was defined as a sonographic evidence of an intrauterine gestational sac. A live birth was defined as the birth of an infant after 24 weeks of gestation with postnatal evidence of life. Multiple pregnancy was defined as the observation of >1 intrauterine gestational sac [8].

Statistical analysis

Statistical Package for the Social Sciences version 19 was used for statistical analyses (IBM, Armonk, NY, USA). The data were given as means ± standard deviations. In variables with a normal distribution, group means were compared with independent t-tests. Variables with a non-normal distribution were compared using the Mann-Whitney U-test, and categorical variables were tested using the chi-square test. Cumulative pregnancy rates according to the number of interventions were determined with the Kaplan-Meier test. A p-value of <0.05 was accepted as statistically significant.

Results

Distribution of patients

Of 104 patients with a diagnosis of WHO type 1 anovulation, 99 were treated with hMG or rec LH + rec FSH in a total of 220 cycles. Treatment was denied in 5 patients, one of whom had Sheehan syndrome. There were 3 patients with pituitary tumours treated with surgery, and 1 patient with chronic liver disease. The mean age of the study patients was 27.8 ± 4.6 years (range, 19–39 years). In the group that received treatment, 2 patients had Kallman syndrome and 1 patient underwent surgery for cerebral haemorrhage. There were 25 patients with secondary amenorrhoea and 74 patients with primary amenorrhoea. Of all patients, 9 had secondary infertility and the remaining 90 had primary infertility. Two patients had a family history of HH (Table 1).

Rec FSH + rec LH was given in 37 cycles, and hMG was used in 183 cycles. The administered LH dose was 75 IU; the FSH and hMG doses were given according to the gonadotropin response

Table 1
Comparison of cycle characteristics between hMG and rec FSH + rec LH.

Parameters	rec FSH + rec LH (n = 37)[¶]	hMG (n = 183)[¶]	p-Value
Age (years)	27.8 ± 5.4 (26)	27.8 ± 4.4 (27)	0.64
[&]BMI (kg/m^2)	24.6 ± 2.9 (24)	25.3 ± 4.5 (24)	0.58
[&]E2 + P (pretreatment) (months)	16.4 ± 21.9 (24)	17.2 ± 19.0 (12)	0.21
[&]FSH (mIU/mL)	2.0 ± 2.2 (0.8)	1.3 ± 1.4 (0.6)	0.06
[&]LH (mIU/mL)	1.5 ± 2.4 (0.3)	0.5 ± 0.6 (0.2)	0.07
[&]E2 (pg/mL)	17.0 ± 11.1 (14.6)	15.5 ± 12.2 (13)	0.35
[&]TSH (mU/L)	2.3 ± 1.8 (1.9)	2.1 ± 3.4 (1.5)	0.08
Prolactin (ng/mL)	12.6 ± 10.7 (10.5)	16.0 ± 34.7 (8.9)	0.84
FSH dose	138.5 ± 39.8 (150)	157.4 ± 58.6 (150)	0.11
LH dose	94.6 ± 32.9 (75)	157.4 ± 58.6 (150)	*0.000*
[&]hCG days	16.9 ± 4.6 (16)	16.1 ± 4.3 (15)	0.33
Endometrial thickness	9.7 ± 2.1 (10)	9.7 ± 2.4 (10)	0.98
Dominant follicle >18 mm	0.7 ± 0.7 (1)	0.9 ± 1.1 (1)	0.83
Dominant follicle 14–18 mm	1.9 ± 1.2 (2)	2.1 ± 1.7 (2)	0.82
[#]Cycle cancellation	3 (8.1%)	53 (29%)	*0.008*
[#]ß-hCG (+)	6 (16.2%)	22 (12.2%)	0.48

[¶] Values are presented as mean ± standard deviation (median).
[#] Values are presented as number (percentage, %).
[&] BMI, body mass index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; hMG, human menopausal gonadotropin; E2, oestradiol; P, progesterone; TSH, thyroid-stimulating hormone; hCG, human chorionic gonadotropin.

of the patient (Table 2). In 6 (2.7%) of the cycles, the patients discontinued the treatment because of prolonged unresponsiveness (Table 2). The patient flowchart in Fig. 1 summarizes the chronological order of the successively used treatment options.

Patient demographics

On physical examination, infantile external genitalia were found in 6 (6.06%) and uterine hypoplasia was detected in 9 (9.09%). The ovaries were polycystic in 3 (3.03%) of the patients and had a multicystic appearance in 4 (4.04%). The ovaries could not be visualized using transvaginal ultrasonography in 92.3% of the patients.

The mean age of the patients was 27.8 ± 4.6 years. The mean body mass index was 24.4 kg/m^2. The mean age at menarche was 17.5 ± 4.9 years, and the average infertility period was 36 months. The E2 + P pretreatment period was 12 months. The hormone values were as follows: FSH, 1.4 ± 1.6 mIU/mL; LH, 0.7 ± 1.2 mIU/mL; E2, 13 (15.8 ± 12.0) pg/mL; and AMH, 2.1 (2.6 ± 1.2) ng/mL (Table 1).

Table 2
Comparison of cycle 1 and cycle 2 characteristics among the patients.

Parameters		Cycle 1 (n = 99)[¶]	Cycle 2 (n = 71)[¶]	p-Value
FSH dose		133.5 (40.2) (150)	165 (57.5) (150)	*0.000*
LH dose		127.4 (43.4) (150)	155.2 (62.6) (150)	*0.000*
hCG days		17.2 (5) (17)	15.5 (3.8) (15)	*0.010*
[&]Endometrial thickness		9.5 (2.5) (10)	99.6 (2.4) (10)	0.630
[&]TPMSC		78.1 (78.3) (55.6)	78.7 (78.4) (55.6)	0.180
Dominant follicle >18 mm		0.8 (1) (1)	0.8 (1) (1)	0.752
Dominant follicle 14–18 mm		1.8 (1.4) (2)	2.1 (1.8) (2)	0.279
[#]Gonadotropin	hMG	71 (81.8%)	57 (88.7%)	0.687
	FSH + LH	18 (18.2%)	13 (18.3%)	
[#]Cycle cancellation		33 (33.3%)	13 (18.8%)	*0.021*
[#]Bhcg (+)		10 (10.1%)	10 (14.3%)	0.426

[¶] Values are presented as mean ± standard deviation (median).
[#] Values are presented as number (percentage, %).
[&] BMI, body mass index; TPMSC, total progressive motile sperm count; FSH, follicle-stimulating hormone; LH, luteinizing hormone; Hmg, human menopausal gonadotropin; BMI, body mass index; E2, oestradiol; P, progesterone; TSH, thyroid-stimulating hormone; hCG, human chorionic gonadotropin.

Follicular development

A dominant follicle was observed in 80.1% of the first cycles and in 91.5% of the second cycles. The treatment lasted for 17.2 ± 5.0 and 15.5 ± 3.8 days until the hCG administration day in the first and second cycles, respectively, and the difference was statistically significant ($p < 0.05$). When the first and second cycles were compared, the cycle cancellation rate was found to be 33.3% in the first cycles and 18.8% in the second cycles, with a statistically significant difference ($p < 0.05$) (Table 3). 14 patients underwent the fourth cycle. Of these, one cycle resulted in pregnancy, four cycles were cancelled (two had more than 3 growing follicles and two had no growing follicles) and two subsequently underwent the fifth cycle (which did not conceive). These 14 patients were not included in the comparison of cycle outcomes due to the small sample size, and thus Table 3 was only consistent of the data regarding patients who underwent one to three cycles.

Follicular size, follicle count, and endometrial thickness

The mean number of dominant follicles >18 mm was 1.0 (0.8 ± 1.1), and the mean number of follicles that were between 14 and 18 mm was 2.0 (2.1 ± 1.6). The mean endometrial thickness was 10 mm (9.7 ± 2.3 mm).

Cycle cancellation

The cycle cancellation rate was 8.1% (n = 3) in cycles performed using rec gonadotropins and 29% (n = 53) in patients stimulated with hMG, with a statistically significant difference ($p < 0.05$). The reasons for cancellation were absent follicular development in 22 cycles (10%), hyperstimulation in 28 cycles (12.7%), and treatment discontinuation in 6 cycles (2.7%). Among the cycle cancellations, 23 (33.3%) occurred in the first cycle and 13 (18.8%) were due to a lack of response.

Pregnancy rates and outcomes

The pregnancy rates were 12.7% and 28.3% per cycle and per patient, respectively. The rate of pregnancy in hCG-triggered patients (successful cycle) was 17.1% per cycle. No statistically

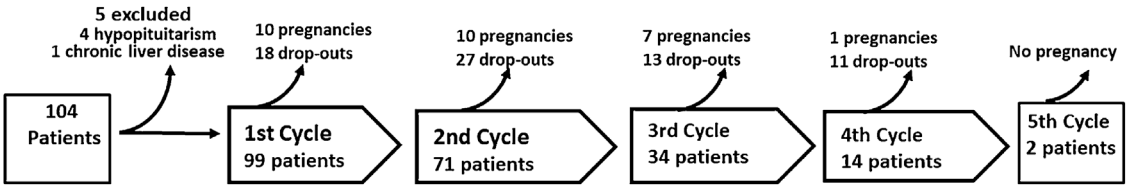

Fig. 1. Treatment flowchart for the patient cohort.

Table 3
Cumulative follicular development rates and pregnancy rates in patients treated with concomitant follitropin alpha and luteotropin alpha and hMG.

	Cycle 1 (N = 99)			Cycle 2 (N = 71)			Cycle 3 (N = 34)		
	hMG (n)	rec LH + rec FSH (n)	***Total %(n/N)***	hMG (n)	rec LH + rec FSH (n)	***Total %(n/N)***	hMG (n)	rec LH + rec FSH (n)	***Total %(n/N)***
Cumulative follicular development rate[*,α,β]	65	15	***80.8% (80/99)***	52	13	***91.5% (65/71)***	27	6	***97% (33/34)***
Cumulative follicular development rate, patients who received hCG[*,α,β]	53	13	***66.6% (66/99)***	45	13	***80.2% (57/71)***	22	6	***82.3% (28/34)***
Cumulative pregnancy rate[*,α,β]	9	1	***10.1% (10/99)***	7	3	***14% (10/71)***	5	2	***20.5% (7/34)***
Cumulative pregnancy rate, patients who received hCG[*,α,β]	9	1	***14.7% (10/68)***	7	3	***17.5% (10/57)***	5	2	***25% (7/28)***
Cumulative on-going pregnancy rate[*,α,β]	8	1	***9.1% (9/99)***	6	3	***12.6% (9/71)***	5	2	***20.5% (7/34)***
Cycle cancellation[μ,α,β]	30	3	***33.3% (33/99)***	13	0	***18.3% (13/71)***	6	0	***17.6% (6/34)***

Rec, recombinant; hCG, human chorionic gonadotropin; FSH, follicle-stimulating hormone; LH, luteinizing hormone; Hmg, human menopausal gonadotropin.
Data given as % (n/N).
[*] Cycle 1 vs. 2: No significant difference among the groups for the noted variable.
[μ] Cycle 1 vs. 2: A significant difference among the groups for the noted variable ($p < 0.05$).
[α] Cycle 1 vs. 3: No significant difference among the groups for the noted variable.
[β] Cycle 2 vs. 3: No significant difference among the groups for the noted variable.

significant difference was found between any of the parameters when women who conceived were compared with those who did not. The pregnancy rate in the second cycle was 14.1% compared with 10.1% in the first cycle; however, the difference did not reach statistical significance. The pregnancy rate was 12.2% in hMG cycles and 16.2% in cycles with rec LH + FSH, with the difference being not statistically significant. Even more similarly, the cumulative pregnancy rate in patients in whom ovulation could be triggered was 17.6% in the rec FSH + rec LH group and 16.9% in the hMG group. The pregnancy resulted in abortion in two patients. Two patients had a twin pregnancy, and there were only two triplet pregnancies overall. One of the triplet pregnancies spontaneously reduced, whereas the other was subjected to multifoetal pregnancy reduction (MFPR) and continued as a twin pregnancy (Fig. 2).

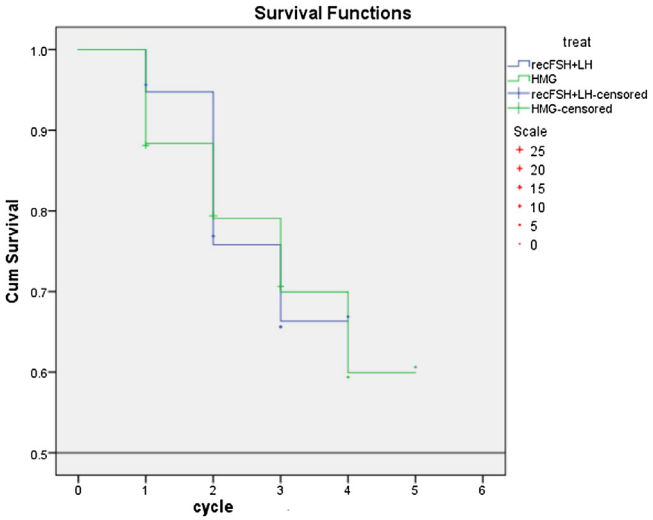

Fig. 2. Pregnancy rates compared between treatment regimens over the cycles.

The mean FSH dose used in the treatment with gonadotropin was 150 IU, and the LH dose was 150 IU. The mean period until the hCG day was 15.5 days, and the mean endometrial thickness on hCG day was 10.0 mm. The dose of gonadotropin was increased in 66.4% of the patients during the treatment. Luteal phase support consisted of E2 + P in 60.5% of the patients and progesterone alone in 39.5%. The regimens used in ovarian hyperstimulation were compared. The LH dose was 75 IU in the recombinant group and 150 IU in the hMG group, and the difference was significant ($p < 0.05$).

In patients who underwent 2 cycles, the cycle characteristics and outcomes of the first cycles were compared with those of the second cycles. The total FSH and LH doses used were significantly higher in the second cycles ($p < 0.05$). The mean number of days until hCG administration was 15.5 days in the second cycles and 17.2 days in the first cycles. The cancellation rate was 33.3% in the first cycles and 18.8% in the second cycles, with a significant difference ($p < 0.05$).

When patients with cancellation of cycles were compared with those without any cycle cancellation, the mean age was lower in the cancellation group and the E2 + P pretreatment period was shorter. It was also observed that the basal FSH, LH, and oestrogen levels at the early follicular phase were lower in the group with cycle cancellations ($p < 0.05$). In this group, the endometrial thickness on hCG day was also less.

Ovarian hyperstimulation developed in 1 patient. Adverse effects such as constipation, nausea, abdominal pain, and headache developed in 25 patients (25.2%). None of the patients discontinued treatment because of adverse effects.

Discussion

HH is a rare, heterogeneous spectrum of disorders characterized by gonadotropin deficiency, hypo-oestrogenism, amenorrhoea, and infertility associated with anovulation, most of which develop as a result of defects in GnRH release. The condition may be congenital, as in IHH, or can develop later in life, as in HP and HA

[2]. Regardless of the underlying aetiology, both FSH and LH are needed to restore normal ovarian function and prevent follicular growth arrest [9,10].

Pulsatile GnRH treatment is an effective and appropriate method to achieve normal ovarian function, with advantages of inducing mono-follicular development, physiologic oestrogen levels, and normal luteal phase function; however, it is not effective in HP and most patients find it difficult to carry a pump continuously [2,7]. Daily injection of gonadotropins is a better tolerated and more suitable treatment option for OI [4]. This therapeutic modality is associated with increased risks of multiple follicular growth and ovarian hyperstimulation syndrome, owing to the supra-physiologic follicular stimulus [11].

Although FSH is the primary hormone for optimal follicular development, LH is also required for the full maturation of the follicle and the fertilization capacity of the oocyte. In embryogenesis, meiotic division, which stops at meiosis I, resumes after LH activity. Another process that is induced by LH is follicular wall proteolysis, which leads to follicle rupture and oocyte release [12]. When only FSH is used for OI, it results in a smaller increase in oestrogen concentration, poor endometrial scores, poor follicular luteinization, and decreased oocyte fertilization rates. As a result of the reduced concentration of LH, ovarian androgen production decreases, leading to diminished ovarian oestrogen synthesis, decreased implantation rates, and increased miscarriage rates [13].

In a rec LH dose study, in the OI of patients with HH, the recommended optimal LH dose was 75 IU. When the LH dose was 75 IU, there was 88% follicular growth, which increased to 100% at 225 IU; however, the fertilization rate decreased when 225 IU LH was used (LH ceiling theory) [14].

In women with HH, the ovarian volume, antral follicle count, and AMH levels do not predict treatment response [15,16]. AMH levels are lower in these women than in normal patients. The level of AMH increases after gonadotropin administration [16]. The absence of tests and findings to detect ovarian reserve makes it difficult to manage the OI of patients with HH. Compared with patients who have other causes of infertility, patients with HH experience more cycle cancellations because of insufficient ovarian response and hyperstimulation syndrome [17].

This retrospective multicentre cohort study included a high amount of data for this uncommon patient group. In the study, 220 OI + IUI cycles were performed in 99 patients with HH. Patients had an average of 2.26 OI + IUI cycles, ranging from one to five cycles. In this study, the response to therapy, cycle characteristics, and pregnancy rates with different LH sources (hMG and rec FSH + rec LH) were investigated. In addition, the characteristics of the patients with at least two OI + IUI cycles were compared. Of the patients, 4 had thyroid surgery and two received medical treatment for adrenal insufficiency.

In our study group, the overall response rate to gonadotropin treatment was 66.6% (66/99) in the first cycles. In the study by Dubourdieu et al., the ovarian response rate to GnRH pulsatile treatment was 73% and that to gonadotropin treatment was 60%. On the other hand, the clinical pregnancy rates were 45% and 15% with pulsatile treatment and gonadotropin treatment, respectively [18].

In many studies, a 74–87% follicular growth rate and a 22% pregnancy rate were reported when FSH and LH were used [11]. The pregnancy rate per cycle was 12.7% (28 patients), and the mean number of OI + IUI cycles per patient was 2.2; 28.3% pregnancy rate was achieved. In our data, the FSH or hMG dose was changed in 66.4% of the cycles during the OI of the patients. Shoham et al. reported a dose change of 33.3% [10]. This is indicative of the difficult management of OI.

In 60.5% of the cycles, luteal phase support was provided with E2 + P and with progesterone in in 39.5%. In their in vitro fertilization study conducted in patients with HH, Mumusoglu et al. reported that progesterone was sufficient for the luteal phase [19].

One of the most important factors affecting OI management in patients with HH is cycle cancellation. From our overall data, hCG could not be given in 25.4% (n = 56) of the cycles, and these cycle were cancelled. The reasons for cycle cancellation were failure to develop any follicles in 10.0% (n = 22) of the cycles, presence of >3 dominant follicles due to excessive response to the stimulation in 12.7% (n = 28), and failure to adhere to the treatment because of prolonged follicular phase and unresponsiveness to the stimulation in 2.7% (n = 6). Cyclic cancellations were seen in 33.3% in the first cycle of OI and in 18.8% in the second cycle, and the difference was statistically significant ($p < 0.005$).

When evaluated according to the LH source used, the frequency of cancellation was 29.0% in the hMG group and 8.1% in the rec FSH + rec LH group, which was statistically significantly different ($p < 0.005$). Rec FSH + rec LH facilitates management and increases the hCG delivery rate.

To our knowledge, there are only 2 literature reports comparing highly purified hMG and recombinant treatment (FSH and LH) in HH cases. Carone et al. reported that the ovulation outcome was better with highly purified hMG than with rec FSH and rec LH, whereas the pregnancy rates were better with the combined recombinant treatment. Papaleo et al. only reported a more favourable pregnancy rate with the combined recombinant treatment option. In our study, a successful follicular development was more probable with the combined recombinant treatment; however, the pregnancy rate could not reach a significantly improved level with the recombinant treatment modality [20,21].

No significant difference was found in the basic and cycle characteristics with respect to conception or the cycle order in successive cycles. The per-cycle pregnancy rate was 12.7% (n = 28), and the per-patient pregnancy rate was 28.3%. The pregnancy rates were 10.1% in the first cycle and 14.1% in the second cycle, and the difference was not statistically significant. According to our data, the cycles that used rec FSH + rec LH as the LH source could be managed more easily and yielded a higher rate of cycles appropriate for hCG triggering. However, these advantages did not influence the pregnancy rates.

Among our patients, 3 women had twin pregnancies and 2 women had triplet pregnancies. One of the triplet pregnancies spontaneously reduced to a twin pregnancy, and the other had a selective MFPR. The rate of multiple pregnancy was 14.2%. Two (7.1%) pregnancies resulted in abortion. The relatively high miscarriage rates reported in the study by Balen et al. were not observed in our study [4]. The rate of on-going pregnancy was 11.8% per cycle and 26.2% per patient.

In this study, the rate of cycles that were appropriate for triggering with hCG was 66.7% and 81.2% in the first and second cycles, respectively. The mean cycle duration (±SD) in the second cycles was also significantly shorter than in the first cycles (15.5 ±3.8 days vs. 17.2 ±5 days, $p < 0.05$). Furthermore, the pregnancy rates were higher in the second cycle. The relatively better course of the second cycles can be attributed to the stimulant effect of the gonadotropins administered in the first cycles, acting as a pretreatment. In 2.7% of the cycles, the patients discontinued the treatment because there were no dominant follicles, and 18.2% of the patients (n = 18) elected not to continue with a second cycle of OI + IUI. Although earlier studies suggested that treatment with OI + IUI was a feasible alternative, our study revealed that about 45% (45 of 99) of the patients being treated conventionally dropped out of our program following the second cycle.

In patients with HH, several studies have reported more successful cycle management and results with gonadotropin pretreatment. Pretreatment with rec LH has been shown to increase

the follicle retrieval and pregnancy rates [13]. Similarly, the results of cycles were more successful in patients who underwent pretreatment with hMG [16]. On the other hand, short-term oestrogen pretreatment has a limited effect on the uterine size [22]. Women with absolute GnRH deficiencies tend to have longer follicular phases because the pituitary gland needs to be primed for several days before active secretion of FSH and LH [2].

Other researchers have sought to increase the success rate of stimulation. Awwad et al. showed that ovarian steriodogenesis, folliculogenesis, endometrial thickening, and follicular luteinization after hCG were improved when daily dosage of rec LH was administered in 4 equal parts during the stimulation [9].

The limitations of this study include the recruitment of patients from multiple centres, the application of treatment by multiple physicians, and the retrospective study design. Experience with patients with HH is gained over many years. Accordingly, physicians are often unable to complete the learning curve for this patient group.

In conclusion, OI with gonadotropins and IUI is a safe, efficient, and relatively cost-effective treatment option in the HH patient group, and reasonable pregnancy rates per cycle and per patient can be obtained. Rec FSH + rec LH facilitates cycle management but does not positively contribute to pregnancy rates and is more expensive than some other feasible options. The finding that the second cycles had improved rates of successful stimulation and pregnancy rates compared with the first cycles is in agreement with the concept of pretreatment with gonadotropins before initiating the definite treatment. However, approximately half of all patients discontinue the treatment and seek alternative treatments. This high cycle cancellation rate seems to be the most obvious reason for discontinuation. Finally, we believe that, to improve patient compliance while maintaining pregnancy success, there is a need for studies investigating treatments that can reduce cycle cancellations.

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