Research Article / Araştırma Makalesi
doi: 10.18678/dtfd.1164685

Duzce Med J, 2023;25(1):21-26
Düzce Tıp Fak Derg, 2023;25(1):21-26

Evaluation of In Vitro Fertilization Outcomes in Women with Hypogonadotropic Hypogonadism

Hipogonadotropik Hipogonadizmli Kadınlarda İn Vitro Fertilizasyon Sonuçlarının Değerlendirilmesi

Kübra DİLBAZ[1]
0000-0002-0592-7644
Oya ALDEMİR[2]
0000-0002-6236-2774
Serdar DİLBAZ[2]
0000-0001-9542-2799
Berna DİLBAZ[2]
0000-0003-1137-8650
Runa ÖZELÇİ[2]
0000-0002-9267-8702
Yaprak ENGİN ÜSTÜN[2]
0000-0002-1011-3848

[1]Department of Obstetrics and Gynecology, Etlik Zübeyde Hanım Women's Health Training and Research Hospital, Ankara, Türkiye

[2]Department of Assisted Reproductive Technology, Etlik Zübeyde Hanım Women's Health Training and Research Hospital, Ankara, Türkiye

Corresponding Author
Sorumlu Yazar
Oya ALDEMİR
oyabircan@yahoo.com

Received / Geliş Tarihi : 21.08.2022
Accepted / Kabul Tarihi : 14.01.2023
Available Online / Çevrimiçi Yayın Tarihi : 17.02.2023

ABSTRACT

Aim: Hypogonadotropic hypogonadism (HH) is a rare clinical condition resulting from gonadal insufficiency due to low pituitary gonadotropin levels. Since ovulation occurs rarely in these patients, the probability of spontaneous pregnancy is very low. The study aimed to evaluate the in vitro fertilization (IVF) treatment outcomes in patients with HH and to compare these results with that of patients with unexplained infertility (UI) who underwent IVF treatment.
Material and Methods: In this study, 36 cycles of 28 HH patients who underwent IVF treatment and 72 cycles of 68 patients who underwent IVF treatment for UI were included. Demographic data, ovarian hyperstimulation and cycle outcomes, clinical pregnancy rates, and predictive factors for clinical pregnancy were evaluated retrospectively, and the two groups were compared.
Results: In the HH group, clinical pregnancy, and live birth rates per cycle after IVF were significantly higher compared with the UI group (n=16, 44.4% vs. n=17, 23.6%, p=0.027; and n=14, 38.9% vs. n=14, 19.4%; p=0.030, respectively). Although the number of antral follicles (p=0.001) and retrieved oocytes (p=0.042) were significantly higher in the UI group, the number of mature oocytes and grade I-II embryos were similar in the HH and UI groups. The total gonadotropin dose used and duration of stimulation in the HH group were significantly higher than in the UI group (both p=0.001).
Conclusion: HH patients responded well to IVF treatment and had better IVF outcomes compared to women who underwent IVF for UI. No prognostic factor that affected pregnancy success in HH patients was detected.
Keywords: Hypogonadotropic hypogonadism; IVF outcomes; unexplained infertility.

ÖZ

Amaç: Hipogonadotropik hipogonadizm (HH), düşük hipofizer gonadotropin düzeylerine bağlı gonadal yetmezlikten kaynaklanan nadir bir klinik durumdur. Bu hastalarda ovulasyon nadiren gerçekleştiği için spontan gebelik olasılığı çok düşüktür. Bu çalışmanın amacı, HH hastalarında in vitro fertilizasyon (IVF) tedavi sonuçlarını değerlendirmek ve bu sonuçları açıklanamayan infertilitesi (Aİ) olan ve IVF tedavisi uygulanan hastalarla karşılaştırmaktır.
Gereç ve Yöntemler: Bu çalışmaya IVF tedavisi uygulanan 28 HH hastasının 36 siklusu ve Aİ nedeniyle IVF tedavisi uygulanan 68 hastanın 72 siklusu dahil edildi. Demografik veriler, ovaryan hiperstimülasyon ve siklus sonuçları, klinik gebelik oranları ve klinik gebelik için prediktif faktörler geriye dönük olarak değerlendirildi ve iki grup karşılaştırıldı.
Bulgular: IVF sonrası siklus başına klinik gebelik ve canlı doğum oranları Aİ grubu ile karşılaştırıldığında HH grubunda anlamlı derecede daha yüksekti (sırasıyla, n=16, %44,4'e karşı n=17, %23,6; p=0,027 ve n=14, %38,9'a karşı n=14, %19,4; p=0,030). Antral folikül sayısı (p=0,001) ve toplanan oosit sayısı (p=0,042) Aİ grubunda anlamlı olarak daha yüksek olmasına rağmen, matür oosit ve grade I-II embriyo sayısı HH ve Aİ gruplarında benzerdi. HH grubunda kullanılan toplam gonadotropin dozu ve stimülasyon süresi Aİ grubuna göre anlamlı derecede daha yüksekti (her iki p=0,001).
Sonuç: HH hastaları, IVF tedavisine iyi yanıt verdiler ve Aİ nedeniyle IVF uygulanan kadınlara oranla IVF sonuçları daha iyi oldu. HH hastalarında gebelik başarısını etkileyen herhangi bir prognostik faktör saptanmadı.
Anahtar kelimeler: Hipogonadotropik hipogonadizm; IVF sonuçları; açıklanamayan infertilite.

Presented orally at the TSRM 2021 - 9th Reproductive Health and Infertility Congress (November 11-14, 2021; Antalya, Türkiye).

INTRODUCTION

Hypogonadotropic hypogonadism (HH) is a rare clinical syndrome caused by hypothalamic or pituitary defects that lead to gonadal insufficiency (1). HH is classified as group 1 ovulation disorders according to the World Health Organization (WHO) classification (2). Depending on the age of onset, patients experience delayed or arrested puberty, secondary amenorrhea, and infertility. Biochemically, it is characterized by low serum sex steroid hormone levels, low or normal luteinizing hormone (LH), and low follicle stimulating hormone (FSH) levels (3). Since ovulation occurs rarely in these patients, the probability of spontaneous pregnancy is very low. Therefore, fertility in these patients is achieved by assisted reproductive techniques (4).

As it is a rare disease, there are a limited number of studies evaluating the reproductive capacity and infertility treatment outcomes in women with HH. These patients appear to be definite candidates for ovulation induction with exogenous gonadotropins (5). Studies have found that the duration of ovarian stimulation is long and the total gonadotropin dose used is high in HH patients (5,6). In the literature, pregnancy outcomes in patients who underwent in vitro fertilization (IVF) for HH were compared with the IVF outcomes of different infertility groups (5,7,8), and the outcomes were reported to be comparable and even better in patients with the diagnosis of HH.

In this study, we aimed to evaluate the treatment results of patients with HH who underwent IVF treatment and to compare these results with the results of patients who underwent IVF for unexplained infertility (UI).

MATERIAL AND METHODS

In this study, the records of the patients who attended to the Etlik Zübeyde Hanim Women's Health Training and Research Hospital, Health Sciences University, Assisted Reproductive Technologies Clinic, Ankara, Turkey between September 2007 and July 2019 for IVF treatment were retrospectively analyzed. A total of 36 IVF cycles of 28 patients diagnosed as HH were examined as the study group. It was decided to recruit twice the number of study patients as the control group and 72 IVF cycles of 68 patients determined by randomization table among the patients with an International Statistical Classification of Diseases and Related Health Problems (ICD) code of N97.9 diagnosed as UI during the time span were evaluated. The study was approved by the institutional ethics committee (22/07/2020, 2020/100) and was conducted in accordance with the Declaration of Helsinki. At the beginning of the treatment, all patients were informed that the treatment process data could be used in scientific research and consent had been obtained.

In the study group, patients aged 18-35 years old who were diagnosed as HH with a basal serum FSH level <5 mIU/ml and LH level <5 mIU/ml, body mass index (BMI) below 30 kg/m^2, and who received IVF treatment in our hospital were included. Patients over 35 years of age, patients with BMI >30 kg/m^2, concomitant male factor, diminished ovarian reserve (DOR), and/or endometriosis or leiomyoma of the uterus were excluded. In the UI group, the inclusion criteria were being aged 18-35 years, having normal ovarian reserve tests (day 3 basal serum FSH level ≤10 mIU/mL and estradiol (E2) level ≤80 pg/ml, serum anti-Müllerian hormone (AMH) level >1.1 ng/ml and antral follicle count >5), normal hysterosalpingography and normal spermiogram values in accordance with the WHO criteria, Patients with endometriosis, endocrine pathology, leiomyoma were also excluded from the control group.

In the UI group, standard gonadotropin releasing hormone agonist (GnRH-a) or gonadotropin releasing hormone antagonist (GnRH-ant) protocols were applied after the patient's baseline evaluation. Ovarian hyperstimulation was started on the 2nd or 3rd day of menstruation using human menopausal gonadotropin (hMG, Menogon, Ferring, Turkey or Merional, IBSA, Turkey) in the HH patient group and recombinant FSH (Gonal F, Merck Serono, İstanbul, Turkey or Puregon, Organon, İstanbul, Turkey) and/or hMG was used in the UI patient group. In both groups, the dose of gonadotropins was personalized according to the patient's age, antral follicle count, and BMI, and necessary dose changes were made according to the ovarian response. Patients were monitored with serial transvaginal ultrasonography (TVUSG) for follicular development and serum E2, LH, and progesterone level measurements until the ovulation trigger. Recombinant human chorionic gonadotropin (hCG) was applied when at least 3 follicles reached a mean diameter of 18 mm. The oocyte retrieval (oocyte pick-up, OPU) procedure was performed 34-36 hours following hCG administration with TVUSG-guided aspiration.

All mature oocytes were inseminated using an intracytoplasmic sperm injection (ICSI) procedure. The presence of fertilization was confirmed by the appearance of two pronuclei 18-20 hours after ICSI. Day 3 embryos were classified in accordance with the embryo classification system 61-65 hours after ICSI using the number, size, and symmetry of the cells and the degree of fragmentation (9). At the blastocyst stage, embryo scoring was based on the equal-sized blastomere number and presence of adhesion, visible blastocyst cavity and inner cell mass, zona pellucida thickness, and trophectoderm with adequate cellular continuity (10).

In the presence of an available embryo(s), embryo transfer (ET) was performed under the guidance of transabdominal ultrasonography.

Luteal phase support was started for all patients following the OPU procedure with vaginal progesterone (Crinone 8% gel, Serono, İstanbul, Turkey) or vaginal progesterone plus 100 mg intramuscular progesterone (Progestan, Kocak, İstanbul, Turkey). The pregnancy test was performed on the 14th day after OPU and in case of a positive test, βhCG measurement was repeated 2-4 days later. Patients with sufficient elevation were called for a follow-up 14 days later and an ultrasonographic examination was performed. The presence of a fetal heartbeat was considered as clinical pregnancy. Luteal support was continued until 12 weeks of gestation.

The ET could not be performed when i) no follicular development was observed with ovarian stimulation, ii) no mature oocytes were retrieved, and iii) fertilization failure or embryo development arrest was encountered.

Demographic characteristics, ovarian hyperstimulation and OPU outcomes, embryo development, ET, and clinical pregnancy and live birth rates of the HH patients

undergoing IVF treatment were evaluated. The data obtained were compared with the data of the patients who underwent IVF with the diagnosis of UI.

Statistical Analysis

Data analysis was done with IBM SPSS v.22.0 package. Descriptive statistics were presented as mean±standard deviation and median (minimum-maximum) for continuous variables, and as numbers and percentages for categorical variables. Whether the distribution of continuous variables was normal was evaluated with the Shapiro-Wilk test. In cases where normal distribution was obtained, the groups were compared with Student's t-test, and in cases where normal distribution was not achieved with the Mann-Whitney U test. The Pearson chi-square or Fisher's exact test was used to compare the categorical variables. For $p < 0.05$, the results were considered statistically significant.

RESULTS

The study included 28 patients who underwent IVF treatment for HH and 68 patients who underwent IVF treatment for UI. The data from 36 cycles of 28 patients in the HH group and 72 cycles of 68 patients in the UI group were evaluated. The demographic characteristics of the patients were shown in Table 1.

The total gonadotropin dose used and the duration of ovarian hyperstimulation in the HH group were significantly higher than in the UI patients (p=0.001). However, the number of oocytes retrieved (p=0.042) and serum progesterone level on the day of OPU (p=0.020) were higher in the UI group than in the HH group, and these differences were statistically significant. On the other hand, mature oocyte count, fertilized oocyte count, grade I-II embryo count, and ET rate were similar in both groups. The cycle characteristics of the patients were shown in Table 2.

There was no statistically significant difference between the number of patients who underwent ET in the HH group and in the UI group (p=0.120). Pregnancy occurred in 17 of 36 cycles (47.2%) in the HH group and the clinical pregnancy rate was 44.4% (n=16). In the UI group, 20 of 72 cycles (27.8%) resulted in pregnancy. In the HH group, the clinical pregnancy rate was 44.4% (n=16/36) per cycle and 57.1% (n=16/28) per patient whereas, in the UI group, the clinical pregnancy rate was 23.6% (n=17/72) per cycle and 25.0% (n=17/68) per patient. Clinical pregnancy rates per cycle and per patient were significantly higher in the HH group compared with the UI group (p=0.027, and p=0.003, respectively). The data on pregnancy outcomes were compared in Table 3.

The demographic characteristics and cycle outcomes of the HH patients with and without clinical pregnancy were compared and no significant difference was found apart from duration of infertility, serum E2 level on ET day, and the number of patients who underwent ET (Table 4). The duration of infertility was significantly longer and serum E2 level on ET day was significantly higher in patients who could not achieve clinical pregnancy (p=0.019, and p=0.011, respectively).

Table 1. The demographic characteristics of the patients

	HH (n=28)	UI (n=68)	p
Age (years)	30 (23-35)	32 (23-34)	0.858
Height (cm)	163.5 (146-178)	153.7 (144-179)	**0.001**
Weight (kg)	66 (47-80)	55 (43-94)	**0.001**
BMI (kg/m^2)	24.7 (18.4-30.0)	23.1 (18.9-31.6)	**0.002**
FSH (mIU/ml)	0.37 (0.0-4.6)	3.85 (0.7-9.8)	**0.001**
LH (mIU/ml)	0.20 (0.0-3.6)	4.82 (1.4-12.6)	**0.001**
E2 (pg/ml)	14.5 (3.0-54.0)	56.2 (11.8-181.0)	**0.001**
Duration* (months)	69 (18-168)	72 (24-228)	0.315

HH: hypogonadotropic hypogonadism, UI: unexplained infertility, BMI: body mass index, FSH: follicle stimulating hormone, LH: luteinizing hormone, E2: estradiol, *: duration of infertility, data presented as median (minimum-maximum)

DISCUSSION

Hypogonadotropic hypogonadism is a rare disorder characterized with hypothalamic or pituitary defects that lead to gonadal insufficiency (1) with a spectrum of clinical symptoms depending on the age of onset and the degree of FSH and LH deficiency. Fertility is reduced in these patients as a result of anovulation, therefore assisted reproductive technologies are provided to achieve pregnancy (4). The infertility treatment protocol in HH

Table 2. Comparison of the in vitro fertilization cycle characteristics of the HH and UI groups

	HH (n=36)	UI (n=72)	p
Total gonadotropin dose (IU)	4045±1370	1950±936	**0.001**
Ovarian stimulation duration (days)	11.2±1.6	9.1±3.1	**0.001**
Antral follicle count	6.5 (0-30)	14 (2-44)	**0.001**
E2 level on OPU day (pg/ml)	1376.75±1015.43	1515.63±1197.44	0.552
Progesterone level on OPU day (ng/ml)	0.18±0.30	0.95±1.82	**0.020**
Endometrial thickness on OPU day (mm)	9.8±2.4	8.8±3.5	0.139
Number of oocytes retrieved	9 (0-35)	13 (2-43)	**0.042**
Number of mature oocytes	7 (1-26)	9 (0-30)	0.580
Number of fertilized oocytes	4 (0-21)	5 (0-25)	0.069
Number of good quality embryos	1 (0-3)	1 (0-3)	0.246
ET ratio, n (%)	29 (80.6)	66 (91.7)	0.120
Progesterone level on ET day (ng/ml)	61.57±34.42	93.59±64.69	0.077
E2 level on ET day (pg/ml)	1515.87±1287.22	1780.19±1217.49	0.154
Endometrial thickness on ET day (mm)	9.5±2.2	10.3±1.9	0.075

HH: hypogonadotropic hypogonadism, UI: unexplained infertility, OPU: oocyte pick-up, E2: estradiol, ET: embryo transfer, descriptive statistics of the variables were presented as mean±standard deviation or median (minimum-maximum)

Table 3. Comparison of the in vitro fertilization cycle outcomes of the patients with HH and UI

	HH (n=36)	UI (n=72)	p
Number of cycles with ET, n (%)	29 (80.6)	66 (91.7)	0.120
Implantation rate, n (%)	17 (47.2)	20 (27.8)	**0.045**
Clinical pregnancy rate per cycle, n (%)	16 (44.4)	17 (23.6)	**0.027**
Clinical pregnancy rate per patient, n (%)	16/28 (57.1)	17/68 (25.0)	**0.003**
Biochemical pregnancy, n (%)	1 (2.8)	3 (4.2)	0.999
Clinical pregnancy outcomes, n (%)			
Live birth rate per cycle	14 (38.9)	14 (19.4)	**0.030**
Live birth rate per patient	14/28 (50.0)	14/68 (20.6)	**0.004**
Miscarriage rate	2 (5.6)	3 (4.2)	0.999

HH: hypogonadotropic hypogonadism, UI: unexplained infertility, ET: embryo transfer, data presented as n (%)

Table 4. Comparison of demographic characteristics and IVF cycle data in patients with HH who achieved clinical pregnancy and who did not

	Clinical Pregnancy (n=16)	No Pregnancy (n=20)	p
Age (years)	29.1±4.1	29.8±3.22	0.970
BMI (kg/m^2)	25.1 (18.6-30.0)	23.9 (18.4-30.0)	0.626
Duration of infertility (months)	51 (18-132)	72 (36-168)	**0.019**
FSH (mIU/ml)	0.32 (0-4.59)	0.61 (0.01-3.70)	0.737
LH (mIU/ml)	0.10 (0-3.60)	0.25 (0.07-2.09)	0.680
E2 (pg/ml)	13.95 (3.00-54.00)	17.05 (5.00-43.72)	0.737
Total gonadotropin dose (IU)	3776±1134	4260±1528	0.300
Ovarian stimulation duration (days)	11.3±1.4	11.2±1.7	0.835
Antral follicle count	7 (3-18)	5 (0-30)	0.228
E2 level on OPU day (pg/ml)	1096±795	1600±1131	0.142
Number of oocytes retrieved	10 (4-35)	8.5 (0-27)	0.970
Number of mature oocytes	9 (3-26)	7 (1-17)	0.760
Number of good quality embryos	1 (1-3)	0.5 (0-3)	0.239
E2 level on ET day (pg/ml)	987±800	2166±1494	**0.011**
Endometrial thickness on ET day (mm)	9.5±2.5	9.5±1.8	0.966

BMI: body mass index; FSH: follicle stimulating hormone; LH: luteinizing hormone; E2: estradiol, OPU: oocyte pick-up; ET: embryo transfer, descriptive statistics of the variables were presented as mean±standard deviation or median (minimum-maximum)

patients is not clear yet. In HH patients, both FSH and LH are required for ovarian hyperstimulation to achieve full maturation of follicles and to obtain oocytes with fertilization capacity. In our study, the IVF outcomes in HH patients were investigated, and 16 clinical pregnancies occurred in these patients with 14 live births. The rate of achieving clinical pregnancy with IVF treatment in HH patients was found to be 44.4% per cycle and 57.1% per patient, and the live birth rate was 38.9% per cycle, 50% per patient. It has been concluded that successful results can be obtained with IVF in HH patients.

Previous studies have shown that the duration of ovarian hyperstimulation and total gonadotropin dose used in HH patients is higher than in patients with other infertility etiologies (5,6). Similarly, in our study, we found that the HH patient group required longer and higher doses of gonadotropin administration than the patients with UI. This can be explained by the presence of silent ovaries that need activation before a follicular response can be obtained. However, it has been shown that high gonadotropin doses may have adverse effects on the oocytes or embryos (11,12) and may impair fertilization. The results regarding the fertilization rate in HH patients are conflicting. Gaffari et al. (13) concluded in their study that the fertilization rate was higher in patients with tubal infertility compared with the HH patient group whereas Ulug et al. (5) found no difference in terms of fertilization rate between patients who underwent IVF for tubal infertility and HH. Kumbak et al. (7) on the other hand reported a higher fertilization rate in HH patients than in UI patients. Despite the differences in fertilization rates in all these studies, the number of mature oocytes and good-quality embryos were reported to be similar (5,7,13). In our study, the number of mature oocytes, fertilization rate, and the number of good-quality embryos were found to be similar in the HH group and the control group and it was concluded that high-dose gonadotropins did not have a negative effect.

In previous studies, the IVF outcomes of HH patients were compared with the outcomes of patients who underwent IVF for different etiologies. In a study similar to the presented study performed by Kumbak et al. (7) the IVF outcomes of 27 patients with HH and 39 patients with UI were compared and the pregnancy rate was found to be 59% in HH patients and 46% in patients with UI. It was stated that there was no significant difference in pregnancy

rates between the two groups. Ulug et al. (5) compared the IVF results of 58 HH patients with the results of patients with tubal infertility. ET was performed in 53 of 58 (91.3%) HH patients. In the presented study, the ET ratio in the HH group was slightly lower than the ratio in the UI group (80.6% vs 91.7% respectively) but the difference was not statistically significant. Ulug et al. (5) reported that 30 patients (51.7%) achieved pregnancy, and the pregnancy rate per ET was 56.6% which was found to be similar with the pregnancy rate of women with tubal factor infertility. In a recent study performed by Zhang et al. (14), the live birth rate of the first fresh cycle was found to be higher in the control group which included patients with tubal or male factor infertility compared with the HH group but the difference was not statistically significant. In our study, the clinical pregnancy rate per cycle and per patient after IVF treatment in HH patients was found to be significantly higher, than that of women with UI (44.4% per cycle and 57.1% per patient versus 23.6% per cycle and 25.0% per patient). The reported pregnancy rates after IVF-ET treatment in women with UI vary between 20.7 to 45.8% in the literature (15-17). The reason for this wide range can be explained by the fact that the success of achieving pregnancy with IVF in UI patients is affected by other factors including age, BMI, duration of infertility, and basal gonadotropin levels.

In another study, Yılmaz et al. (2) compared the IVF outcomes of HH patients with couples who had IVF treatment for male factor infertility. While the pregnancy rate was 30% (10/33) in patients with HH, this rate was 31.4% in women who underwent IVF for male factor infertility in their study, and they stated that the IVF treatment results were similar in both groups. In a similar study, Yıldırım et al. (8) examined the IVF outcomes in 13 women with HH and compared the results with the outcomes of women with tubal factor infertility. In conclusion, they reported that 4 (30%) of 13 HH patients achieved pregnancy, and the pregnancy and live birth rates were similar with tubal factor infertility patients.

When the prognostic factors for achieving pregnancy in infertile patients other than the HH group basal serum FSH, LH, E2, and serum AMH levels are found to be associated with ovarian response to hyperstimulation and IVF outcomes. However, these factors cannot be used in women with HH as the basal gonadotropin levels are very low. In our study, it was shown that the basal FSH, LH, and E2 levels, albeit low, were not associated with IVF treatment results in HH patients. Eroglu et al. (18) reported that higher E2 level on hCG day, increased endometrial thickness, and a higher number of oocytes retrieved were the factors affecting the ongoing pregnancy rates in the HH group. We found that the number of oocytes retrieved and the endometrial thickness on ET day were similar in the HH patients who achieved clinical pregnancy and who did not, but higher E2 levels were measured on ET day in HH patients who did not get clinical pregnancy.

CONCLUSION

In conclusion, the IVF outcomes in HH patients are quite promising, and clinical pregnancy and live birth rates are higher compared with the patients undergoing IVF with the diagnosis of UI.

Ethics Committee Approval: The study was approved by the Ethics Committee of Etlik Zübeyde Hanım Women's Health Training and Research Hospital (22.07.2020, 100).

Conflict of Interest: None declared by the authors.

Financial Disclosure: None declared by the authors.

Acknowledgments: None declared by the authors.

Author Contributions: Idea/Concept: KD, SD, BD, YEÜ; Design: KD, OA, SD, RÖ; Data Collection/Processing: KD, OA, RÖ; Analysis/Interpretation: KD, OA, BD, YEÜ; Literature Review: KD, SD, RÖ; Drafting/Writing: KD, OA, BD; Critical Review: SD, BD, RÖ, YEÜ.

REFERENCES

1. Silveira LF, MacColl GS, Bouloux PM. Hypogonadotropic hypogonadism. Semin Reprod Med. 2002;20(4):327-38.
2. Yilmaz S, Ozgu-Erdinc AS, Yumusak O, Kahyaoglu S, Seckin B, Yilmaz N. The reproductive outcome of women with hypogonadotropic hypogonadism undergoing in vitro fertilization. Syst Biol Reprod Med. 2015;61(4):228-32.
3. Unuane D, Tournaye H, Velkeniers B, Poppe K. Endocrine disorders & female infertility. Best Pract Res Clin Endocrinol Metab. 2011;25(6):861-73.
4. Eser A, Bostancı Ergen E. Infertility treatment results in hypogonadotropic hypogonadism cases. J Gynecol Obstet Neonatol Med. 2016;13(4):160-3. Turkish.
5. Ulug U, Ben-Shlomo I, Tosun S, Erden HF, Akman MA, Bahceci M. The reproductive performance of women with hypogonadotropic hypogonadism in an in vitro fertilization and embryo transfer program. J Assist Reprod Genet. 2005;22(4):167-71.
6. Lewit N, Kol S. The low responder female IVF patient with hypogonadotropic hypogonadism: do not give up! Fertil Steril. 2000;74(2):401-2.
7. Kumbak B, Kahraman S. Women with hypogonadotropic hypogonadism: cycle characteristics and results of assisted reproductive techniques. Acta Obstet Gynecol Scand. 2006;85(12):1453-7.
8. Yildirim G, Ficicioglu C, Attar R, Akcin O, Tecellioglu N. Comparision of reproductive outcome of the women with hypogonadotropic hypogonadism and tubal factor infertility. Clin Exp Obstet Gynecol. 2010;37(2):120-2.
9. Baczkowski T, Kurzawa R, Głabowski W. Methods of embryo scoring in in vitro fertilization. Reprod Biol. 2004;4(1):5-22.
10. Gardner DK, Lane M, Stevens J, Schlenker T, Schoolcraft WB. Blastocyst score affects implantation and pregnancy outcome: towards a single blastocyst transfer. Fertil Steril. 2000;73(6):1155-8.
11. Liu S, Feng HL, Marchesi D, Chen ZJ, Hershlag A. Dose-dependent effects of gonadotropin on oocyte developmental competence and apoptosis. Reprod Fertil Dev. 2011;23(8):990-6.
12. Edgar DH, Whalley KM, Mills JA. Effects of high-dose and multiple-dose gonadotropin stimulation on mouse oocyte quality as assessed by preimplantation

development following in vitro fertilization. J In Vitro Fert Embryo Transf. 1987;4(5):273-6.
13. Ghaffari F, Arabipoor A, Lankarani NB, Etminan Z, Tehraninejad ES. Assisted reproductive technique outcomes in hypogonadotropic hypogonadism women. Ann Saudi Med. 2013;33(3):235-40.
14. Zhang CM, Zhang H, Yang R, Chen LX, Liu P, Li R, et al. The reproductive outcome of women with hypogonadotropic hypogonadism in IVF. Front Endocrinol (Lausanne). 2022;13:850126.
15. Guzick DS, Sullivan MW, Adamson GD, Cedars MI, Falk RJ, Peterson EP, et al. Efficacy of treatment for unexplained infertility. Fertil Steril. 1998;70(2):207-13.
16. Reindollar RH, Regan MM, Neumann PJ, Levine BS, Thornton KL, Alper MM, et al. A randomized clinical trial to evaluate optimal treatment for unexplained infertility: the fast track and standard treatment (FASTT) trial. Fertil Steril. 2010;94(3):888-99.
17. Kansal-Kalra S, Milad MP, Grobman WA. In vitro fertilization (IVF) versus gonadotropins followed by IVF as treatment for primary infertility: a cost-based decision analysis. Fertil Steril. 2005;84(3):600-4.
18. Eroglu M, Helvacioglu C, Eser AÇ, Sayıcı D, Arınkan A, Şahin S. What are the factors affecting IVF success in women with hypogonadotropic hypogonadism? Eur Rev Med Pharmacol Sci. 2021;25(24):7750-3.