Annals of Clinical and Analytical Medicine
Original Research

Latent ovarian stimulation in the management of infertile patients with hypogonadotropic hypogonadism

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Abstract

Aim: This study was designed to determine the effects of different treatment approaches on clinical pregnancy and live birth rates in patients with infertility due to hypogonadotropic hypogonadism (HH).

Material and Methods: The files of 31 patients with HH who applied with the complaint of infertility were retrospectively reviewed. Different infertility treatment protocols were applied to 21 of these cases, and the total number of cycles in which treatment was applied was recorded as 36. Of the 36 cycles, 22 were ovulation induction plus timed sexual intercourse, 3 were ovulation induction plus IUI, and the remaining 11 cycles were IVF/ICSI. Clinical pregnancy and live birth rates were determined as the primary outcome of our study.

Results: Twelve (33% of 36 cycles) of 21 patients conceived and 9 (25% of 36 cycles) had a live birth. When subgroup analysis was performed, pregnancy was detected in 9 cases (41%; 9/22) in the OI group, while 6 cases (27%; 6/22) had live births. In the IUI group, pregnancy was detected in 2 cases (66%; 2/3) and live birth in 2 cases (66%). In the IVF group, pregnancy was detected in only 1 case (9%), and live birth- in 1 case (9%; 1/11). Two out of 3 patients who received 75 IU / day latent ovarian stimulation with HMG for 3 months became pregnant.

Discussion: Latent ovarian induction with low doses of HMG in infertile patients with HH sensitizes developing follicles to exogenous gonadotropins and contributes to clinical pregnancy and live birth rates.

Keywords

Hypogonadotropic Hypogonadism; Infertility; Assisted Reproductive Technology; Latent Stimulation; Pregnancy

DOI: 10.4328/ACAM.20774 Received: 2021-07-06 Accepted: 2021-07-27 Published Online: 2021-08-06 Printed: 2021-08-15 Ann Clin Anal Med 2021;12(Suppl 3): S343-346
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Introduction

Hypogonadotropic hypogonadism (HH) is classified as group 1 anovulation according to the World Health Organization (WHO) classification of female infertility [1]. It can also be called central hypogonadism or hypothalamic amenorrhea. In amenorrhea due to HH, either GnRH release is insufficient, or the pituitary is resistant to the GnRH effect [2]. In patients with HH, FSH, LH and estradiol levels are lower than normal [3]. Although estrogen/progesterone withdrawal bleeding is observed, progesterone withdrawal bleeding does not occur. In addition to primary or secondary amenorrhea, different clinical findings such as anosmia, osteopenia and short stature can be seen. The ovaries and uterus are smaller than expected due to estrogen deficiency secondary to FSH and LH deficiency. Serum AMH values may sometimes be low and sometimes close to normal. Secondary sex characteristics of those with a clinical picture of primary amenorrhea are generally not well developed. Its incidence is seen as 1/50000 in women and 1/10000 in men [2]. Approximately 5-10% of the patients presenting with anovulation complaints make up this group of patients. Genetic reasons have been blamed in the etiology and more than 20 genes have been described.

In patients with HH suffering from infertility are attempted to be treated with pulsatile GnRH treatment or the combined use of gonadotropic hormones such as FSH, LH and hCG. Assisted Reproductive Techniques (ART) are mostly used in infertile cases due to HH. Before ART, ovulation induction (OI) followed by timed sexual intercourse or intrauterine insemination (IUI) may be tried. In cases that do not respond to IUI treatment, one of the controlled ovarian hyperstimulation (COS) protocols is used [3-5]. There is no standard protocol applied in the treatment of infertility due to HH. While some authors suggest starting with high dose gonadotropin, such as 450 IU, some authors advocate the Step-down protocol [4]. This study was designed to determine the effects of different treatment approaches on clinical pregnancy and live birth rates in patients with infertility due to HH.

Material and Methods

This retrospective study was carried out following the approval of Mustafa Kemal University Tayfur Ata Sökmen Medical Faculty Ethics Committee (Prot no:2021/09/02- 01/07/2021). The files of patients with HH who applied to Mustafa Kemal University Tayfur Ata Sökmen Faculty of Medicine, Department of Obstetrics and Gynecology between 2013-2020 with the complaint of infertility were retrospectively reviewed. Screening of medical records revealed 31 cases meeting HH criteria. Different infertility treatment protocols were applied to 21 of these cases, and the total number of cycles in which treatment was applied was recorded as 36. The remaining 10 cases were not included in the evaluation because they did not receive any infertility treatment. Of the 36 cycles, 22 were ovulation induction plus timed sexual intercourse, 3 were ovulation induction plus IUI, and the remaining 11 cycles were IVF/ICSI.

Patients diagnosed with HH were selected among infertile cases and their demographic and hormonal characteristics were recorded. The treatment protocols applied to the patients, the drug doses used, and the duration of infertility were also recorded. Clinical pregnancy and live birth rates were determined as the primary outcome of our study. All participants underwent routine laboratory and radiological examination to diagnose the underlying factors of infertility. After 3-7 days of abstinence, a semen analysis was performed. Hysterosalpingography was performed in all participants. Basal hormone profiles of all cases were examined on the 2nd or 3rd day of menstruation, after hormone replacement therapy, and the diagnosis of HH was confirmed. Endometrial thicknesses in all cases diagnosed with HH were less than 5 mm, and while there was no progesterone withdrawal bleeding, estrogen or estrogen plus progesterone withdrawal bleeding occurred.

Besides amenorrhea, decreased uterine and ovarian dimensions were interpreted as the absence of the trophic effect of estrogen. This study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the local Ethics Committee. In additon to patients aged 18-45 years with a BMI between 20-35 kg/m2 and without any systemic disease, those with FSH <2.5 mIU/mL, LH <2.5 mIU/mL, endometrium thickness <4 mm, normal sperm analysis and HSG were included in the study. Estradiol value should be less than 60 pg/mL on the 2nd day of the cycle, and the values measured on the 3rd day were <80 pg/mL. Pituitary or adrenal tumor, endocrinological disorders were excluded from the study.

COS protocol for IVF/ICSI

Cycloprogynova (Bayer Türk Kimya Sanayi. Ldt. Şti. İstanbul, Turkey) was started 3 months before starting COS in infertile patients scheduled for IVF/ICSI. The COS protocol was started on the 2nd or 3rd day of the cycle for the patients who had menstruation following the use of cycloprogynova for three months. No rFSH preparations were needed in any of the HH cases. They received daily human menopausal gonadotropin (HMG) preparation: Menogon (75 IU Ferring, Copenhagen, Denmark), or Merional (75 IU IBSA, Switzerland). In addition to the measurement of serum E2 values on the 4th and 5th days of HMG treatment, follicle dimension and endometrial thickness were measured by USG. While antagonist treatment was initiated in patients with a follicle diameter of 14 mm and in those with a sufficient estrogen elevation, the antagonist was not used in patients with low estrogen levels. When the mean diameter of two or three leading follicles reached 17 mm or more, hCG (Pregnyl amp 5000 IU 1x2, Organon, Oss, The Netherlands) or ovitrelle 250 microgram /0.5 ml was used to trigger ovulation.

In cases with ovulation induction, sexual intercourse was recommended 36 hours after hCG administration, while IUI was performed 36 hours after hCG in patients who underwent IUI. The oocyte pick-up was carried out in IVF/ICSI group following ovulation trigger, at least 35 and maximum 36 hours after administration. In the presence of a positive pregnancy test, luteal support was continued and USG was performed at the 4th week of the transfer and the presence of gestational sac and thus clinical pregnancy was confirmed. Clinical pregnancy rate is defined as the evidence of a gestational sac, confirmed by ultrasound examination. The live birth rate is defined as the delivery of a live fetus after 24 completed weeks of gestational age.

Statistical Analysis

Descriptive statistics were expressed as frequency, percentage,

mean, and standard deviation. Categorical variables were analyzed using Pearson's chi-square and Fischer's exact tests. The normality of numeric variables was tested with the Kolmogorov -Smirnov test. One sample t- test was used to analyze numerical variables. All statistical analyses were performed using the SPSS (Statistical Package for the Social Sciences, SPSS Inc., Chicago, IL, USA) 21.0 package program. P<0.05 were considered statistically significant.

Results

The total number of infertile patients with hypogonadism who applied to our outpatient clinic was 31. Twenty-one patients received infertility treatment in our outpatient clinic, and 10 patients went to other centers for treatment after diagnosis. Twenty-one patients underwent 36 cycles of treatment. Twenty-two of them had timed intercourse, 3 had IUI, and the remaining 11 had IVF/ICSI. The mean age of the patients who were treated for infertility was 26.47 ± 5.22 years (OI: 26.07 ± 4.59; IUI: 28.00 ± 1.00; IVF: 27.29 ± 6.07). Two of our 21 patients were over the age of 35 and pregnancy could not be achieved. The remaining 19 patients were below 33 years of age. The mean duration of infertility was recorded as 5.37 ± 4.15 years for all patients. Mean basal FSH levels of the patients were 0.68 ± 0.72 mIU/mL, LH levels 0.37 ± 0.36 mIU/mL, and E2 levels were 28.89 ± 22.07 pg / mL. The mean daily HMG administered to the patients was calculated as 350.00 ± 101.50 IU. The mean induction time was recorded as 13.00 ± 3.86 days (OI: 13.05 ± 4.38; IUI: 10.33 ± 1.15; IVF: 13.64 ± 3.14). Mean total gonadotropin dose was 4222.27 + 1433.44 I.U (Table 1).

E2 levels on the day of hCG were 1845.32 ± 1092.32 pg/mL (OI: 1909.33 ± 1725.37; IUI: 1741.67 ± 38.19; IVF: 1866.90 ± 695.32). Endometrial thickness measured by USG on the same day was found to be 8.84 + 1.74 mm. Twelve (33% of cycles) of 21 patients conceived and 9 (25%) had a live birth. When subgroup analysis was performed, pregnancy was detected in 9 cases (41%) in the OI group, while 6 cases (27%) had live births. In the IUI group, pregnancy was detected in 2 cases (66%) and live birth in 2 cases (66%). In the IVF group, pregnancy was detected in only 1 case (9%), and live birth in 1 case (9%). During 36 cycles, IUMF was detected in 2 cases, spontaneous abortion in 1 case, and OHSS in 2 cases. One triplet pregnancy and one twin pregnancy occurred in our patients who conceived. When twin pregnancy was 21 weeks, two of the fetuses died (Table 1). After administration of HMG 75 IU/day for 3 months to 2 patients who could not get pregnant with IVF/ICSI, one of the patients became pregnant with IVF/ICSI and gave a live birth at term, the other patient became pregnant with twins with OI and timed intercourse and gave a twin live birth at 35 weeks. After HMG 75IU/day was administered for 3 months to 2 patients who did not respond to COS, IVF was performed, but pregnancy could not be achieved. Three of our patients, who could not conceive in the first cycle with OI and timed sexual intercourse, became pregnant with OI and timed sexual intercourse in the second cycle and gave live birth.

Discussion

HH is an uncommon but treatment-resistant cause of infertility. Although gonadotropins and pulsatile GnRH are used in its treatment, there is no standard treatment protocol. Increasing the sensitivity of follicles to HMG before treatment may increase the response to the COS protocol to be made. In this study, we discussed the effect of latent ovarian stimulation with HMG on clinical pregnancy and live birth rates. The demographic and clinical data of our patients with HH who participated in the study are shown in Table 1. We found the average age of the participants to be 26.47 ± 5.22. Eser et al. [4] found the mean age of HH patients to be 30.7, Kıyak et al. 27.8 [6] and Gustova et al. [5] stated that it was 33. We found the duration of infertility as 5.37 ± 4.15 years. Eser et al. estimated the duration of infertility in HH patients for 4.7 years [4]; Kumbak et al. reported it as 9.3 ± 6.1 years [7]. Our findings are consistent with the literature in terms of patient age and duration of infertility. Basal FSH and LH values of our patients were found to be 0.68 ± 0.72 mIU/mL and 0.37 ± 0.36 mIU/mL, respectively, in accordance with the literature. While Yılmaz et al. reported FSH values as 0.89 ± 0.73 mIU/mL [3], Eser et al. reported them as 1.1 mIU/mL [4]. The basal E2 value of our patients was 28.89 ± 22.07 pg/ml, which is similar to the literature data [6,8]. The

Table 1. Demographic characteristics of infertile patients due to hypothalamo hypopituitary hypogonadism and ovarian induction data and pregnancy status according to ART type

Parameters	Applied Assisted Reproductive Technology			All cycles (n=36)
	OI (n=22)	IUI (n:3)	IVF/ICSI (n:11)	
Age (years)	26.07±4.59	28.00±1.00	27.29±6.07	26.47±5.22
Infertility duration (years)	4.36±3.20	2.17±1.04	8.18±4.87	5.37±4.15
FSH (mIU/mL)	0.63±0.76	0.73±1.10	0.77±0.58	0.68±0.72
LH (mIU/mL)	0.30±0.29	0.53±0.58	0.35±0.39	0.37±0.36
E2 (pg/ml)	25.05±20.09	57±32.92	28.91±19.28	28.89±22.07
Daily HMG dose (IU)	346.25±118.18	325.00±86.60	363.64+74.47	350.00±101.50
Induction time (days)	13.05±4.38	10.33±1.15	13.64±3.14	13.00±3.86
Total HMG dose (IU)	4191.32+1754.45	3325.00±826.14	4520.46±746.31	4222.27+1433.44
E2 on the day of hCG (pg/ml)	1909.33±1725.37	1741.67±38.19	1866.90±695.32	1845.32±1092.32
ET on the day of hCG (mm)	8.5±1.05	7.66±0.58	9.40±2.12	8.84+1.74
Clinical pregnancy n(%)	9 (41%)	2 (66%)	1 (9%)	12 (33%)
Live births n(%)	6 (27%)	2 (66%)	1 (9%)	9 (25%)

FSH: Follicle Stimulating Hormone, LH: Luteinizing Hormone, E2: Estradiol, GH: Gonadotropic Hormone, ET: Endometrium thickness, OI: Ovulation Induction, IUI: Intra Uterine Insemination, IVF: In-Vitrofertilization, ART: Assisted Reproductive Technology, n: Count of cycles.

participants' average daily dose of HMG was 350 IU. Kumbak et al. (IVF) 325 IU [7], Ghaffari et al. 350 IU [8], Yılmaz et al reported it as 380 IU [3]. We recorded the average induction time as 13 days. Gustavo et al. reported this period as 13 days [5], Ghaffari et al. 13.8 days [8], Kumbak et al. reported it as 14 days [7]. We determined that the average total gonadotropin dose applied was 4222 units. Gustavo et al. stated this dose as 2700 IU, Kumbak et al. 4537 IU [7] and Yılmaz et al. reported it as 4741 IU [3]. Our E2 values, measured on the day of hCG and endometrial thickness measurements, were found to be similar to the literature data [3,4,6,7].

While 12 of the 21 patients participating in the study became pregnant (33 % of cycles), 9 patients (25%) had a live birth. In the timed sexual intercourse group, 9 patients (9/22, 41%) became pregnant, 6 of them (27%) gave live birth. In the IUI group, two out of 3 cases conceived, while both cases (66%) had live births. Only one case conceived in the IVF group (9%) and that patient had a live birth (9%). While the pregnancy rate in HH patients was reported as 12.2% by Kıyak et al. [6], it was noted as a 19.4% by Ghaffari et al [8]. Live birth rates were reported by different authors as 15.2%, 30% [3], 59.3 [7] and 69.2% [5]. As a result, pregnancy rates of all our cases are compatible with the literature. The high level of success in the timed sexual intercourse group may be due to the fact that our patients were young or unconsciously not did not undergo treatments that weaken their ovarian reserve. Our pregnancy success in IVF patients was 9%, and this rate is very low. When compared with the IUI group, patients in the IVF group are treatment-resistant and elderly patients.

As a complication, IUMF was detected in 2, abortion in 1, and OHSS in 2 cases. One of our pregnant patients had triplet pregnancy and one had twin pregnancy. Ulug et al. reported the rate of multiple pregnancy as 46.6% and the rate of abortion as 3.4% [1]. Ozcil reported the contribution of ART to twin pregnancies as 21%, and the fetal mortality rate as 20% in twin pregnancies with ART [9]. Gao et al reported abortion and multiple pregnancy in HH patients [10].

After the administration of HMG 75 IU/day for 3 months to 2 patients who could not get pregnant with IVF/ICSI, one of the patients became pregnant with IVF/ICSI, the other patient became pregnant with twins with OI and timed intercourse. After HMG 75 IU/day was given for 3 months to 2 patients who did not respond to COS, these patients responded to COS; IVF was performed. Three of our patients, who could not conceive in the first cycle with OI and timed sexual intercourse, became pregnant with OI and timed sexual intercourse in the second cycle.

Conclusion

Dormant primordial follicles under long-term HMG effect begin to grow into primary follicles and reach the preantral and antral stages, respectively [11]. This process takes approximately 72 days. Since there is no GnRH release in HH patients or the pituitary is insensitive to GnRH, FSH and LH release is either absent or insufficient. As a result, the follicles wait in the dormant phase and the follicles cannot reach further stage. Kumbak et al. stated that in order to create a follicular response to HMG, the silent ovaries should be activated first and the ovaries should be made sensitive to gonadotropes [7]. At least 72 days and 75 IU/day HMG priming may be required to complete this process and stimulate dormant follicles. At the end of this process, COS can be started by increasing the dose applied in accordance with the step-up protocol [12,13]. As a result, latent ovarian induction with low dose HMG in infertile patients with HH sensitizes follicles to gonadotropins. Applying COS to sensitized ovaries according to the step-up protocol will both increase the number of follicles and oocytes collected. Thus, latent ovarian stimulation can be considered capable of increasing pregnancy rates.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Funding: *None*

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

References

1. 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.

2. Hasdemir PS, Terzi H, Koltan S. O. Hipogonadotropik hipogonadizm olgularına yaklaşım: infertilite tedavisi ve uzun dönem yönetim. Kocaeli Tıp Dergisi. 2015; 4(1):13-18.

3. 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.

4. Eser A, Ergen EB. Hipogonadotropik Hipogonadizm Olgularında İnfertilite Tedavisi Sonuçları (Results of Infertility Treatment in Hypogonadotropic Hypogonadism Cases). Jinekoloji-Obstetrik ve Neonatoloji Tıp Dergisi/ Journal of Gynecology-Obstetrics and Neonatology Medicine. 2016; 13(4):160-3.

5. Cecchino GN, Canillas GM, Cruz M, García-Velasco JA. Impact of hypogonadotropic hypogonadism on ovarian reserve and response. J Assist Reprod Genet. 2019; 36(11):2379-84.

6. Kıyak H, Bulut B, Karacan T, Özyürek E, Gedikbaşı A, Api M. Management of ovulation induction and intrauterine insemination in infertile patients with hypogonadotropic hypogonadism. Journal of Gynecology Obstetrics and Human Reproduction. 2019; 48(10):833-8.

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. 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.

9. Özçil MD. İkiz Gebelikler ve Yardımcı Üreme Teknikleri ile Oluşan İkiz Gebeliklerin Feto-maternal Etkilerinin Karşılaştırılması (Comparison of Feto-maternal Effects of Twin Pregnancies Created by Assisted Reproductive Techniques and Twin Pregnancies). J Acad Res Med. 2021; 11(1):17-23.

10. Gao Y, Yu B, Mao J, Wang X, Nie M, Wu X. Assisted reproductive techniques with congenital hypogonadotropic hypogonadism patients: a systematic review and meta-analysis. BMC Endocr Disord. 2018; 18(1):85.

11. Öktem Ö, Urman B. Over hayat döngüsünü anlamak (Understanding the ovarian life cycle). Türk Jinekoloji ve Obstetrik Derneği Dergisi/ Journal of the Turkish Society of Gynecology and Obstetrics. 2011; 8(2):71-82.

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. Sato F, Marrs RP. The effect of pregnant mare serum gonadotropin on mouse embryos fertilized in vivo or in vitro. J In Vitro Fert Embryo Transf. 1986; 3(6):353-7.

How to cite this article:

Mustafa Dogan Ozcil. Latent ovarian stimulation in the management of infertile patients with hypogonadotropic hypogonadism. Ann Clin Anal Med 2021;12(Suppl 3): S343-346