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CASE REPORT

Application of Human Menopausal Gonadotropins in the Treatment of Idiopathic Hypogonadotropic Hypogonadism (IHH)-Based Infertility in Females: A Case Report

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Rationale: Idiopathic hypogonadotropic hypogonadism (IHH) is a prevalent congenital genetic disorder with multiple inheritance patterns. IHH can manifest as normal hypogonadotrophic sexual hypofunction (nIHH) or with an abnormal sense of smell, known as Kallmann. It primarily affects the production and effectiveness of gonadotropin-releasing-hormone (GnRh), leading to reduced follicle-stimulating hormone and luteinizing hormone levels. This results in infertility and underdeveloped secondary sexual characteristics.

Patient Concerns: A 29-year-old female presented with infertility.

Diagnosis: IHH diagnosis was confirmed through magnetic resonance (MR) scan, endocrine tests, physical examination, and B ultrasonic inspection. Additionally, genetic studies, including chromosome analysis, were conducted for the patient. The results confirmed no genetic abnormalities or concerns.

Interventions: The patient underwent multiple ovulation induction programs.

Outcome: After several ovulation induction cycles, the patient conceived and delivered a live baby.

Lessons: For IHH patients, a tailored human menopausal gonadotropin (HMG) dose is recommended. High-dose HMG can benefit those with poor follicular response. The addition of letrozole (5–7.5mg) may enhance follicular response during stimulation. Our approach, which emphasizes the combined use of high-dose HMG, letrozole, and the adjustment of FSH and LH ratios, offers a unique perspective compared to traditional treatments. If HMG treatment is ineffective, alternative ovulation induction methods, such as r-fsh combined with r-lh or HMG combined with rLH, can be considered. Adjusting the FSH and LH ratio and varying rFSH and rLH additions might help achieve dominant follicles and live birth in resistant cases. This case report underscores the potential benefits of our regimen, suggesting its consideration for future research and clinical applications.

Keywords: HMG, IHH, infertility, rLH

Introduction

Idiopathic hypogonadotropic hypogonadism (IHH) is a complex disorder with diverse genetic underpinnings. While it stands as one of the most prevalent congenital genetic conditions, its inheritance can manifest in various forms such as autosomal dominant, autosomal recessive, and X-linked patterns.[1] The condition can be categorized into two primary types: normal hypogonadotrophic sexual hypofunction (nIHH) and a variant with an impaired sense of smell, termed Kallmann syndrome. A significant challenge in managing IHH is the compromised functionality of gonadotropin-releasing-hormone (GnRh), which often leads to inadequate secretion of follicle-stimulating hormone and luteinizing hormone.[2] In the current medical landscape, the hallmark of infertility in IHH patients is evident through delayed secondary sexual characteristics, often

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accompanied by the absence or underdevelopment of primary amenorrhea and halted follicular growth. Sex hormone replacement therapy emerges as a foundational treatment for IHH-induced infertility, aiming to foster the development of female secondary sexual characteristics and sustain an artificial menstrual cycle. With the right therapeutic interventions, notably the administration of gonadotropin-releasing hormone, IHH patients can achieve successful follicular development and eventual pregnancy.[3]

In this study, we chose HMG over rFSH because HMG provides both FSH and LH activities, which can be beneficial for patients with IHH who might require both hormones for optimal follicular development. rFSH, being a pure FSH preparation, might not offer the same breadth of hormonal support in such cases. Furthermore, we included letrozole in the ovulation induction process due to its ability to increase endogenous FSH production by inhibiting estrogen synthesis. While both exemestane and anastrozole are aromatase inhibitors like letrozole, letrozole has been more commonly used and studied in ovulation induction, offering a more established safety and efficacy profile in this context.

The patient gave consent for these studies and their publication and this report was approved by the Ethics committee of Integrative Medicine Research Centre of Reproduction and Heredity, the Affiliated Hospital of Shandong University of Traditional Chinese Medicine.

Case Presentation

A 29 year-old female patient was admitted to our center due to infertility challenges. She had never had a natural menstruation, with her first menstruation occurring after induction using Estradiol Valerate Tablets and progestin at the age of 17. Up to the time of admission, her post-estrogen-progesterone sequential treatment entailed taking Estradiol Valerate Tablets (1mg/day) for 21 days from the fifth day of previous menstruation, and oral progesterone capsules (200mg/day) for 11–16 days. Her menstruation occurred 3–7 days after stopping the progesterone capsules intake. The patient got married at age 26 and engaged in sexual intercourse 1–2 times a week. However, despite not using any method of contraception, she had not conceived for four years. Besides being healthy and lacking a history of surgery, the patient had the following characteristics; height of 175 cm, weight of 77 kg, normal smell, flat breasts, naive vulva, no pubic hair, naive labia minora, free vagina, small cervix, smooth, anterior uterine position, small, and no visible abnormalities in both appendices. Blood tests on the third day of menstruation revealed low FSH (0.66mU/mL), LH<0.1mU/mL, E2<18.35pg/mol, T<0.09, PRL (179), TSH (2.61 chromosome 46). Fallopian tube angiography showed bilateral patency in 2017, while B ultrasound (on the third day of menstruation) revealed uterine measurements of 4.29×4.51×3.04 cm, linear endometrium, and right ovary of size 3.13×1.10 cm, with 2–3 visible small follicles.

On January 9, 2021, the patient underwent a pretreatment for three menstrual cycles at our health center. Additionally, male semen assessment was performed on the same day and found to be normal. On April 4, 2021 (4th day of menstruation), she commenced the HMG (75U/ day) treatment that lasted for 7 consecutive days. On April 11, 2021, B ultrasound detected a follicle on the right side with the largest size of 0.3cm, 6–7 small follicles, and 4–5 small follicles on the left. HMG was then increased to 150U/ day for 7 consecutive days. On April 18, B-ultrasound detected 5–6 small follicles with a maximum size of 0.5cm on the right side, and more than 10 small follicles with a maximum size of 0.45cm on the left side. HMG was further increased to 225U/ day for 7 consecutive days. On April 24, B-ultrasound detected 2–3 small follicles on the right side and 6–7 small follicles on the left side. Administration of HMG225U/ day was further continued for 4 consecutive days and on April 28, the largest follicle size on both the the right and left side was 0.45cm. On May 4, the largest follicle size on both the right and left side was still 0.45cm. HMG was further increased to 300U/ day for 5 consecutive days and on May 9, the largest follicle on the right side was 0.55 cm, while the largest follicle on the left side was 0.5 cm. Take Estradiol Valerate Tablets 2mg/ day for 10 days, Progesterone capsule 0.2g/ day for 9 days, During the 35-day period of this cycle, HMG6675U (75 vessels) were used. However, no dominant follicles were obtained.

On May 23, 2021, the patient was pretreated with climen for two menstrual cycles, and ovulation induction was commenced on July 20 (4th day of menstruation). HMG (150U/ day) was administered for 7 days, from July 27. On the right, 2×0.55 cm follicles with 4–5 small follicles were measured, while on the left, 10.45 cm follicles with 5–6 small follicles were measured. HMG (225U/ day) and add letrozole (5mg/ day) were then administered for 5 consecutive days. On August 1, 4–5 small follicles were measured on the right side while 5–6 small follicles were measured on the left side. HMG (225U/ day) and letrozole (5mg/ day) treatment was further continued for 3 days and on August 4, there were 4–5 small follicles on the right

side and on the left side 1.0cm with 5–6 small follicles. HMG was further increased to 300U/ day and administered for 4 days, without letrozole. On August 8, there were 2–3 small follicles on the right and 2–3 small follicles on the left. In addition, blood test results performed on the same day revealed LH: 0.26miu/mol and E2:10pg/mol. The stimulation was then stopped and the patient given a pretreatment of kelingmont for two menstrual cycles.

The third ovulation induction commenced on November 2, 2021 (4th day of menstruation), with the administration of HMG (225U/ day) and letrozole (5mg/ day) for 5 days. On November 7, 6–7 small follicles on the right side and 5–6 small follicles on the left side were measured. HMG (225U/ day) and letrozole (5mg/ day) treatment was continued for 9 days. On November 15, follicle of 0.25 cm ×2 was measured on the right side while the echo on the left side was rather firm. The same treatment was further continued for 5 days and on November 18, 4–5 small follicles were measured on the right side and 3–4 small follicles on the left side. Letrozole was then increased to 7.5mg/ day and administered alongside HMG (225U/ day) for 4 days. On November 22, B-mode ultrasound revealed no change before bilateral follicular. Triptorelin Acetate (0.05mg) was administered for two days, while letrozole (7.5mg/ day) and HMG (375U/ day) were administered for four days. On November 29, 3–4 small follicles were measured on the right side and 4–5 small follicles on the left with one 0.2cm follicles were measured. Subsequently, Triptorelin Acetate was withdrawn, and HMG (375U/ day) with letrozole (7.5mg/ day) treatment continued for 5 days. One small follicle on the right side and one small follicle on the left side were measured on December 4. HMG (375U/ day) and letrozole (7.5mg/ day) treatment was continued for another 4 days. On December 8, a 0.2cm follicle at the right side of the left echogen was relatively solid. In this cycle, HMG increased to 375U/ day, while letrozole remained constant (7.5mg/ day). However, no dominant follicles were obtained, and the patient was pretreated with Femoston for 3 menstrual cycles.

On March 5, 2022 (5th day of menstruation) blood test results revealed FSH:0.38mU/mL, LH:0.02mU/mL, E2:10pg/mol, TSH:1.46μU/mL and endometrial:0.3cm. The patient was given Estradiol Valerate (2mg / day) for 5 days and on March 10, a 0.3cm follicle was measured on the right side with 6–7 small follicles, while on the left side a 0.3cm follicle was measured with 9–10 small follicles. Letrozole and HMG were then administered at 2.5mg/ day and 225U/ day, respectively, for 7 days. On March 17, one 0.4cm follicle was measured on the right side with 7–8 small follicles, and one 0.5cm follicle was measured on the left side with 4–5 small follicles. Letrozole (5mg/ day) and HMG (225U/ day) treatment was further continued for 6 days And on March 23, a 0.2cm follicle was measured on the right side with 5–6 small follicles, while 4–5 small follicles were measured on the left side. Letrozole treatment was stopped and increased HMG dose of 300U/ day administered for 5 days. On July 28, a 0.3cm follicle on the right side with 3–4 small follicles, and 2–3 small follicles on the left side were measured. HMG (450U/ day) and Luveris (rLH) dose of 75U/ day were then administered for 4 days. On April 1, one 0.5cm follicle was measured on the right side with 6–7 small follicles and two 0.4cm follicles on the left side, with 3–4 small follicles. A small amount of vaginal bleeding was observed on the first day of rLH administration. HMG (450U/ day) and rLH (75U/ day) treatment was continued for 3 days. On the right side, the following follicle measurements were obtained on April 6; 1.0cm×2, 0.95cm×2, 0.9cm, and 0.85cm, with 9–10 small follicles. On the left side, follicle measurements of 1.05cm, 1.0cm, and 0.95cm were obtained with 6–7 small follicles. HMG (450U/ day) and rLH (75U/ day) treatment was further continued for 3 days. The follicle was measured On April 9, follicle measurements obtained from the right side were; 1.7cm, 1.55cm×2, 1.4cm, 1.3cm×2, 1.25cm, 1.2cm, 1.1cm×2, 1.05cm, 0.9cm×2, 0.8cm, 0.75cm×2, 0.7cm×2, and 0.6cm, with 2 small follicles. On the left, 1.45cm, 1.35cm, 1.25cm, 1.15cm, 1.1cm×2, 0.95cm, 0.9cm×2, and 0.85cm were measured with 2 small follicles. HMG was changed to 225U/ day, and was administered alongside (rLH 75U/ day) for 2 days. Blood test was done on April 11 which revealed LH: 0.25mU/mL, E2:783pg/mol, and P: 0.78ng/mol. Follicles on the right side measured 2.05cm, 1.9cm, 1.8cm×2, 1.75cm, 1.55cm, 1.45cm×2, and 1.25cm, with 9–10 small follicles. On the left side, follicle measurements of 1.65cm, 1.45cm×2, 1.25cm, and 1.2cm were obtained with 4–5 small follicles. Since double triggers are used for better follicular maturation and discharge, dapicta (traprilin acetate) 0.1mg and HCG (6000U) were administered to the patient on April 11, and she was instructed to engage in sexual intercourse for the next three days. On April 15, B-ultrasound detected one luteal on both sides. Progesterone injection (20mg/ day) was administered for 14 days, and an early pregnancy test conducted two weeks later (April 19). The early pregnancy test was positive and blood test results conducted on the same day revealed E2:264pg/mol, P: 6.63ng/mol, and β-hcg: 1123.81miu/mol. On June 25, B-mode ultrasound showed fetal bud: 0.8 cm, fetal heart: 121 times/min, and the early pregnancy was consistent with 7+ gestational weeks. The (Table 1) compares the four drug regimens for ovulation induction.

Table 1 Four Ovulation Cycles Description

Date	Ovulatory Stimulant Drugs	Daily Dosage	Total	Ovulation Trigger
2021.4.4–2021.5.9	HMG	HMG 75U/d×7d HMG 150U/d×7d HMG225U/d×11d HMG 300U/d×5d	HMG 6675U	No dominant follicles
2021.7.20–2021.8.8	HMG	HMG 150U/d×7d (HMG 225U/d+LE 5mg/d) ×8d HMG 300U/d×4d	HMG 4050U LE 40mg	No dominant follicles
2021.11.2–2022.12.8	HMG+LE+TA	(HMG 225U/d+LE 5mg/d) ×19d (HMG 225U/d+LE 7.5mg/d) ×4d (TA 0.05mg/d+LE 7.5/d+HMG 375U/d) ×2d (HMG 375U/d+LE 7.5mg/d) ×11d	HMG 10050U TA 0.1mg LE 97.5mg	No dominant follicles
2022.3.10–2022.4.11	HMG+rLH+LE	(HMG 225U/d+LE 2.5mg/d) ×13d HMG 300U/d×5d (HMG 450U/d+rLH 75U/d) ×4d (HMG 450U/d+rLH 75U/d) ×6d (HMG 225U/d+rLH 75U/d) ×2d	HMG 9375U LE 32.3mg Rlh 900U	TA 0.1mg hCG 6000U

Abbreviations: HMG, human menopausal gonadotropin; r-LH, Recombinant human luteinizing hormone; hCG, human chorionic gonadotropin; TA, Triptorelin Acetate; LE, Letrozole.

Discussion and Conclusion

While various treatment regimens exist for IHH, our approach offers a unique perspective, particularly in the combined use of high-dose HMG, letrozole, and the adjustment of FSH and LH ratios. The novelty of our method lies in its tailored approach, taking into consideration the patient's specific response threshold and the observed benefits from varied HMG dosing.

IHH is a disease characterized by low Gn production. However, in women with infertility issues, exogenous Gn can be administered for ovulation induction therapy. The cumulative pregnancy rate for multiple ovulation-promoting treatment cycles have the potential to reach up to 72%. HMG is a simple and readily available ovulatory drug.[4] Compared with FSH, HMG requires lesser dose, and has higher daily HCG estrogen level and ovulation rate. In addition, HMG induces higher blood progesterone concentration in luteal phase than FSH.[5,6] Since the uterus of HH female ovary is often dormant for a long time, the application of OC or exogenous estrogen pretreatment can increase FSH receptor and LH receptor of follicle, and also reduce the amount and time of drugs used in promoting ovulation. Moreover, after 2–3 menstrual cycles, endometrial repair may help improve the late embryo implantation rate.[7,8]

To improve peripheral efficiency in the ovaries, letrozole (LE) was included in the second and third treatment cycles. Contrary to the previous statement, LE inhibits aromatase activity, leading to a reduction in estrogen synthesis and an increase in androgens. The increase of follicle androgens results in an increased FSH receptor expression, which in turn causes follicular development. Additionally, the accumulation of androgen in the follicle stimulates insulin-like growth factor I (IGF - I), and increases the expression of other autocrine and paracrine factors. This enhances the effect of HMG by improving the ovarian hormone reactivity.[9] In this study, the maximum letrozole dose administered was 7.5 mg/day, and aided in ovulation.[10] Since the response threshold of follicles to HMG vary among HH patients, HMG administration should be varied to determine the effective dose for promoting ovulation. However, in cases with poor ovulation promotion response, a higher dose of HMG can be initially administered to trigger the process, before being decreased gradually.[11] The upper limit of HMG dosage for use during ovulation promotion still remains unclear. In this case, the maximum amount of HMG used was 450 units/day, while the maximum reported amount of HMG was 600 units per day. The most commonly recommended doses of HMG are 75, 150, and 225 units per day.[12,13] A 2:1 ratio of FSH to LH in the first half of the ovulation cycle has been shown to be more favorable for follicular development. In this case, the dominant follicles were obtained in the last ovulatory cycle by adding rLH, suggesting that either the purified rLH was more effective than the LH contained in HMG, or the ratio of FSH to LH changed, leading to the formation of multiple dominant follicles.

From our observation on multiple cycles of ovulation induction therapy performed on this type of IHH patient, we recommend a varied HMG dose administration based on the patient's threshold. In addition, high-dose HMG should be used to initiate the descending regimen for patients with poor follicular response in low-dose or incremental regimen. Based on the previous follicular response of the same patient, 450–600 units of HMG were used to initiate the follicular stimulation. Further, we observed that addition of letrozole 5–7.5mg could improve the daily follicular response during the stimulation process. For patients with unsatisfactory effect from HMG treatment, other ovulation induction schemes such r-fsh combined with r-lh, HCG as the alternative of r-lh, or HMG combined with rLH, can be selected. In addition, changing the ratio of FSH and LH applications, and the varied addition of rFSH and rLH, may help HH patients with poor ovulation promotion response, to obtain dominant follicles and achieve live birth.

In conclusion, our observations from this case study underscore the potential benefits of our tailored regimen for IHH patients. The combination of varied HMG dosing, letrozole addition, and adjustments in FSH and LH ratios presents a promising approach that warrants further investigation in larger clinical studies. Compared to traditional treatments, our method offers a fresh perspective that could potentially benefit a wider range of IHH patients.

Abbreviations

MR, Magnetic Resonance; IHH, idiopathic hypogonadotropic hypogonadism; HMG, human menopausal gonadotropin; r-LH, Recombinant human luteinizing hormone; hCG, human chorionic gonadotropin; GnRh, gonadotropin-releasing hormone.

Data Sharing Statement

The datasets generated during the present study are available from the corresponding author on reasonable request.

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Disclosure

The authors report no conflicts of interest in this work.

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