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Case Series

Hypogonadotropic Hypogonadism: Ovulation Induction with Gonadotrophins

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Abstract

Ovulation induction was performed in four women with hypogonadotropic hypogonadism, using human menopausal gonadotrophin with follicle stimulating hormone, in varying doses. One patient with Sheehan's syndrome, while three patients of congenital hypogonadotropic hypogonadism, were treated with gonadotrophins for fertility promotion. In these patients, folliculogenesis was considered as optimum, when a follicle of size 17 mm or more, was achieved. Follicle development in our patients was monitored with transvaginal ultrasonography alone, and serum estradiol assays were not performed, to keep the cost of treatment low. The duration of induction to obtaining a mature follicle, in this study varied from twelve to thirty seven days. Intrauterine insemination or *in-vitro* fertilization were not used as an adjunct to ovulation induction, for enhancing fertility in this study. All four women conceived within 1 - 2 cycles of ovulation induction and a single embryo was visualised on ultrasonography. A careful dose titration of gonadotrophins provided fertility, while preventing both ovarian hyperstimulation and multiple pregnancy; making the study unique and admirable.

Keywords: *Hypogonadotropic Hypogonadism; Ovulation Induction; Gonadotrophins*

Abbreviations

HH: Hypogonadotropic Hypogonadism; HMG: Human Menopausal Gonadotrophin; LH: Luteinizing Hormone; FSH: Follicle Stimulating Hormone; TVS: Transvaginal Sonography; MRI: Magnetic Resonance Imaging; rh LH: Recombinant Human Luteinizing Hormone; rh FSH: Recombinant Follicle Stimulating Hormone, T4: Thyroxine

Introduction

Hypogonadotropic hypogonadism, WHO type 1 anovulatory syndrome is a rare disorder, with failure of ovarian function, secondary to a disturbance in the function of hypothalamic-pituitary system. It has three subsets, that include congenital hypogonadotropic hypogonadism, hypopituitarism and hypothalamic amenorrhoea. It is a heterogenous disorder characterized by suboptimal luteinizing and follicular stimulating hormones, with resulting hypoestrogenism; causing arrest of folliculogenesis, amenorrhoea and infertility [1]. Induction of fertility in these patients is long and arduous, with no specified protocols; that can be used with ease. Ovulation induction can be performed with pulsatile GnRH, Human Menopausal Gonadotrophin (HMG), Recombinant follicle stimulating hormone and luteinizing hormone. GnRH administration is done with GnRH pumps delivering GnRH pulses, subcutaneously at intervals of between 60 and 120 minutes. Letterie., *et al*. however suggested a better outcome with pulse frequencies of 90 and 120 minutes [2]. GnRH therapy requires an

intact pituitary gland, and this therapy is unsuitable for patients with pituitary damage following postpartum haemorrhage, or patients with operated pituitary tumours. Gonadotrophins have been used in several studies with success, both for hypothalamic and pituitary disorders [3].

Case Presentation

Case presentation 1

A 29 years old, married woman presented in the infertility clinic, with amenorrhoea for last three and a half years. She was taking some cyclic hormone therapy for preceding three years, and now was eager to conceive. She was 5 feet 5 inches tall, weighing 58 kg. Transvaginal sonography (TVS) was performed, which revealed a small uterus, an antral follicle count of 2 in each ovary, and an endometrial thickness of 2.0 mm. Endocrinal assays were done, which revealed low luteinizing hormone (LH), low follicle stimulating hormone levels (FSH) and low serum estradiol levels.

Hormone	Patient value	Normal values
Luteinizing hormone	< 0.10	1.90 - 12.50 (Follicular phase) m IU/ml
Follicle stimulating hormone	0.50	2.50 - 10.0 (Follicular phase) m IU/ml
T4 (Thyroxine)	8.21	4.5 - 12.6 mcg/dl
Thyroid stimulating hormone	1.94	0.27 - 4.20 m IU/ml
Serum Prolactin	5.32	4.79 - 23.3 ng/ml
Serum Estradiol	< 5.0	> 40 pg/ml
Serum Cortisol	12.08	4.30 - 22.40 (Morning serum) mcg/dl

Table 1*: Hormone levels in case 1.*

A magnetic resonance imaging of the brain was performed, and no intracranial lesion was found. The patient was tested for smell with asafoetida powder; which could not be judged by the patient. The patient was thereby diagnosed, as having Kallmann's syndrome.

The patient was provided replacement therapy, with 12.5 mg of levothyroxine, calcium, vitamin D3, estradiol valerate 2 mg for 28 days and medroxyprogesterone 5 mg concurrently, with last 10 days of estradiol. After 2 cycles of estrogen plus progesterone therapy, the patient started with menstruation. She was continued with the same therapy, for 1 more month and was advised to come on day 2 of her cycle. On TVS performed on day 2 of the cycle, the uterus size was 70 x 37 x 25 mm, and was taken up for fertility management. The patient was started with l-methyl folate 1 mg and estradiol valerate 2 mg once daily. HMG protocol was provided to her, for induction of ovulation. Injection HMG 75 IU was given for 4 days and the dose increased to 150 IU for next 4 days. On day 10 of the cycle, HMG dose was enhanced to 225 IU for 4 days, followed by a further HMG dose increment to 300 IU, continuing for following 4 days. Few small sized follicles were visible after 16 days of HMG administration. Now HMG was continued in the dose of 300 IU, with no further enhancement and injection FSH 75 IU, was added to the protocol for following 4 days. The dose of FSH was increased by 75 IU, every 4 days, till folliculogenesis was complete. The maximum dose of HMG provided to the woman was 300 IU and FSH dose given was 375 IU. On day 38, two follicles more than 17 mm were seen on TVS and injection HCG 10,000 IU was given to induce follicular rupture. Patient was advised midcycle coitus,

and follicular rupture was confirmed on sonography. Luteal phase support was provided with micronized vaginal progesterone 200 mg twice daily for 10 days and estradiol valerate was also continued for 15 days. The woman, however did not conceive and reported to us, when her menstruation began.

Induction of ovulation was again planned for her, after establishing bilateral tubal patency, with hysterosalpingography. Considering the long induction to follicle formation period in the last cycle, ovulation induction this time was begun with a higher starting dose of HMG. Injection HMG 150 IU was given similarly for 4 days, and enhanced to 300 IU, for next 4 days. On day 9 of cycle, Injection FSH 75 IU, was added to HMG 300 IU and both continued for 4 days. The dose of FSH was enhanced after every 4 days, while keeping HMG dose constant at 300 IU; till we reached a dose of FSH 225 IU. Transvaginal sonography was performed at an interval of 4 days to check the size of follicle. On day 31 of cycle a 13.5 mm follicle was visualised. Thereby, follicular study was now performed every alternate day. The doses of HMG 300 IU and FSH 225 IU were kept the same as earlier, ignoring any further increment for following 2 days. On day 33, three follicles with median follicle sizes 15 mm,15 mm and 15.5 mm were delineated. FSH administration was now stopped and only HMG 300 IU was continued. On day 34 of cycle, 3 follicles of 17.5 mm size were found and follicular rupture triggered with injection HCG 10,000 IU. Luteal phase support was given with micronized vaginal progesterone and estradiol was also continued for 2 weeks. Patient reported this time, with a positive Elisa test for pregnancy, and a single gestation sac was visualised on day 45, since her date of last menstrual period. There were no complications in the antenatal period and she had an easy full term vaginal delivery (Figure 1).

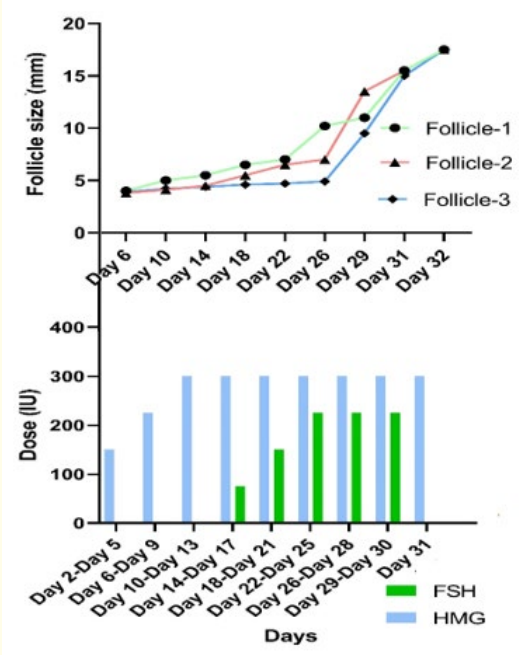

Figure 1: *Folliculogenesis and HMG/FSH dose chart in case 1.*

Case presentation 2

A 28 years old woman presented with secondary amenorrhoea following massive postpartum haemorrhage after delivery in her village. She was suspected of hypopituitarism, owing to pituitary ischaemia after haemorrhage and hypovolemic shock. Her hormonal assays revealed a low LH, low FSH, low prolactin, low cortisol and low thyroxine (T4) levels (Table 2). She was already on levo thyroxine

87.5 mcgm and the dose was enhanced to 112.5 mcgm. Magnetic resonance imaging revealed empty sella sign, while IGF-1 testing was ignored by the patient. She was diagnosed as a case of Sheehan's syndrome with hypopituitarism, and she was provided with replacement therapy with sequential estradiol valerate with progesterone and prednisolone 3.75 mg daily, in two divided doses. Menstruation began after 2 cycles of hormone replacement therapy and was taken up for ovulation induction.

Hormone	Patient value	Normal values
Luteinizing hormone	1.50	1.90 - 12.50 m IU/ml (Follicular phase)
Follicle stimulating hormone	2.20	2.50 - 10.0 m IU/ml (Follicular phase)
T4 (Thyroxine)	8.60	4.5 - 12.6 mcg/dl
Serum Prolactin	1.50	4.79 - 23.3 ng/ml
Serum Estradiol	12.30	> 40 pg/ml
Serum Cortisol	1.43	4.30 - 22.40 (Morning serum) mcg/dl
Thyroid stimulating hormone	0.439	0.27 - 4.20 m IU/ml

Table 2: *Hormone levels in case 2.*

Injection HMG was begun in a dose of 150 IU for 5 days, accompanied with 2 mg estradiol valerate once daily and l-methyl folate. She was called after 5 days, and the dose of HMG was enhanced to 225 IU; the same continued for 5 days. On day 8 of the cycle, she reported with breakthrough bleeding, and the induction process was stopped; considering a slow rise of estrogen levels. She was continued with estradiol and progesterone and was called on day 2, of the next menstrual cycle. In this cycle, she was started with Injection HMG 150 IU for 4 days and on day 6, the dose of HMG was enhanced to 225 IU, continued for next 4 days. On day 11 of the cycle, small antral follicles were visible, and the HMG dose was further increased to 300 IU, continued for 4 days. She was given HMG 300 IU, for one more day and reported on day 19, with mean follicle sizes; 18 mm, 15.8 mm, 13.3 mm, and an endometrial thickness of 8.1 mm. Injection HCG 10,000 IU were administered to trigger follicular rupture, and luteal phase was supported with vaginal progesterone. On day 32, she presented with a serum beta HCG value of 193.0 m IU/ml, and after 7 days, TVS revealed a single gestation sac (Figure 2).

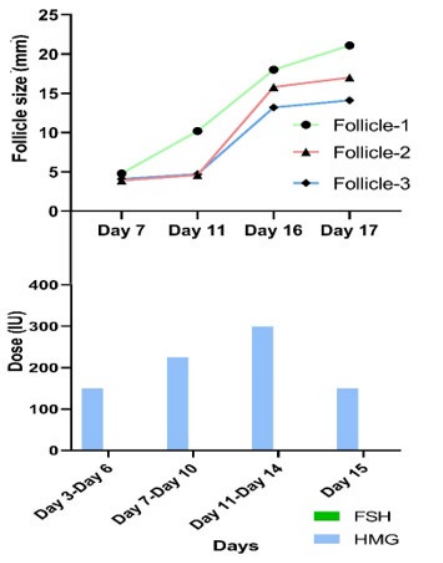

Figure 2: *Folliculogenesis and HMG/FSH dose chart in case 2.*

Case presentation 3

A 27year old woman presented with primary amenorrhoea, menstruating irregularly in response to cyclically given oral contraceptive pills. She had average body mass index, and was considered for investigations (Table 3).

Hormones	Patient value	Normal Values
Luteinizing hormone	1.47	1.90 - 12.50 m IU/ml (Follicular phase)
Follicle stimulating hormone	3.46	2.50 - 10.0 m IU/ml (Follicular phase)
Serum estradiol	< 11.80	> 40 pg/ml
T4 (Thyroxine)	4.91	4.5 - 12.6 m gm/dl
Thyroid stimulating hormone	2.20	0.27 - 4.20 m IU/ml
Serum cortisol	2.34	4.30 - 22.40) mcg/dl (Morning serum)
Serum prolactin	1.10	4.79 - 23.3 ng/ml

Table 3: *Hormone levels in case 3.*

The hormone assays revealed a low estradiol, low LH, normal FSH, low S. cortisol, low T4 and low prolactin levels. TVS revealed a suboptimal uterine size, with an endometrial thickness 3 mm. An MRI was performed, that revealed no intracranial lesion. A diagnosis of HH (WHO type I), was considered. The patient was replaced with levothyroxine 50 mcgm, prednisolone 3.75 mg, and cyclic estradiol with progesterone therapy. The woman desired fertility, therefore tubal patency, and adequate husband semen parameters were confirmed. After 2 cycles of estradiol with progesterone treatment, she was taken up for ovulation induction, from day2 of her menstruation.

The patient was started with 2 mg estradiol once daily, and injection HMG 75 IU were given for 4 days. Follicular study was planned and the dose of HMG was enhanced after 4 days by 75 IU, continued for successive 4 days. The increment in HMG dose was done periodically every 4 days and a dose of HMG300IU, was achieved. On day 14 of the cycle, an antral follicle measuring 11.6 x 8 mm was visualised. Now a ceiling was applied on HMG dose at 300 IU, and FSH 75 IU was added to the regimen for 4 days. The same dose of HMG 300 IU with FSH 75 IU, was continued and, TVS was performed, to determine follicle size. On day 22 of cycle, a follicle of median size 19mm was seen on TVS. The endometrial thickness was 10 mm, and injection HCG 10,000 IU, was given as an LH trigger. Frequent intercourse was advised and luteal phase support was provided with vaginal progesterone. However, conception was not achieved in

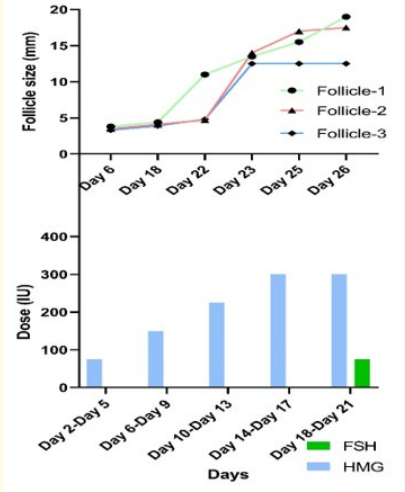

Figure 3: *Folliculogenesis and HMG/FSH dose chart in case 3.*

The patient was again induced in the next cycle, following a similar gonadotrophin protocol. The patient in this cycle conceived, and TVS revealed a single gestation sac with a viable embryo. The patient had an uneventful course in pregnancy and delivered a female baby at term, weighing 2.75 kg.

Case presentation 4

An 18 year old girl presented with primary amenorrhoea, and was diagnosed as congenital hypogonadotropic hypogonadism, after investigations and MRI. She was provided with replacement therapy with levothyroxine, estradiol valerate and medroxyprogesterone, with last 10 days of estradiol therapy. She began with menstruation and continued therapy for 4 years, with regular follow up.

The woman was now 22 years old; had got married and desired pregnancy. Ovulation induction was planned for her. She was started with injection HMG 75 IU for 4 days, enhanced to 150 IU after 4 days. On day 9 of cycle, a 13 mm median size follicle was seen on TVS and thereby the same dose of HMG 150 IU was continued. On day 13 of cycle an 18.5 mm follicle size was achieved. Follicular rupture was triggered with Injection HCG 10, 000 IU, while estradiol 2 mg once daily was continued for 15 days and luteal phase support provided with vaginal progesterone. The patient conceived in the same cycle, with a single embryo visualised on TVS. Unluckily, the patient had an incomplete abortion due to low lying placenta, in the second trimester. She again, presented for ovulation induction after a few months. This time as well, ovulation induction was performed similarly and the woman conceived in the same cycle. A single viable fetus was seen on TVS and, she delivered a healthy male baby at term.

Discussion

Ovulation induction has been performed in HH women with GnRH, HMG, rh FSH and rh LH in various combinations and dosage protocols.

Pulsatile GnRH, can be used in women with hypothalamic hypogonadism, with a hypothalamic cause for HH, only in the presence of an intact pituitary gland. The advantage of GnRH therapy is a 25% pregnancy rate, per GnRH treatment cycle, as observed by Messinis., *et al* [4]. However, the disadvantage observed with GnRH, is that the pump delivering GnRH, has to remain connected with the body throughout the day for several days, and refilled at regular intervals. Side effects like skin infections, skin reactions and local venous thrombosis at the pump infusion site have also been reported [5].

Our patients were given two cycles of estrogen + progesterone combination, before ovulation induction was begun. In an earlier study, it was found that patients with HH were treated with gonadotrophins for 6 cycles with ovulation induction, but did not conceive. These women were, then given pretreatment with estrogen + progestogen combination, before induction. It was found that 28 out of 30 women conceived within the next 4 cycles [6]. In another study, a woman with earlier operated craniopharyngioma, was induced with gonadotrophins for several cycles, with no success. In this patient, conception occurred when conjugated equine estrogen was provided with HMG [7].

In women with HH, good ovulatory results are seen with combined administration of both FSH and LH, which can be provided with HMG, or a combination of rh FSH and rh LH. Women with HH have an endogenous deficiency of LH, and thereby in some studies, it was found that women given FSH alone required more doses of gonadotrophins; in comparison to those, who received LH supplementation also with FSH [8].

Ovulation Induction in our study was begun with HMG 75 - 150 IU, with dose enhancement being done after every 4 days. FSH was added to the protocol, after 300 IU HMG dose was achieved, while folliculogenesis was still not adequate. In a double blinded pilot study,

where follicle formation was studied on 20 women, with rh LH 225 IU alone (8 women), rh FSH alone (6 women), or rh LH alone (6 women). In the study, Loumaye., *et al*. found a significant higher rate of follicular growth arrest in women given rh LH alone, in comparison to those given rh FSH alone and rh LH/rh FSH. These observations provided evidence in favour of the "LH ceiling effect"; that overdosing with rh LH, in late follicular phase suppresses follicular development [9]. Hence, when a dose of HMG 300 IU (LH 150 IU) was achieved in our patients, FSH was added and further all increments in gonadotrophin doses, were made only with FSH. A dominant follicle was achieved in twelve to thirty seven days of gonadotrophin administration in our patients with HH.

The dose of HMG/FSH varied in all patients and maximum daily dose of gonadotrophin provided in our patients was 675 IU, containing HMG 300 IU and FSH 375 IU, and the longest induction to follicle formation period was 37 days. The highest dose of gonadotrophins required for folliculogenesis, in this study was in the patient with Kallmann 'syndrome, suggesting a more severe gonadotrophin deficiency.

In our patients, gonadotrophin doses were titrated only with follicle size measurement with TVS. Estradiol levels were not measured to check follicle growth; thereby reducing the cost of fertility treatment. Hussein., *et al*. has published a study of 104 patients, where ovulation induction was done with HMG or recombinant human LH + FSH, accompanied with IUI; with success [10]. However in our patients, no IUI or IVF were applied with ovulation induction; thus reducing the economic burden on the patents.

In several studies, multiple pregnancy has been suggested, when gonadotrophins are used to induce ovulation, in cases with HH. They have advised a cycle cancellation, if 3 or more mature follicles (> 16 - 17 mm) or a large number of intermediate sized (10 - 15 mm follicles) are visualised [3]. In our study, a singleton pregnancy was conceived in all 4 cases treated here. This was achieved with a careful dose titration of gonadotrophins and an optimally timed LH trigger. Frequent follicular the monitoring was performed in this study, after a follicle size of 12 - 13 mm was achieved. The dose of HMG/FSH was thereby adjusted scrupulously, to avoid multiple follicle formation and prevent ovarian hyperstimulation as well.

Regarding the obstetric outcome, the pregnancy course remained uneventful in all women. There was a decrease in T4 levels during pregnancy, due to increase in the demands of the fetus; for which the dose of levothyroxine was enhanced periodically. There was complete lactation failure in all the patients and the infants had to be nurtured with formula feeds.

Conclusion

Infertility in hypogonadotropic hypogonadism, is difficult to treat, with no clearly defined protocols; as HH is a rare entity. Induction with HMG and FSH in combination is a promising therapy, especially in low resource countries, where GnRH is not available, or cost is an important hindrance. The ovulation protocol with HMG and FSH is long and arduous; but success can be obtained, without intrauterine insemination and *invitro* fertilization. HMG +FSH combination is a relatively less expensive treatment modality, as compared to pulsatile GnRH and Recombinant gonadotrophins. This study provides details about the dose protocol used for ovulation induction in women with HH, providing good fertility outcome, but carefully avoiding multifetal pregnancy and ovarian hyperstimulation.

Conflicts of Interest

None.

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