Reproductive outcomes in women with hypogonadotrophic hypogonadism, a case series study

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Abstract

Background: Hypogonadotropic hypogonadism (HH) is a rare condition in which there is gonadal hypofunction due to absence of gonadotropin drive. In this condition, there are very low serum levels of gonadotropins. Pituitary gland may itself have some disease or disorder, or there may be loss of gonadotropin-releasing hormone (GnRH) pulses from the hypothalamus. The pharmacological interventions in HH women formed the basis for superovulation strategies for assisted reproduction techniques (ART) with a special reference to the role of LH and its impact on oocyte and embryo quality.

Results: The medians ±inter quartile ranges for number of oocytes retrieved, number of MII oocytes, and number of embryos transferred were 5±7, 4±3, and 3±1 respectively. The pregnancy rate was 31.5% for this group of patients. The live birth rate and miscarriage rate were 21% and 11.5% respectively.

Conclusion: The reproductive outcomes of patients of hypogonadotrophic hypogonadism are reasonable after ICSI and clinical trials are recommended to corroborate this concern.

Keywords: Hypogonadotrophic, Hypogonadism, Reproduction, ICSI, Outcome, Pregnancy rate

Background

Gonadotropin-releasing hormone (GnRH) acts via the GnRH receptor, which is expressed on gonadotropic cells in the anterior pituitary gland. This action regulates both synthesis and release of gonadotrophs such as luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which control gonadal maturation and adult reproductive physiology via the hypothalamic–pituitary–gonadal (HPG) axis [1].

Hypogonadotropic hypogonadism (HH) diagnosis was based on clinical history of primary or secondary amenorrhea, negative progestin challenge, serum levels of both FSH and luteinizing hormone (LH) < 5 IU/L, accompanied by serum estradiol levels below 20 pg/mL. [2].

Hypogonadotropic hypogonadism (HH) has multiple etiologies and is characterized by ovulation disorders, low levels of endogenous gonadotropins, and estrogen deficiency caused by hypothalamic pituitary failure [3].

Congenital hypogonadotropic hypogonadism (CHH) is caused by deficient production, secretion, or action of GnRH, a key neuropeptide that orchestrates mammalian reproduction [4].

The congenital form is known as idiopathic HH, and accounting for approximately 40-60% of all cases [5]. When the condition is acquired, it is usually characterized by functional amenorrhea with low estrogen levels in women with a low body mass index (BMI) [6].

CHH can present solely as congenital GnRH deficiency or be associated with other developmental anomalies such as cleft lip or palate, dental agenesis, ear anomalies, congenital hearing impairment, renal agenesis, bimanual synkinesis, or skeletal anomalies [7, 8].
Puberty can be induced by oral or preferably transdermal estradiol administration in girls. Estrogen treatment increases uterine size and combined estrogen and progestin therapy induces monthly withdrawal bleeding but does not induce ovulation. For fertility, gonadotropins or GnRH therapies are necessary and effective [9].

HH patients will likely require either hormonal replacement therapy to regularize their cycles or ART depending on their reproductive desire. Low complexity techniques can be offered, but many women will need in vitro fertilization (IVF) [10].

There is limited evidence for ovarian response and reproductive outcomes of HH patients who undergo IVF. Some studies have reported similar overall IVF performance in this group of patients compared to other infertility causes [11].

Being a rare condition, there are a limited number of studies evaluating the reproductive capacity and infertility treatment outcome of women with HH.

Because of this limitation, this study was conducted, aimed to evaluate the reproductive outcome of this group of patients and to help clinicians to select the proper management for these patients.

Methods
This is a case series study including 19 patients who attended the assisted reproduction unit, Al-Azhar University, Cairo, Egypt, in the period from May 2016 to March 2019 with confirmed diagnosis of congenital hypothalamic hypogonadotropic hypogonadism and planned for ICSI. HH diagnosis was based on a clinical history of primary or secondary amenorrhea, ultrasound picture of small size ovaries, negative progestin challenge, and serum levels of both FSH and luteinizing hormone (LH) < 1 IU/L [5], accompanied by serum estradiol levels below 20 pg/mL [3]. Considering that the patients included in this study had no previous normal cycles.

All patients were received combined oral contraceptives containing estrogen and progesterone (Gynarena, Bayer Pharma AG, Berlin, Germany). 2 months before stimulation to help endometrial regeneration and regulation of the cycle. Ovulation induction was started at the second day of bleeding by 150-225 IU of human menopausal gonadotrophin (hMG, Menogon, 75 IU, Ferring Pharmaceuticals). Follicular tracking was continued until scanning showed at least 3 mature follicles. Triggering was performed by human chorionic gonadotrophin (Pregnyl 10000 IU, Organon, Kloosterstraat, Netherlands) administered intramuscularly followed by ovum pick up 36 h later. Embryo transfer was done at day 2-5 after pick up. Luteal phase support by vaginal progesterone gel (Crinone gel 8%, Merck-Serono, Germany) was given for 2 weeks until pregnancy was confirmed, then it was continued during the first trimester. Pregnancy was followed until delivery, where miscarriage rate and live birth rate were estimated. The primary outcome was the pregnancy rate. The secondary outcome was the live birth rate and miscarriage rate.

Statistical analysis
Statistical analysis was performed using Microsoft Excel 2013 (Microsoft Company, USA) and soft package of statistical analysis (SPSS version 22, IBM Company, Chicago, USA). The Normality of data was tested using normality tests (Kolomogrov, Semirenov test of normality). The data was presented by median and inter-quartile range (IQR) for quantitative data. Frequency and percentages were used for presentation of qualitative data. Mann Whitney test was used for the comparison between qualitative data and Fisher exact or -square tests were used for the comparison between categorical data.

Results
Medians ±IQRs for age, BMI, total dose of stimulation, and duration of stimulation were 29±6, 30.9 ±5, 5250 ±2100, and 15±3 respectively (Table 1). The outcomes of ICSI for the 19 patients were (median ± IQR were 1826 ± 2473, 10 ±1, 5±7, 4±3, 1±1, 0±2, 3±1, 2±1, 0±0) for E2 and endometrial thickness at the day of triggering, oocyte number, MII oocyte, MI oocytes, germinal vesicles, embryos number, grade A and B embryos respectively. Four cases got pregnant with the pregnancy rate of 31.6%. Four cases were delivered four term babies with live birth rate 4/19 (21%) while two cases showed first trimestric abortion with miscarriage rate of 10.5% (Table 2 and Fig. 1).

Discussion
The median number of oocytes retrieved in the current study was four. The lower number of oocytes retrieved may be explained by the study of Bry-Gauillard et al. [12], who assessed the number of antral follicles of 39 patients with isolated HH and observed a significantly lower AFC compared to 41 healthy controls. Interestingly, persistent FSH deficit in isolated HH can lead to diminished ovarian size and reduced AFC and in turn the number of oocytes retrieved [13].

Despite the similarity of results between this study and the study by Bry-Gauillard et al., the patients included were the patients with isolated HH while the patients in our study were the patients with congenital HH.

Another study with HH patients due to multiple etiologies also reported lower AFC [2]. However, many authors reported normal follicular count, but these results could be explained by the type of patients in the studies where women with small-sized ovaries who showed multi follicular or normal-sized ovaries as in cases of functional hypogonadism were included [9].
Some studies have evaluated the efficiency of different protocols and reproductive outcomes in this group of patients [14, 15]. They generally showed good response and high pregnancy rates, even though higher gonadotropin doses are usually required [16–18]. Our results prove these findings in view of good pregnancy rate (31%) and relatively high dose of stimulation (median ± IQR, 5250 ±2100) but low oocytes number (median ± IQR, 5±7).

Because of the low levels of FSH and LH, downregulation by either gonadotrophins-releasing hormone agonist (GnRH a) or antagonist (GnRH ant) was not required based on the results claim from detrimental effect of the pituitary suppression in women with congenital HH, on

| Variable                          | Median ± IQR*(Minimum.-Maximum.) | Mean ±SD |
|-----------------------------------|----------------------------------|----------|
| Age (years)                       | 29±6 (23-40)                     | 28.89±4.126 |
| Body Mass Index(BMI)              | 30.9 ±5 (25-38)                  | 31.27±3.357 |
| Total dose of stimulation         | 5250 ±2100 (2700-8100)           | 5080±1527 |
| Duration of stimulation           | 15± 3 (11-18)                    | 14.58±2 |

*As non-normal data distribution, the values were estimated by median and inter-quartile range (IQR)

| Variable                          | Median ± IQR*(Minimum.-Maximum.) | Mean ±SD |
|-----------------------------------|----------------------------------|----------|
| E2 at day of triggering           | 1826 ±2473 (789-5732)            | 2495±1471 |
| Endometrial thickness at the day of triggering | 10 ±1 (8-14)                  | 10±1.5 |
| Oocyte number                     | 5±7 (1-13)                       | 6.3±3.4 |
| MII Oocytes                       | 4±3 (1-10)                       | 4±2.4 |
| MI Oocytes                        | 1±1 (0-4)                        | 1.5±0.9 |
| GVs                               | 0±2 (0-3)                        | 0.79±1.2 |
| Embryos number                    | 3±1 (1-3)                        | 2.5±0.7 |
| Grade A embryos                   | 2±1 (0-3)                        | 2.2±0.84 |
| Grade B embryos                   | 0±0 (0-1)                        | 0.21±0.41 |
| Pregnancy rate                    | 31.5% (6/19)                     |          |
| Miscarriage rate                  | 10.5% (2/19)                     |          |
| Live birth rate                   | 21% (4/19)                       |          |
implantation and live birth rates [19]. Unlike our study, the previous results were applied to the patients with congenital and functional hypogonadism.

In all patients, we started with a stimulation dose of 150-225 IU. However, some studies had recommended to start with a dose not exceeding 75 IU and step up after 5 to 7 days [9]. This conflict may be resolved by the differences in patients selected.

Stimulation can be started on any day during amenorrhea or after an E + P withdrawal bleeding. Two to three months priming with sequential E + P treatment may improve response.

In a study by Yaldirim et al., they reported that patients with HH should be given oral contraceptives for at least 2 months before controlled ovarian hyper stimulation treatment to change the hypo estrogenic environment and to improve endometrial development [20].

In some studies, this priming is not required. A novel concept of LH priming has been suggested. Pretreatment with 300 IU SC of rLH for 7 days immediately preceding the rFSH significantly decreased the requirement of FSH [21].

In a review article of several studies published from 1966 to 1984, the pregnancy rate varied from 16 to 78% in different studies [22]. This coincides with our results (pregnancy rate 31%).

The live birth rate (LBR) in the current study was 21% which is approximately around the rate reported in the clinical trial conducted by Firouzeh et al. [23], where they compared the live birth rate after ICSI in 81 cases of HH with 88 cases with tubal factor infertility. However, no significant difference was detected.

In the current study, hMG was used for stimulation. However rFSH can be used only if combined with rLH as evidenced by many studies [24–26]. Interestingly, in the study by Kumback and Kahraman, they reported similar results if any of both stimulations was used [15].

Descriptive studies showed that the results of ART in HH patients treated with HMG were comparable to those in women with tubal factor infertility and unexplained infertility [16, 20].

In addition, earlier meta-analysis showed that when a GnRH a long protocol was used, hMG was superior to using only rFSH in IVF/intra-cytoplasmic sperm injection (ICSI) treatment [27, 28].

There have been several studies to increase the success rate with FSH and LH. As a result of these studies, it seems that a combined stimulation with FSH and LH is the best treatment option. However, it was concluded that the FSH/LH ratio should be 2/1 in the first half of the stimulation cycle, and 1/2 in the second half [14, 29, 30].

In patients with congenital HH, there is a lack of gonadotropin throughout the life, so there may be adverse effects of long-term LH deficiency on ovarian response and embryo implantation.

Due to the very low incidence of HH, many studies have been done to evaluate the influence of LH on follicular growth and oocyte quality in downregulated patients undergoing an IVF procedure [31, 32].

Several clinical studies have shown that a low concentration of LH leads to reduced ovarian estradiol biosynthesis because of the reduced thecal production of androgen precursors and consequently causes higher implantation failure and early pregnancy loss rates [32–34].

In contrary to this proposal, Yaldrim et al. compared HH patient ART outcomes with mild and moderate male factor infertility patients. They found that the response to fertility treatment in these patients was at least as good as in the control group [20].

In another prospective study by Yalmaz et al. [11], they reported that the duration of stimulation was longer and total gonadotropin dose was higher in the HH group. However, there were no differences in human chorionic gonadotropin (hCG) day estradiol levels, endometrial
thickness on hCG day, total oocyte number retrieved, MII oocyte number, or pregnancy rate.

To obtain acceptable rates of pregnancy with minimal side effects, determining the ovarian response before treatment is crucial. However, predicting the ovarian response to treatment of patients with HH is difficult because the lower level of gonadotropin, small ovaries, and amenorrhea renders ovarian reserve tests unreliable.

Sonnez et al. [35] found that the level of anti-Mullarian hormone (AMH) is correlated with ovarian response in patients with HH. Unfortunately, in this study, AMH was not done for all patients, firstly, because of the cost; secondly, because it is not a routine for the diagnosis of patients with HH.

Understanding of the molecular genetics of CHH is mandatory to know about the pathophysiology of this syndrome and to improve the treatment strategy.

Although patients with HH have a long-term estrogen deficiency, their response to controlled ovarian hyperstimulation treatment is like normal women as proved by previous studies and potentially by the current study. However, the HH group is heterogeneous and estimating their ovarian reserve is not always possible before treatment.

Several strengths are recognized in the design of this study. First, the prospective nature of the study made it more likely that the data collected would be complete. Also, consecutive patients were included in this series. Selection bias was limited because all patients who started stimulation protocol in the observed period were included in the study. The authors justly did not overstep the goal of a case series, as their goal was to present their results with conventional stimulation protocol. Because patients were followed until the end of treatment, this study is complete with regard to the report for potential complications associated with the treatment.

However, keeping the methodological limitations of a case series in mind, we cannot apply this conclusion to clinical practice before more evidence is obtained from randomized trials. Nevertheless, with good design and conduction, this study can be a sensible alternative to studies with higher levels of evidence, with the additional advantage of saving a lot of time and money.

**Conclusion**

The results of this study were considered reasonable if compared to the reproductive outcomes of patients with other infertility causes like tubal factor. So, we can conclude that there are no precautions that should be taken, or adverse effects expected, like cycle cancelation or empty follicle syndrome, when starting ovarian stimulation during ICSI cycles in patients of hypogonadotropic hypogonadism. Clinical trials are recommended to corroborate this concern.

**Abbreviations**

CHH: Congenital hypogonadotropic hypogonadism; GnRH: Gonadotropin releasing hormone; AMH: Anti-Mullerian hormone; HCG: Human chorionic gonadotrophin; ICSI: Intracytoplasmic sperm injection

**Acknowledgements**

The authors introduced many thanks to embryology units’ staff for their support and valuable data provided until finishing this work.

**Authors’ contributions**

AA: data collection and review writing. MA: statistical analysis, review writing. AF: paper revision and editing. All authors have read and approved the manuscript.

**Funding**

No funding was introduced either by individuals or organizations.

**Availability of data and materials**

Data is available upon request.

**Declarations**

**Ethics approval and consent to participate**

The study had been approved by university medical ethical committee (registry number, GYN_305 MedResearch_0000305) and all patients in the study had been signed for a written consent before procedure.

**Consent for publication**

All authors agreed for publication upon acceptance of the paper.

**Competing interests**

The authors did not report any conflict of interest.

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**Received: 2 May 2020 Accepted: 25 March 2021**

**Published online:** 19 April 2021
