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REPRODUCTIVE PHYSIOLOGY AND DISEASE

Impact of hypogonadotropic hypogonadism on ovarian reserve and response

Gustavo N. Cecchino[1,2,3] · Guillermo M. Canillas[3] · María Cruz[3] · Juan A. García-Velasco[2,3]

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Abstract

Objective To evaluate the hormonal profile, antral follicle count (AFC) and ovarian response of patients with hypogonadotropic hypogonadism (HH).

Design Observational retrospective cohort including infertile women with HH undergoing assisted reproductive treatment (ART).

Setting University-affiliated infertility center.

Patient(s) Thirty-three women with HH who underwent ART between January 2007 and September 2018. The control group comprised 66 age-matched counterparts with tubal or male factor infertility. The patients with an abnormal karyotype, and those presenting primary or secondary amenorrhea due to other causes, were cautiously excluded.

Intervention(s) None.

Main outcome measure(s) The primary outcome was serum levels of anti-Müllerian hormone (AMH) and AFC. We also investigated whether HH impacts ovarian response and reproductive outcomes.

Result(s) Although AFC was similar between groups, HH patients showed significantly higher AMH levels (4.6 ± 2.7 ng/mL vs. 3.0 ± 1.9, $p = 0.010$) and lower basal FSH and LH. While the HH group needed longer stimulation [13 days (11–26) vs. 10 (7–14), $p < 0.001$] and higher gonadotropin doses [2700 IU (825–6300) vs. 2100 (425–5000), $p = 0.038$], no significant differences were detected in either the number or maturity of retrieved oocytes, or in the fertilization rate, number of embryos transferred, implantation rate, clinical pregnancy rate and live birth rate per cycle.

Conclusion(s) HH patients present higher AMH levels, but similar AFC. Despite requiring longer stimulation and higher gonadotropin doses, ovarian response and reproductive outcomes seem unaffected.

Keywords Hypogonadotropic hypogonadism · Infertility · ART · Anti-Müllerian hormone · Pregnancy

Introduction

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 [1]. The congenital form is known as idiopathic HH, with Kallmann's syndrome accounting for approximately 40–60% of all cases [2]. 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) [3].

Ovarian reserve tests are used to predict the response to ovarian stimulation in assisted reproductive treatments (ARTs). Currently, no perfect exam to assess the reproductive prognosis exists, but antral follicle count (AFC) and serum anti-Müllerian hormone (AMH) levels have good predictive

Gustavo N Cecchino and Guillermo M Canillas contributed equally to this work.

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✉ Gustavo N. Cecchino
gusta.nardini@gmail.com

1 Department of Gynecology, Federal University of São Paulo, Rua Napoleão de Barros 632, Vila Clementino, São Paulo, SP 04024-002, Brazil

2 Department of Gynecology and Obstetrics, Rey Juan Carlos University, Avenida de Atenas s/n, Alcorcón, 28922 Madrid, Spain

3 IVIRMA Global Madrid, Avenida del Talgo 68, Aravaca, 28023 Madrid, Spain

value being superior to day-3 follicle stimulating hormone (FSH) [4, 5]. Although evidence suggests that AFC and AMH are great predictors of ovarian reserve in the general population, knowledge on its clinical applicability for HH patients is lacking [4].

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) [6]. In an ovarian suppression context, low AMH levels might be expected. Nevertheless, basic experimental research and clinical studies have demonstrated an inverse correlation between FSH and AMH values [3, 5, 7, 8].

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 [9–11]. Given the extremely low incidence of HH, compelling evidence for several aspects relevant to reproductive medicine is lacking. Indeed, there is no prospective study sufficiently powered to provide conclusive data. Thus, we aimed to explore the hormonal profile along with the ovarian response and reproductive outcomes of patients undergoing ART due to HH.

Materials and methods

Study design and population

We conducted an observational retrospective cohort that included 33 women with HH who underwent ART at 13 IVIRMA clinics in Spain between January 2007 and September 2018. As our primary objective was to compare hormonal profile, ovarian response, and reproductive outcomes, the control group comprised 66 age-matched counterparts (two controls/case) with tubal or male factor infertility.

HH diagnosis was based on a 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 [3, 12]. The exclusion criteria were amenorrhea due to polycystic ovary syndrome (PCOS) or outflow tract disorders, Asherman's syndrome, altered serum thyroid-stimulating hormone (TSH) and prolactin (PRL) levels, and an abnormal karyotype.

Besides matching the control group according to patient's ages, other inclusion criteria were infertility due to tubal or male factor, normal serum levels of TSH and PRL, BMI between 18 and 30 kg/m^2, age at menarche varying from 8 to 16 years, normal pubertal development, regular menstrual cycles, no previous IVF, and normal ovarian reserve confirmed by basal FSH < 10 IU/L and AFC ≥ 5.

Data were anonymously extracted from our institutional repository software platform, which holds patient's medical records from all IVIRMA clinics worldwide. An exploratory analysis was carried out to review the quality of the information, while integrity and accuracy were double-checked (GNC and GMC) to assure appropriateness. Whenever any included participant had more than one IVF cycle, data of the first cycle resulting in ovarian puncture were analyzed, even if no eggs were retrieved. Thus, only one IVF cycle of each participant was analyzed.

Ovarian stimulation protocol, ovum pickup, and embryo transfer

Considering that the patients included in this study had no previous cycles in our clinics, the type of treatment was defined according to the patient's needs (e.g. timed intercourse, artificial insemination or IVF). An individualized controlled ovarian stimulation (COS) protocol and the starting gonadotropin dose were established by a specialist physician according to the patient's baseline characteristics. Sonographic cycle monitoring started on stimulation day 5 and every 2 days thereafter. When the size of at least two follicles reached a mean diameter of 17–18 mm, serum estradiol and progesterone were assessed. Final oocyte maturation was performed with human chorionic gonadotropin (hCG), followed by oocyte retrieval 34–36 h later.

Conventional IVF or intracytoplasmic sperm injection (ICSI) was performed depending on sperm quality, and fertilization was confirmed 16–18 h later. Embryo cleavage was recorded every 24 h. Fresh embryo transfer was carried out either at cleavage or blastocyst stage, under luteal support with vaginal progesterone 400 mg/12 h. Whenever necessary, embryos were cryopreserved and frozen-thawed embryo transfer was performed after hormonal replacement therapy for endometrial preparation as described elsewhere [13]. In case of pregnancy, hormonal support was maintained until pregnancy week 12.

Ethical approval

The Ethics Committee of the University Hospital Puerta de Hierro Majadahonda approved the study protocol (Identification Code 1802-MAD-014-JG; February 26, 2018), which also complied with the Spanish law on assisted reproductive technologies. The need for informed consent was waived owing to the retrospective design of this study, as stated in the Institutional Review Board approval letter.

Statistical analysis

Considering the retrospective design and the very low HH prevalence in the female population, it was not possible to

Table 1 Patients' AFC and basal hormonal profiles

	HH	Control	*p* value
Age (years)	33 (26–49)	34 (30–35)	0.821
AFC	16 (1–30)	13 (5–36)	0.688
AMH (ng/mL)	4.6 ± 2.7	3.0 ± 1.9	*0.010*
FSH (mIU/mL)	2.6 ± 2.2	7.0 ± 3.1	*< 0.001*
LH (mIU/mL)	1.2 ± 1.5	4.7 ± 1.9	*< 0.001*

estimate sample size. However, a sample larger than 30 cases is believed to be of clinical relevance. The continuous variables were reported as mean ± standard deviation and compared using the ANOVA test when normal distribution was proven. Otherwise, data were expressed as medians with ranges and compared by the Mann-Whitney *U* test. The categorical variables were reported as percentages and analyzed by the Fisher's exact test or chi-square test, as appropriate. Statistical significance was set at a two-tailed p value of < 0.05. The analysis was performed using SPSS v24 (SPSS Inc., Chicago, IL, USA).

Results

AFC and hormonal profile

The analysis included 33 women with HH and 66 age-matched controls fulfilling all the inclusion criteria. The baseline characteristics for AFC and the hormonal profile of both groups are shown in Table 1. As expected, both basal FSH and LH were significantly lower in the HH group (2.6 ± 2.2 mIU/mL vs. 7.0 ± 3.1, $p < 0.001$ and 1.2 ± 1.5 mIU/mL vs. 4.7 ± 1.9, $p < 0.001$), respectively. The median patient age and AFC were similar in both groups, but the mean AMH level in the HH group was 1.5-fold higher than that of the control group (4.6 ± 2.7 ng/mL vs. 3.0 ± 1.9, $p = 0.010$). Importantly, data on AMH values were available for only 19 patients from the HH group and for 46 controls.

COS parameters and ovarian response

In this section, we excluded seven patients from the HH group: three underwent artificial insemination, two couples had timed intercourse, there was one egg donation cycle, and one spontaneous pregnancy. Therefore, the population consisted of 26 women in the HH group and 62 controls. Four controls were excluded due to missing data. Table 2 summarizes the main findings on the cycle parameters and ovarian response. Of note, only six patients (30%) in the HH group were stimulated without pituitary suppression while the remaining patients were given a gonadotropin-releasing hormone (GnRH) antagonist protocol.

The ovarian response assessed by the total number of retrieved oocytes and the number of mature oocytes did not show any difference between groups. Likewise, the serum estradiol and progesterone levels on the day of ovulation trigger were comparable. However, the HH patients required a significantly longer stimulation [13 days (11-26) vs. 10 (7-14), $p < 0.001$] and higher gonadotropin doses [2700 IU (825–6300) vs. 2100 (425–5000), $p = 0.038$]. The total gonadotropin dose was higher in the HH group because they required a longer treatment duration in order to achieve an adequate follicular growth, once the mean dose of gonadotropin per day was similar in both groups. However, the total mean LH dose in the HH group was significantly higher (1176 ± 505 IU vs. 355 ± 316 IU, p < 0.001), while there was no difference regarding the mean FSH dose (1748 ± 968 IU vs. 2005 ± 735 IU, p = 0.169). Importantly, there were no cases in which we failed to recover oocytes after ovarian puncture.

Reproductive outcomes

The reproductive outcomes of the 26 infertile patients with HH and the 62 controls who underwent IVF demonstrated no significant differences, as shown in Table 3. Indeed, the fertilization rate and live birth rate per cycle were similar between groups, as was the mean number of embryos

Table 2 Cycle parameters and ovarian response to COS

	HH	Control	*p* value
Days of stimulation	13 (11–26)	10 (7–14)	*< 0.001*
Gonadotropin doses (IU)	2700 (825–6300)	2100 (425–5000)	*0.038*
LH dose (IU)	1176 ± 505	355 ± 316	*< 0.001*
FSH dose (IU)	1748 ± 968	2005 ± 735	0.169
Estradiol (pg/mL)	2350 ± 1396	2070 ± 1292	0.368
Progesterone (ng/mL)	0.8 ± 0.6	0.6 ± 0.4	0.075
Number of oocytes	13.5 (2–22)	9 (2–34)	0.510
Number of mature oocytes	8.5 (1–20)	7 (2–28)	0.765

Table 3 Main reproductive outcomes

	HH	Control	*p* value
Fertilization rate (%)	75.6 ± 0.3	71.3 ± 0.3	0.471
Mean number of embryos transferred	1.50 ± 0.51	1.53 ± 0.53	0.794
Total number of embryos transferred	40	124	–
Cleavage stage (%)	21 (52%)	15 (12%)	
Blastocyst (%)	19 (48%)	109 (88%)	
Implantation rate:			
Per cycle (%)	59.2 ± 0.4	48.1 ± 0.4	0.273
Per embryo transfer (%)	57.7 ± 0.4	42.6 ± 0.5	0.145
Clinical pregnancy rate per cycle (%)	69.2 ± 0.5	59.7 ± 0.5	0.470
Live birth rate per cycle (%)	61.5 ± 0.5	53.2 ± 0.5	0.490

transferred. Only two patients from the HH group and nine controls did not reach embryo transfer in our series.

Discussion

Our findings suggest that women with HH present high AMH levels, regardless of ovarian suppression. Despite knowing that these patients require higher gonadotropin doses and longer COS, this is surprisingly relevant considering the high AMH values. It is noteworthy that the ovarian response and reproductive outcomes following IVF were not affected.

Interestingly, the AFC in this cohort was similar between groups. Previous studies have reported conflicting results, but several aspects should be taken into account. Bry-Gauillard et al. [14] assessed the number of antral follicles of 39 patients with isolated HH and observed a significantly lower AFC compared to 41 healthy controls. Importantly, patients with isolated HH present a persistent and profound FSH deficit, which can lead to diminished ovarian size and reduced AFC [15]. Conversely, women with acquired functional hypothalamic amenorrhea are usually exposed to FSH and this deficit seems lower [16], except in cases of severe anorexia in which ovaries are often small with a few detectable antral follicles [17]. In fact, some authors have described polycystic-appearing ovaries in many cases of functional hypothalamic amenorrhea [18–21].

Another study with HH patients due to multiple etiologies also recorded lower AFC [12]. However, the authors included only women with small-sized ovaries. Several of our patients presented multifolicular or normal-sized ovaries, especially in cases of functional hypogonadism, which could explain the normal AFC. While evaluating small antral follicles (2–5 mm) and larger follicles (6–10 mm), Jonard et al. [3] documented similar number of small follicles in patients with functional hypothalamic amenorrhea compared to those with preserved ovarian function. They concluded that a subtle FSH deficiency in this context does not impair follicle growth but affects the shift to selectable follicles, which is highly dependent on FSH [22]. We accounted for follicles between 2 and 10 mm to perform AFC.

Consistent with our data, other authors have found significantly higher AMH levels in HH patients with functional hypothalamic amenorrhea [3, 21]. In our series, we included not only patients with functional HH, but also those with congenital HH. Interestingly, both groups presented with high AMH levels and, to the best of our knowledge, this had not yet been described. A negative correlation between FSH and AMH has been reported in the early follicular phase and in PCOS patients [5, 7]. This indicates that FSH and estrogen may play a role in the downregulation of AMH and AMHRII mRNA expression in preantral follicles, as experimental data propose [8]. Unfortunately, one of the largest studies on HH patients requiring IVF treatment did not analyze AMH behavior [12].

In 1988, the possibility of using exogenous gonadotropins to achieve multiple follicular growth in women with complete gonadotropin deficiency was demonstrated for the first time [23]. Thus far, some studies have evaluated the efficiency of different protocols and reproductive outcomes in this group of patients [24–27]. They generally show good response and high pregnancy rates, even though higher gonadotropin doses are usually required [11, 28, 29]. Our results corroborate these findings.

We did not intend to evaluate which COS protocol is better for HH patients undergoing IVF. It is widely accepted that these women benefit from LH activity supplementation during COS [29–31], and ovulation induction should be performed with hCG and not with a gonadotropin-releasing hormone agonist [32, 33]. Nonetheless, many factors that influence the assisted reproductive treatments of infertile women with HH remain unknown.

Recently, it has been shown that pituitary suppression during COS in women with congenital HH could possibly have a detrimental effect on implantation and live birth rates [34]. Our findings do not support this notion, and this could have been influenced: (1) aside from congenital, we also included functional HH; (2) only six out of 26 patients in the HH group were stimulated without pituitary suppression, which hampers an adequate statistical analysis for comparison; and (3) avoiding pituitary suppression would be unlikely to influence our results since the implantation and live birth rates in our cohort were notably high.

Some limitations should be recognized. The retrospective design of our study and the small sample size did not allow us to perform subset analyses and to properly investigate other variables that could impact reproductive outcomes (i.e., number and quality of embryos). Also, we included HH patients due to multiple etiologies, which could have influenced our results once congenital and acquired HH display distinct features, as previously discussed. On the other hand, while considering the extremely low incidence of women with HH, especially when pursuing ARTs, our series is relatively large and addresses relevant findings that may be useful for patient counseling. Another strength of our work is that most patients were treated according to current ARTs protocols, contrasting with many previous studies that may have used outdated therapeutic approaches.

Conclusion

The HH patients presented increased AMH levels and required longer stimulation as well as higher gonadotropin doses to achieve similar reproductive outcomes compared to the patients with tubal or male factor infertility. Basic research is needed to better understand not only the biological mechanisms that regulate both ovarian biomarkers and response in this group of patients but also their implications.

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Author's contributions JAGV designed the study. MC performed data extraction. GNC was responsible for the statistical analysis. GNC and GMC performed the exploratory analysis, assessed data quality, and wrote the first manuscript draft. JAGV and MC critically revised the manuscript. All the authors approved the final version of the manuscript.

Compliance with ethical standards The Ethics Committee of the University Hospital Puerta de Hierro Majadahonda approved the study protocol (Identification Code 1802-MAD-014-JG; February 26, 2018), which also complied with the Spanish law on assisted reproductive technologies. The need for informed consent was waived owing to the retrospective design of this study, as stated in the Institutional Review Board approval letter.

Conflict of interest The authors declare that they have no conflict of interest.

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