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Comparison of outcomes between pulsatile gonadotropin releasing hormone and combined gonadotropin therapy of spermatogenesis in patients with congenital hypogonadotropic hypogonadism

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Abstract

Background To evaluate whether there was a difference in outcome between pulsatile gonadotropin releasing hormone (GnRH) therapy and human chorionic gonadotropin/human menopausal gonadotropin (hCG/HMG) therapy for induction of spermatogenesis in post-pubertal male patients with congenital hypogonadotropic hypogonadism (CHH).

Methods This was a single-center retrospective cohort study conducted at the Andrology Center of a university hospital. A total of 155 postpubertal CHH patients who met the inclusion criteria underwent spermatogenic induction at the same andrology center. All patients used pulsatile GnRH therapy or hCG/HMG therapy for at least 6 months. The effects of spermatogenic induction therapy and testicular growth were evaluated. Logistic regression analysis was used to identify statistically significant factors which could predict the outcome of treatment.

Results There was no difference in the efficiency of successfully inducing spermatogenesis between pulsatile GnRH therapy and hCG/HMG therapy (82.1% vs. 75.8%, P: 0.356), nor was there a difference in sperm concentration category (SCC) (P: 0.284). However, the mean time required for pulsatile GnRH therapy was shorter (12.34 vs. 14.74 months, P: 0.038). At the treatment endpoint, total testicular volume (TTV) was greater with pulsatile GnRH therapy compared

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with hCG/HMG therapy (15 vs. 12 ml, P: 0.010), and there was still no difference in SCC (P: 0.310). Multivariate logistic regression analysis showed that only baseline TTV was statistically significant predictor of induced spermatogenic success (odds ratio, OR: 1.156, 95% confidence interval, CI: 1.013, 1.319). The area under receiver operating characteristic curve was 0.635, a sensitivity of 0.661, and a specificity of 0.588. In addition, multiple linear regression analysis demonstrated that younger age at treatment initiation and higher baseline TTV were significantly associated with increased sperm concentration at the end of treatment.

Conclusion Pulsatile GnRH therapy was similar to hCG/HMG therapy in inducing spermatogenesis in post-pubertal CHH patients, but it took less time and was more beneficial to testicular development. Larger baseline TTV may mean a better spermatogenic outcome. It was necessary for patients to have more information about spermatogenesis therapy in order to make reasonable medical decisions.

Clinical trial registration number Chinese Clinical Trial Registry. ChiCTR2400086876. Retrospectively registered on July 5, 2024.

Keywords Congenital hypogonadotropic hypogonadism, Gonadotropin therapy, Pulsatile gonadotropin-releasing hormone therapy, Spermatogenesis

Introduction

Congenital hypogonadotropic hypogonadism (CHH) is a rare condition caused by gonadotropin-releasing hormone (GnRH) deficiency which can lead to male infertility and even azoospermia [1]. The prevalence of CHH in the general population is approximately 1/10,000–1/48,000, with more males than females [2, 3]. Patients are classified into two categories based on olfactory status, those presenting with anosmia are considered to have Kallmann syndrome (KS), which account for about 1/3 of all CHH, and others with normal olfactory function are defined as normosmic congenital hypogonadotropic hypogonadism with normal olfactory sensation (nCHH), which account for about 2/3 [4]. Infertility is treatable in most patients with CHH, and they have the opportunity to obtain their own offspring, especially with Proven fertility preservation techniques and assisted reproductive technologies. Pulsatile GnRH and combined gonadotropin (human chorionic gonadotropin/human menopausal gonadotropin, hCG/HMG) therapy had both been shown to be effective in inducing spermatogenesis in approximately 60-85% of patients [5]. Previous meta-analyses based on numerous small-sample clinical studies had shown that induction of spermatogenesis by pulsatile GnRH and hCG/HMG was almost equally effective [6, 7]. Whereas, hCG/HMG could be more cost-effective and practical and more readily available in most countries in clinic, so hCG/HMG therapy may be more commonly used in most medical centers [8].

In recent years, however, some studies had reported that pulsatile GnRH therapy induced spermatogenesis faster and more effectively than hCG/HMG [9, 10]. So, the current debate over whether there were differences in efficiency and sperm output between the two therapies continued still, and discussion of the preferred option remained an ongoing concern in the field of andrology. Therefore, the aim of this study was to compare the efficacy, speed, and capability of pulsatile GnRH and hCG/HMG therapies in inducing spermatogenesis in patients with CHH and to provide the basis for the choice of treatment regimen in the clinic.

Materials and methods

Cohort construction and data collection

We designed a retrospective cohort which included a total of 155 male patients with CHH treated at the Department of andrology of West China Second University Hospital of Sichuan University during October 2016 to December 2022 who met the study criteria. Inclusion criteria for the diagnosis of CHH were: Males aged 16 years and older with incomplete development of secondary sexual characteristics and testicles; serum total testosterone (TT) levels < 1 ng/mL, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels below the normal range; normal prolactin; normal thyroid and adrenal function; no space-occupying lesions or previous surgical changes on sellar region magnetic resonance imaging (MRI). Exclusion criteria included patients who were not azoospermic, previous hormone replacement therapy (including testosterone, hCG, pulsatile GnRH, and hCG/HMG therapy), and discontinuation or change of treatment regimen by themself.

The study was approved by the Ethics Committee of the West China Second University Hospital of Sichuan University (Project number: 2024158). Patients chose one of the two treatment regimens and signed an informed consent form voluntarily, after being fully informed that pulsatile GnRH therapy or hCG/HMG therapy was available for induced spermatogenesis of CHH currently. Patients were included in the pulsatile GnRH therapy group and the hCG/HMG therapy group according to their chosen treatment regimen.

Within one month before the start of treatment, total testicular volume (TTV) of all patients was measured by

Prader orchidometer (for undescended testes, testicular volume was defined as 1 mL). And at least 2 semen analyses were performed according to the World Health Organization 2010 standards [11]. Serum sex hormone assessment was also performed, and venous blood samples were taken from each patient between 8:00 a.m. and 11:00 a.m. after an overnight fast, and serum TT, FSH, LH, and estradiol (E2) were measured.

Interventions and follow-up

Pulsatile GnRH therapy: Gonadorelin (Fengyuan Pharmaceutical Co., Anhui Province, China) was subcutaneously administered via a portable infusion pump (Weichuang Medical Science Co., Shanghai, China). The starting dose was 10–15 μg/90 min, and the dose was adjusted to maintain LH and FSH levels between 3 and 10 IU/L.

hCG/HMG therapy: HCG (2000 to 5000 U, Livzon Pharmaceutical Co., Guangdong, China) & HMG (75 to 150 U, Livzon Pharmaceutical Co.) were combined and administered intramuscularly every 72 h. The gonadotropin dose was adjusted to maintain the serum TT level at 2.5 to 5 ng/mL.

All patients underwent at least once serum sex hormone test, semen analysis, and measurement of TTV by Prader orchidometer within every 3 months during the treatment period, and were treated continuously for at least 6 months. To assess the effectiveness of induced spermatogenesis, sperm concentration grades were categorized as azoospermia, cryptospermia (sperm identified within a pelleted specimen), extreme oligozoospermia (<1 M/mL), severe oligozoospermia (1–5 M/mL), oligozoospermia (5–15 M/mL), and normozoospermia (>15 M/mL) according to the recommendations of the World Health Organization sperm concentration category (SCC) [11]. Successful induction of spermatogenesis was defined as the SCC at least to cryptospermia, and the length of treatment at this point was recorded. The treatment endpoint was defined as the point in time at which treatment was discontinued, at which point the duration of treatment, SCC, TTV, and serum sex hormone levels were recorded.

Statistical analyses

SPSS 27 (IBM Corp., Armonk, NY, USA) software was used for data analysis. Normally distributed data were presented as mean ± standard deviation (s.d.), non-normally distributed data were presented as median and interquartile range (IQR), and categorical variables were presented as numbers (percentages). The t-test was performed for normal distribution variables, and non-parametric tests were used for other continuous and hierarchical variables. Categorical variables were compared using the $\chi 2$ test. Multiple regression analysis was employed to investigate potential factors influencing spermatogenesis induction outcomes. Statistical significance was set at $P < 0.05$.

Results

Characteristics of patients with CHH

Of the 155 patients with CHH who met the inclusion criteria, 56 were in the pulsatile GnRH group and 99 in the hCG/HMG group; the demographic and clinical characteristics of the patients were shown in Table 1. There were no significant differences in diagnosis, age, history of cryptorchidism, baseline TTV, serum FSH, LH and TT between the two groups. All patients with a history of cryptorchidism underwent orchidopexy prior to initiating treatment.

There was no difference in the efficacy of the pulsatile GnRH group and the hCG/HMG group in successfully inducing spermatogenesis (82.1% vs. 75.8%, P: 0.356), and the median duration of treatment was 12 months in both groups, but the mean time required was shorter in the pulsatile GnRH group (12.34 vs. 14.74 months, P: 0.038). There was also no difference in SCCs at this time (P: 0.284).

Table 1 Baseline characteristics of CHH patients treated with induced spermatogenesis

	Total patients with CHH (*n* = 155)	Pulsatile GnRH group (*n* = 56)	hCG/HMG group (*n* = 99)	*P* value
Diagnoses				
KS		11(19.6%)	22(22.2%)	
nCHH		45(80.4%)	77(77.8%)	0.706
Age (y)	24(19, 29)	22(18, 29)	25(19, 29)	0.313
History of cryptorchidism	25(16.1%)	11(19.6%)	14(14.1%)	0.371
TTV (ml)	4(2, 6)	4(2, 6.75)	4(2, 6)	0.403
FSH (IU/L)	0.8(0.3, 1.3)	0.9(0.3, 1.7)	0.7(0.4, 1.2)	0.412
LH (IU/L)	0.1(0.1, 0.4)	0.2(0.1, 0.5)	0.1(0.1, 0.4)	0.131
TT (ng/ml)	0.22(0.14, 0.41)	0.25(0.13, 0.44)	0.21(0.14, 0.40)	0.819
E2 (pg/ml)	12.3(11.8, 18)	14.3(11.8, 20.8)	11.8(11.8, 16.9)	0.084

CHH: congenital hypogonadotropic hypogonadism; GnRH: gonadotropin-releasing hormone; hCG/HMG: human chorionic gonadotropin/human menopausal gonadotropin; KS: Kallmann syndrome; nCHH: hypogonadotropic hypogonadism with normal olfactory sensation; TTV: total testicular volume; FSH: follicle-stimulating hormone; LH: luteinizing hormone; TT: total testosterone; E2: estradiol

Table 2 Characteristics of pulsatile GnRH and hCG/HMG therapy at treatment endpoints in patients

		Pulsatile GnRH group (*n* = 56)	hCG/HMG group (*n* = 99)	*P* value
SCC				
	azoospermia	10 (17.9%)	24 (24.2%)	
	cryptospermia	0 (0.0%)	2 (2.0%)	
	extreme oligozoospermia	3 (5.4%)	10 (10.1%)	
	severe oligozoospermia	8 (14.3%)	15 (15.2%)	
	oligozoospermia	10 (17.9%)	13 (13.1%)	
	normozoospermia	25 (44.6%)	35 (35.4%)	0.120
TTV (ml)		15(10, 22)	12(8, 19)	**0.010**
TT (ng/ml)		3.17(1.98, 4.75)	3.51(2.28, 6.02)	0.159
E2 (pg/ml)		32.1(20.6, 37.1)	36.8(20.2, 48.5)	**0.038**
Total treatment time (m)		12.5(9, 20)	18(12, 24)	**0.022**

CHH: congenital hypogonadotropic hypogonadism; GnRH: gonadotropin-releasing hormone; SCC: sperm concentration category; TTV: total testicular volume; TT: total testosterone; E2: estradiol

Table 3 Sperm motility and sperm morphology in patients with sperm concentration ≥ 1 m/ml at treatment endpoints

	severe oligozoospermia (*n* = 23)	oligozoospermia (*n* = 23)	normozoospermia (*n* = 60)	*P* Value
percentage of total forward motile spermatozoa (%)	43.5 (21.0, 51.5)	43.0 (31.3, 62.5)	49.0 (30.8, 60.3)	0.603
percentage of spermatozoa with normal morphology (%)	3.4 (1.5, 6.3)	3.4 (2.4, 4.9)	5.1 (2.3, 7.7)	0.161

Table 4 Characteristics of patients with successful or failed spermatogenic induction therapy

	Success group (*n* = 121)	Failure group (*n* = 34)	*P* value
Therapy			0.356
GnRH	46(38.0%)	10(29.4%)	
hCG/HMG	75(62.0%)	24(70.6%)	
Diagnosis			0.557
KS	27(22.3%)	6(17.6%)	
nCHH	94(77.7%)	28(82.4%)	
Age (y)	24(19, 29)	23.5(19, 30)	0.859
History of cryptorchidism	18(14.9%)	7(20.6%)	0.424
TTV (ml)	4(2, 8)	3(2, 5)	**0.014**
FSH (IU/L)	0.8(0.3, 1.4)	0.8(0.4, 1.1)	0.955
LH (IU/L)	0.2(0.1, 0.5)	0.1(0.1, 0.2)	**0.041**
TT (ng/ml)	0.23(0.15, 0.43)	0.19(0.11, 0.35)	0.143
E2 (pg/ml)	13.0(11.8, 18.5)	11.9(11.8, 15.3)	0.582
Total treatment time (m)	16(10, 21)	12(8.8, 24)	0.219

GnRH: gonadotropin-releasing hormone; hCG/HMG: human chorionic gonadotropin/human menopausal gonadotropin; KS: Kallmann syndrome; nCHH: hypogonadotropic hypogonadism with normal olfactory sensation; TTV: total testicular volume; FSH: follicle-stimulating hormone; LH: luteinizing hormone; TT: total testosterone; E2: estradiol

At the treatment endpoint, pulsatile GnRH had a shorter treatment duration and higher TTV compared with the hCG/HMG group, but there was no difference in TT levels and SCCs (see Table 2). When the sperm concentration was not less than 1 M/mL, there was no statistical difference in the percentage of total forward motile spermatozoa, and percentage of spermatozoa with normal morphology among severe oligozoospermia, oligozoospermia and normozoospermia patients (see Table 3).

Predictors of spermatogenesis treatment outcomes in CHH

We categorized all patients into success group and failure group based on inducing spermatogenesis outcomes. Patients in successful group had a greater baseline TTV (4 vs. 3 ml) and higher LH levels (0.2 vs. 0.1 IU/L) compared to whom in failed group, whereas there were no differences in other factors (see Table 4). After evaluating the clinical significance of each variable, binary logistic regression analysis by stepwise variable selection revealed that only baseline TTV was effective in predicting the outcome of spermatogenic therapy (P: 0.031, odds ratios, OR: 1.156). Moreover, the probability of successful spermatogenesis increased with larger baseline TTV. The corresponding area under the curve (AUC) of the receiver operating characteristic (ROC) curve was 0.635. Youden index showed the best cut-off value for predicting successful spermatogenesis was 0.748, and when it was greater than this value, successful spermatogenesis

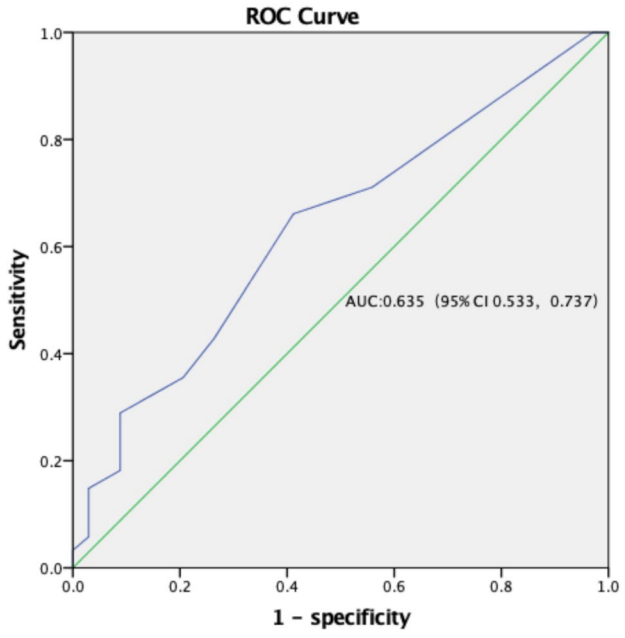

Fig. 1 Receiver operating characteristic curve analysis of the prediction model. The area under the receiver operating characteristic curve indicates the prediction capacity of the model. AUC: area under curve

Table 5 Predictive factors prior to spermatogenesis induction therapy associated with endpoint sperm concentration

Variables	B	t	*P* value	R2
Age (y)	-1.021	-2.199	0.029	0.128
TTV (ml)	2.627	4.530	< 0.001	
Constant	28.868	2.460	0.015	

TTV: total testicular volume

would be predicted, with a sensitivity of 0.661, and a specificity of 0.588 (see Fig. 1).

The predicted opportunity of success of inducing spermatogenesis treatment for each CHH patient was calculated as follows:

$$B = 0.582 + (0.145 \times TTV)$$

$$P = {}^{1}/_{(1 + exp(-B))}$$

To further investigate predictors of sperm concentration at treatment endpoint, we performed multiple linear regression analysis. The results demonstrated that younger age at treatment initiation and higher baseline TTV were significantly associated with increased sperm concentration at the end of treatment (see Table 5). The regression model is mathematically expressed as:

$$\lg(sperm\ concentration + 1) = 28.868 + 2.627 \times TTV - 1.021 \times Age$$

Discussion

Our study compared the outcomes of pulsatile GnRH and hCG/HMG therapies for inducing spermatogenesis in patients with CHH in a larger retrospective cohort and found that both were effective and were able to achieve similar SCCs, which was consistent with previous reports [6]. The difference was that pulsatile GnRH therapy could induce spermatogenesis more quickly and attain a greater TTV at the end of treatment. Meanwhile, patients treated with pulsatile GnRH experienced no significant adverse effects, while a few patients with hCG/HMG experienced mild symptoms of breast growth.

Theoretically, pulsatile GnRH therapy could be closer to the physiologic model and restore the function of the pituitary gonadal axis with stable level of sex hormones [12]. In contrast, the relatively crude mode of administration of hCG/HMG therapy may overstimulate the Leydig cells, resulting in the secretion and conversion of sex hormones above normal physiologic levels, leading to an increase of adverse effects (including acne, breast development, etc.). Currently, due to the optimization of hCG/HMG therapy, we adjusted the dosage and frequency of administration with the patient's sex hormone levels to maintain them stable at physiological needs and reduce the incidence of adverse effects [13]. At the same time, it is undeniable that this adjustment in dosing regimen resulted in 26 patients (26.3%) ultimately failing to reach the target testosterone value. However, spermatogenesis was eventually induced in 16 of these patients (Supplemental Table 1). This shows that although serum testosterone levels are not optimal, a relatively stable and slightly lower testosterone level also plays a role in spermatogenesis. Overall, the incidence of adverse events in this study was low. But it was undeniable that the stable regulation of gonadotropin levels by pulsatile GnRH therapy was incomparable to hCG/HMG therapy. It may be more conducive to the maturation of Sertoli cells, Leydig cells, and germ cells in testis, resulting in a larger testicular volume and a faster rate of spermatogenesis [14]. However, despite the advantages of pulsatile GnRH therapy in terms of spermatogenesis speed and testicular growth, these advantages need to be evaluated carefully in view of its more complex administration and higher economic costs.

In the analysis of treatment outcomes, patients who induced spermatogenesis successfully were found to have higher TTV levels. This might mean that such patients had a better reserve of functional testicular cells, since the main components of testicular volume were Sertoli cells and Leydig cells before the proliferation of germ cells in CHH patients. Regression analysis revealed that higher baseline TTV served as a significant predictor of successful spermatogenesis induction and was associated with elevated sperm concentration at treatment

endpoint, further confirming the critical role of testicular reserve function in spermatogenic recovery. Currently, rFSH had been shown to increase Sertoli cell proliferation by mimicking mini-puberty [15]. This ability to improve Sertoli cell reserve and maturation and to mimic normal prepubertal sex hormone changes may explain the better testicular growth and spermatogenesis that had been reported in studies using rFSH pretreatment prior to pulsatile GnRH treatment [16, 17]. In addition, Mao et al. reported that greater TTV was associated with CHH reversal [18]. Unfortunately, however, none of the patients in this study showed reversal at the endpoint of all treatment, which was significantly different from the 10–20% reported previously [19, 20]. Further exploration of the factors that may be associated with the occurrence of the reversal phenomenon was needed, therefore. We also found that the younger age of treatment initiation, the higher sperm concentration at the endpoint of treatment. This suggested that early treatment of CHH patients with induced spermatogenesis yield more favorable results and manifest the importance of early diagnosis and early intervention for CHH. In fact, the time point for the initiation of induced spermatogenic therapy in CHH patients is advancing. With the development of sperm cryopreservation technology, more and more ideas about early fertility preservation are being applied in clinical practice, especially for diseases with a risk of fertility loss [21, 22]. It is reasonable to assume that inducing spermatogenesis at puberty is not only more consistent with normal male physiologic changes and conducive to psychosexual maturation, but also provided a sufficient time window for fertility preservation so that valuable opportunities are not missed.

We noted that 21.9% (34/155) of CHH patients still failed induction of spermatogenic therapy. For this group of patients, some studies had shown that the effectiveness of induced spermatogenic therapy may be elevated after appropriately extending the duration of treatment to 24 months [13, 23, 24]. It should be added that if one treatment regimen was ineffective, then transitioning to another regimen at the appropriate time was also a viable option. Some studies had reported pulsatile GnRH therapy to be effective in patients who had failed hCG/HMG therapy and vice versa [25, 26]. Finally, when azoospermia still persisted after sufficient cycles of induced spermatogenesis treatment, testicular sperm extraction may be attempted [27]. The probability of obtaining spermatozoa can be as high as 90% when combined with microdissection testicular sperm extraction (mTESE) [28]. Among the patients included in this study, three cases who underwent mTESE after failure of induction spermatogenesis treatment obtained sperm successfully. Thus, surgical sperm retrieval can be an important remedy after failed spermatogenic induction therapy.

The study still had more limitations. Firstly, partial data absence may not comprehensively and accurately reflect the overall therapeutic efficacy. In terms of spermatogenesis induction, depending on the spermatogenic cycle, patients would take semen analyzed at least once within every three months during the treatment period. This allows for a possible deviation of up to three months between the time when spermatozoa are first detected in the semen and the time required to actually induce spermatogenesis. Likewise, the SCC provided by trimonthly semen analysis may not fully represent the initial SCC that actually induced spermatogenesis. Regarding genital development, our study did not collect data on penile length in patients following spermatogenesis induction therapy. In fact, penile length serves as a straightforward marker of successful pubertal induction, particularly for patients who did not achieve target testosterone levels. Secondly, only few patients in our study performed genetic screening that we were not able to determine the relationship between the regimen and outcome of spermatogenic induction therapy and genetics. CHH had genetically heterogeneous, and more than 50 genes had been reported to cause CHH or related syndromes, and rare mutations accounted for approximately 30% in addition [29–31]. There were several small samples of studies reporting that gene mutations in *PROKR2* and *FRFR1* may be associated with poor induction of spermatogenic therapy [29, 32]. But even patients with these mutations had more than a 50% chance of inducing spermatogenesis successfully, even in association with CHH reversal [33, 34]. In this study, five patients underwent genetic screening and were found to carry mutations in genes that may cause the disease, namely *ANOS1*, *PROKR2*, *CHD7*, *POLR3B* and *DAX1*. Spermatogenesis was successfully induced in the patient with mutated genes *ANOS1*, *PROKR2*, and *CHD7*. As previously reported, patients with *DAX1* mutations failed. The other patient with mutation *POLR3B* succeeded in obtaining spermatozoa subsequently by mTESE despite failure of spermatogenesis induction. As can be seen from above, it was currently difficult to make strong associations between specific genes and treatment outcomes due to the heterogeneity of the phenotypes of patients with relatively high frequencies of mutations and the presence of a variety of rare mutations. Thirdly, due to limited conditions, our study only evaluated basal sex hormones and did not test inhibin B and anti-Mullerian hormone. This may, to some extent, limit the validity of our prediction model for predicting post-treatment SCC. Although LH is one of the independent predictive factors in the model, the difference is very small in the vast majority of patients and its practical value is very limited. In addition, the evidence from multiple studies shows that variation trend in the above two hormones during spermatogenesis

induction therapy may reflect the process of proliferation and maturation of Sertoli cells in the testicles, just as it occurs during male puberty [35, 36]. We are still continuing our research in this area and hope that we could predict treatment outcomes accurately through these hormones in the future. Finally, this study was a retrospective cohort study of an independent andrology center targeting patients from late adolescence to adulthood who were willing to have children in the future. And multicenter large-scale, prospective, randomized controlled trials were still needed in the future to confirm our findings and expand the target population throughout adolescence. Meanwhile, CHH patients who started testosterone replacement therapy in early adolescence were not included in this study. Although it had been reported that the success of gonadotropin replacement therapy at puberty to induce testicular growth and spermatogenesis was not related to testosterone replacement therapy previously [37]. However, well-designed prospective studies were still needed to assess the outcome of future treatment with induction of spermatogenesis in these patients.

Although there are aspects that need to be improved, our findings still provide more basis for the selection of CHH-induced spermatogenesis therapy and the prediction of spermatogenic outcomes. It helps clinicians to provide more rational advice for CHH patients, that is, to choose treatment options with a comprehensive consideration of efficacy, time cost and economic burden. For example, for patients who had an urgent need for fertility, or who valued testicular development more, pulsatile GnRH therapy may be a better option when finances allowed.

Conclusion

Both pulsatile GnRH therapy and hCG/HMG therapy could induce spermatogenesis in post-pubertal CHH patients, and both had similar effectiveness and spermatogenic outcomes. But pulsatile GnRH therapy induced spermatogenesis faster and leaded to better testicular growth. Pre-treatment baseline TTV could predict whether the therapy would be effective. Higher baseline TTV and earlier treatment initiation age were associated with increased sperm concentration at treatment endpoint. Before starting induction of spermatogenic therapy, clinicians should keep patients well informed about both therapies, especially spermatogenic outcomes, to help them make reasonable medical decisions.

Abbreviations

GnRH	Gonadotropin releasing hormone
hCG/HMG	Human chorionic gonadotropin/human menopausal gonadotropin
CHH	Congenital hypogonadotropic hypogonadism
SCC	Sperm concentration category
TTV	total testicular volume
KS	Kallmann syndrome
nCHH	normosmic congenital hypogonadotropic hypogonadism
TT	Total testosterone
LH	Luteinizing hormone
FSH	Follicle-stimulating hormone
MRI	Magnetic resonance imaging
IQR	Interquartile range
AUC	Area under the curve
ROC	Receiver operating characteristic
mTESE	microtesticular sperm extraction

Supplementary Information

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Supplementary Material 1

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Author contributions

All authors qualify for authorship by contributing substantially to this article. Y.Z. and DM.L. developed the original concept of this study collectively. XH.J., K.T., HZ.B. and GC.Z. contributed to the data acquisition and data interpretation. Y.Z., JT.Y. and DM.L. contributed to data acquisition, statistical analysis, and data interpretation and drafted the manuscript. All authors have contributed to critical discussion and reviewed the final version of the article and approve it for publication.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

All patients (or legal guardians) signed written informed consent forms for participation, and this study was approved by the Ethics Committee of the West China Second University Hospital of Sichuan University (Project number: 2024158). The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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