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Testosterone versus hCG in Hypogonadotropic Hypogonadism – Comparing Clinical Effects and Evaluating Current Practice

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Abstract

Background. Gonadotropin therapy is not typically used for pubertal induction in hypogonadotropic hypogonadism (HH), however, represents a promising alternative to testosterone. It can potentially lead to the maintenance of future fertility in addition to testicular growth. We compared the pubertal effects of human chorionic gonadotropin (hCG) versus testosterone in adolescent males with HH. We evaluated the current practice, among pediatric endocrinologists, to identify barriers against gonadotropin use. *Methods.* In this retrospective review, we compared the effect of testosterone versus hCG therapy on mean testicular volume (MTV), penile length, growth velocity, and testosterone levels. We surveyed pediatric endocrinologists at our center, using RedCap. *Results.* Outcomes were assessed in 52 male patients with HH (hCG, n = 4; T, n = 48) after a mean treatment duration of 13.4 (testosterone) and 13.8 months (hCG; $P = .79$). Final MTV was higher with hCG (8.25 mL) than testosterone (3.4 mL; $P < .001$). The groups did not differ in penile length, growth velocity, or testosterone levels. Survey results showed that more than half the providers were aware of the benefits of gonadotropins, however, 91% were uncomfortable prescribing hCG. Commonly reported barriers to prescribing hCG were lack of experience (62%) and insurance coverage concerns (52%). *Conclusions.* Larger testicular volume predicts faster induction of spermatogenesis. Since hCG promoted better testicular growth, compared to testosterone, it may potentially improve future fertility outcomes in HH patients. Our results identify an opportunity to improve current practice among pediatric endocrinologists worldwide and reduce barriers to prescribing gonadotropins in the adolescent population.

Keywords

hypogonadotropic hypogonadism, pubertal induction, gonadotropin therapy, testosterone, testicular growth

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Introduction

Hypogonadotropic hypogonadism (HH) can be congenital or acquired. Congenital HH is more common in males, with an estimated prevalence of about 1 to 10 in 100,000 live births. About two-thirds of cases are caused by Kallman syndrome, and the other third are considered idiopathic.[1] HH can also be acquired secondary to brain tumors, brain irradiation, or brain trauma. Males with HH have a defect in the hypothalamo–pituitary axis that leads to below-normal luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels, resulting in an absence of testicular maturation and testosterone production. Patients generally present with delayed puberty. For several decades, testosterone has been the primary agent used, worldwide, for pubertal induction in HH males, but this therapeutic strategy suppresses the hypothalamic–pituitary–gonadal axis, in turn suppressing FSH and LH. Although this exogenous treatment approach increases the testosterone levels, this treatment approach results in decreased secretion of endogenous testosterone and decreased testicular growth. Increased testicular growth and larger testicular size are predictive

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of rapid induction of spermatogenesis and unassisted conception,[2] and therefore, considered a surrogate for fertility potential. This has created concerns that prolonged use of testosterone could potentially lead to decreased spermatogenesis and adversely affect fertility. The negative effects of prolonged androgen use on fertility were previously viewed as temporary and reversible with discontinuation of treatment. However, more recent studies demonstrate that prolonged androgen use is independently associated with a decreased likelihood of and longer time to achieving sperm output thresholds and successful conception.[2-4]

Gonadotropin therapy represents an alternative to androgen therapy for stimulation of pubertal changes in HH males. Several reports have described the induction of puberty with various gonadotropin regimens, including human chorionic gonadotropin (hCG) monotherapy, hCG + recombinant FSH (rFSH), human menotropic gonadotropin (HMG), and gonadotropin-releasing hormone. Previous studies on pubertal induction using hCG monotherapy and hCG + rFSH have each shown testicular growth and spermatogenesis in addition to adequate virilizing effects and better quality of life when compared to testosterone alone.[5-9] In addition to larger testicular volumes, prior exposure to gonadotropins was also linked to a favorable response to fertility treatments in adulthood.[4]

Several guidelines recommend different gonadotropin regimens[10-12] for pubertal induction. Results from comparison studies between these regimens have not favored or shown superiority of any one regimen over another. For example, one study demonstrated that prepubescent adolescent males treated with hCG + rFSH had larger testicular volumes than those treated with hCG monotherapy,[13] whereas another study showed no difference in post-treatment testicular growth between different gonadotropin treatment groups.[14] Sperm counts, however, were significantly better with hCG + rFSH in the latter report.[14] Until evidence suggests otherwise, hCG monotherapy may be reasonable to induce secondary sexual characteristics (when current fertility is not needed) and to simplify the regimen without compromising future fertility. Further advantages of hCG monotherapy in comparison to other gonadotropin regimens are that it is a simple regimen, is widely available, and potentially provides better future fertility outcomes compared to testosterone therapy. Multiple adult studies have shown the fertility benefits of gonadotropin therapy, but only a few pediatric studies have involved a direct comparison of therapeutic outcomes between testosterone and hCG therapies.[15,16]

Given the lack of pediatric outcomes, the aim of our study was to compare the effects of approximately 12 months of hCG versus testosterone therapy on pubertal induction in HH males. We hypothesized that in comparison to testosterone therapy, hCG monotherapy would produce similar virilization effects but offer better outcomes with testicular growth. Finally, we surveyed and evaluated the current practice among pediatric endocrinologists, predicting that despite any benefits of gonadotropins, most pediatric endocrinologists would not choose gonadotropins over testosterone therapy because of inexperience with gonadotropin treatments.

Methods

The study was conducted in 2 parts. The first part comprised a retrospective review of patient medical records. The second part consisted of a survey distributed among pediatric endocrinologists to evaluate their current status of practice.

Retrospective Review

This study included pre-pubertal males with HH, referred to the Pediatric Endocrinology Clinic at Texas Children's Hospital between 2012 and 2018.

Inclusion Criteria. We included males aged 13 to 21 years who were diagnosed at our clinic with congenital or prepubertally acquired HH, and who had a testicular volume of <4 mL. Diagnosis of HH had to have been confirmed by hormonal testing (pre-pubertal serum testosterone, LH, and FSH) with or without a failed gonadotropin-releasing hormone stimulation test (LH <4 IU/mL). Patients with congenital HH, Kallman syndrome, or prepubertally acquired HH with or without other anterior pituitary hormone deficiencies were included.

Exclusion Criteria. Patients with constitutional delay of growth and puberty or with a history of precocious puberty were excluded. Also excluded were patients who were untreated or were treated with any therapy for induction other than testosterone or hCG. Those who were lost to follow-up within a year of starting therapy, non-adherent to therapy, or had recent initiation of therapy with inadequate follow-up duration, were also excluded.

Data Collection. Patients were divided into 2 groups based on the treatment they received for induction of puberty (hCG or testosterone). Baseline characteristics, obtained through chart review, included race/ethnicity; mean age at diagnosis of HH; mean testicular volume (MTV); Tanner stage; penile length; testosterone, LH, and FSH level; etiology of HH; the presence of other hormonal deficiencies; and mean age at initiation of therapy. Testosterone levels were assessed by standard

second or third generation laboratory assays including chemiluminescent immunoassay and liquid chromatography tandem mass spectrometry. We also graded the disability of patients based on a binary grading system: Grade 0 – no disability or mild intellectual disability, visual defect/loss, hearing defects/loss, autism, or anosmia; and Grade 1 – moderate to severe intellectual disability, hemiparesis, wheelchair-bound, tracheostomy dependent, or severe global delays.

Our primary endpoints were MTV (mL) and testosterone levels after approximately 12 months of either therapy. Secondary endpoints were Tanner stage, penile length (cm), growth velocity (cm/year), and whether treatment options were discussed and documented by the provider in the electronic medical records.

Provider Surveys

Texas Children's Hospital (TCH) is a regional and national referral center with a robust and large pediatric endocrine department, consisting of 28 board-certified pediatric endocrinologists. We used a survey to assess the current practice among pediatric endocrinologists at TCH. The survey questionnaire was collectively prepared after discussion between several authors and was pre-tested before its distribution. The survey comprised the following 8 questions:

1. How many male patients with HH do you see in a year?
2. What is the average age at which you start treatment of pubertal induction?
3. What percentage of your clinic population that receives treatment for pubertal induction is on testosterone therapy?
4. If cost were not an issue, do you feel there is a benefit of starting gonadotropins over testosterone?
5. Do you discuss treatment options (gonadotropin vs. testosterone) with patients who potentially desire preservation of future fertility?
6. If a family were to opt for gonadotropin therapy, would you initiate treatment yourself or refer to Urology for gonadotropin therapy?
7. How comfortable are you with managing pubertal induction with gonadotropins, monitoring its effects, and titrating its doses?
8. What are the barriers to gonadotropin management?

Statistical Analysis

Summary statistics were used to compare demographic and clinical characteristics between males who received testosterone versus hCG therapy using the Fisher's exact test for categorical variables or Student's t-test for continuous variables.

Survey data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at Texas Children's Hospital. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for data integration and inter-operability with external sources.[17,18]

Ethical Approval and Informed Consent

The study protocol was approved by the Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals (Protocol# H-44670). Informed consent from patients were not needed as the study included a retrospective review of the medical records involving minimal risk to the patients.

Results

Retrospective Review Results

A cohort, consisting of 79 patients, was initially included in our study per our inclusion criteria. Of these, 27 patients ultimately were excluded for the following reasons: non-adherence (n = 7), constitutional delay of growth and puberty or spontaneous puberty (n = 6), recently initiated therapy with inadequate follow-up duration (n = 5), loss to follow-up (n = 4), no therapies yet initiated (n = 3), and history of precocious puberty and leuprolide therapy (n = 2).

Therefore, data for 52 patients were included in the analysis, and baseline characteristics are given in Table 1. Patients in the testosterone group (n = 48) were diagnosed at a mean age of 14.7 years, whereas those in the hCG group (n = 4) at a mean age of 13.9 years ($P = .22$). The age of initiation of therapy for pubertal induction was 15.14 years for the testosterone group and 14.85 years for the hCG group ($P = .66$). The sample population represented a variety of HH etiologies, including tumors of the brain and pituitary, septo-optic dysplasia, pituitary stalk interruption syndrome, HH with anosmia, and idiopathic congenital HH. In the testosterone group, 38 patients had grade 0 or no disability, and 10 had grade 1 disability, whereas the 4 patients in the hCG group had grade 0 disability. Mean MTV (standard deviation [SD]) at baseline was 3.24 mL (1.04) in the testosterone group vs. 2.5 mL (1.0) in the hCG group

Table 1. Baseline characteristics for patients.

Characteristics	Hcg (n = 4)	Testosterone (n = 48)	*P*
Age at diagnosis of HH (mean [SD])	13.9 (0.92)	14.7 (1.29)	.22
Race/ethnicity, n (%)			.84
Hispanic	2 (50)	25 (52)	
White	2 (50)	13 (27)	
Black		7 (15)	
Asian		3 (6)	
Baseline LH (mean [SD])	0.16 (0.17)	0.23 (0.32)	.70
Baseline FSH (mean [SD])	1.04 (1.00)	0.80 (0.76)	.55
Baseline testosterone (mean [SD])	8.65 (6.75)	7.88 (8.08)	.86
Cause of HH, n (%)			
Central nervous system tumor (± radiation)	2 (50)	13 (27)	
Pituitary tumors s/p resection		3 (6)	
Pituitary stalk interruption syndrome		6 (13)	
Septo-optic dysplasia		4 (8)	
HH with anosmia[a]		6 (13)	
Idiopathic	2 (50)	4 (8)	
Pituitary hypoplasia		2 (4)	
Iron overload		2 (4)	
Syndromic[b]		2 (4)	
Mutation in PROKR2 or KAL1		2 (4)	
Hypogammaglobulinemia		1 (2)	
Brain malformations		3 (6)	
Other hormone deficiencies, n (%)			.40
None	1 (25)	9 (19)	
Single hormone deficiency	1 (25)	6 (13)	
Multiple pituitary deficiencies (MPD)	2 (50)	33 (68)	
Prior testosterone treatments, n (%)			1.00
None	4 (100)	39 (81)	
Infancy		5 (10)	
Peri-pubertal 3 month course		4 (9)	
Grade of disability, n (%)			.58
Grade 1 (moderate to severe)	0	10 (21)	
Grade 0 (mild to none)	4	38 (89)	
Baseline MTV (mean [SD])	2.5 (1.0)	3.24 (1.04)	.18
Baseline Tanner stage, n (%)			1.00
1	3 (75)	29 (61)	
2	1 (25)	15 (31)	
3		3 (6)	
4		1 (2)	
Baseline penile length (mean [SD])	6.75 (1.06)	4.63 (1.82)	.13
Baseline height (mean [SD])	155.2 (5.03)	155.3 (13.03)	.98
Baseline height percentile (mean [SD])	7.90 (6.86)	18.48 (22.27)	.35
Age of starting therapy	14.85 (0.32)	15.14 (1.32)	.66

Abbreviation: SD, standard deviation.
[a]Only one patient was positive for KAL1 gene.
[b]Syndromes included CHARGE and Smith–Magenis syndrome.

($P = 0.18$). Mean testosterone (SD) at baseline was 7.88 ng/dL (8.08) in the testosterone group compared to 8.65 ng/dL (6.75) in the hCG group ($P = .86$). The 2 groups did not differ significantly in baseline Tanner stage, penile length, or height. In the testosterone group, most patients were started on intramuscular testosterone therapy (n = 45) at a starting dose of 25 to 50 mg every 4 weeks, whereas some patients were started on daily gel

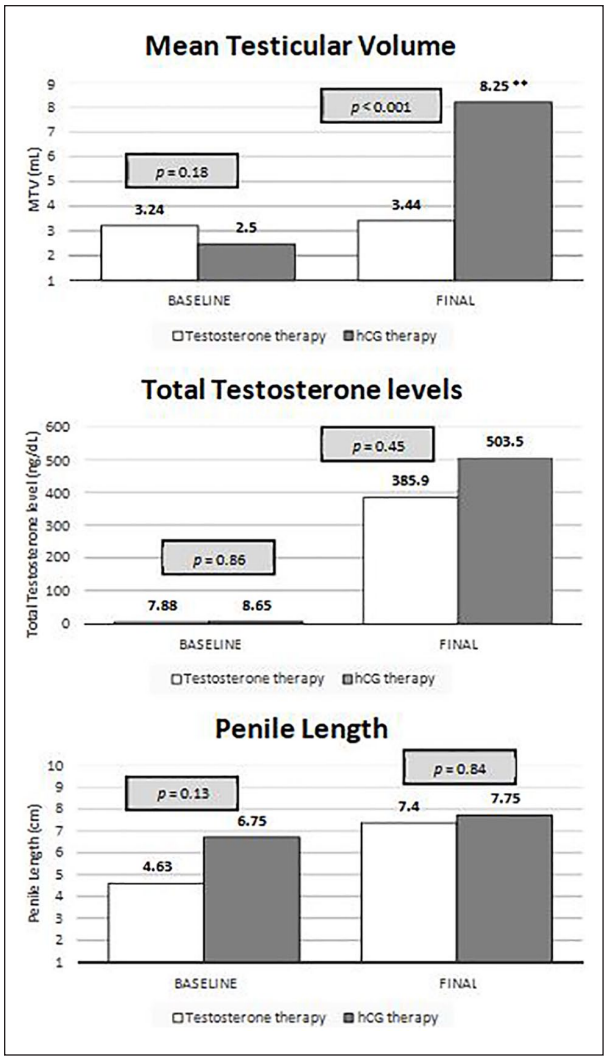

Figure 1. Comparing MTV, testosterone, and penile length between groups.

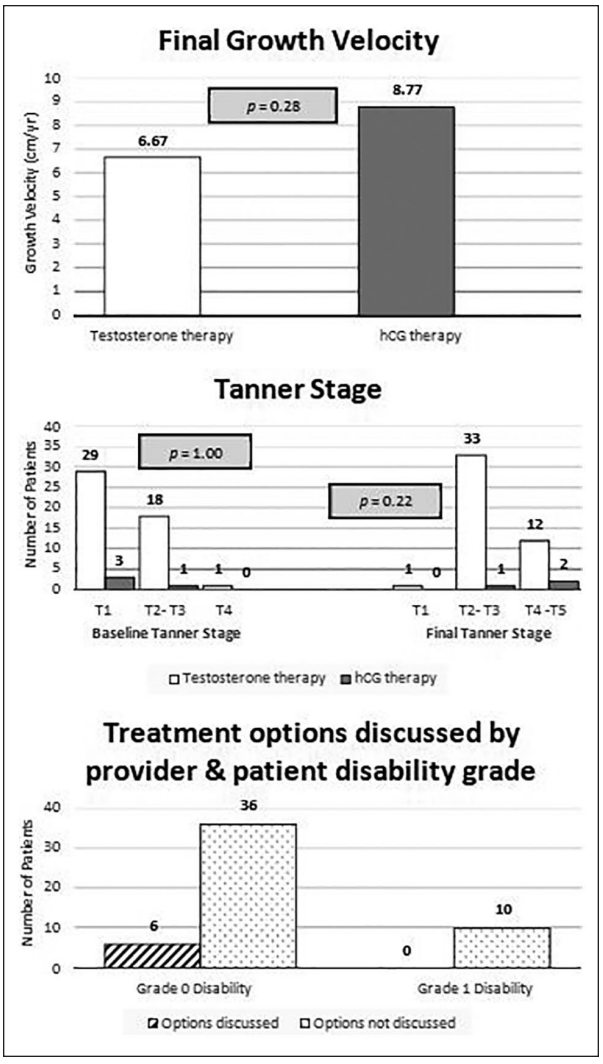

Figure 2. Comparing growth velocity, Tanner stage, and option discussion between groups

application (n = 3). In the hCG group, management was according to the provider's comfort and discretion. Of the 4 patients in the hCG group, 2 patients (both –14.5 years of age) were started on 1500 units twice weekly (Urology provider), 1 patient (15 years of age) was started on 1000 units twice weekly (Urology provider) and 1 patient (15 years of age) was started on 500 units 3 times a week (Endocrinology provider). Mean treatment duration in the testosterone group was 13.4 months compared to 13.8 months in the hCG group ($P = .79$). Figures 1 and 2 show a summary of the treatment outcomes.

Final MTV was documented in only 47 participants (testosterone, n = 43; hCG, n = 4). Mean final MTV (SD) with testosterone therapy was 3.4 mL (1.39) compared to 8.3 mL (4.5) with hCG ($P < .001$).

Final testosterone levels were available in 41 patients (testosterone group, n = 37; hCG, n = 4). Mean final testosterone (SD) was 385.9 ng/dL (295.8) with testosterone therapy, compared to 503.5 ng/dL (283.9) with hCG therapy ($P = .45$).

Tanner stage did not differ significantly between the 2 treatment groups ($P = .22$). Penile length was recorded in only 14 patients (12 on testosterone therapy; 2 on hCG) and did not differ significantly between the 2 groups. The testosterone group had a mean penile length (SD) of 7.4 cm (2.3), compared to 7.8 cm (1.1) in the hCG group ($P = .84$).

Final height and height velocity during the course of treatment were evaluated for all 52 patients. Mean final height (SD) in the testosterone group was 162.6 cm (12.8). For patients on hCG therapy, the final value was

163.6 cm (9.0; $P = .88$). Mean height velocity (SD) in the testosterone group (n = 48) was 6.7 cm/y (3.6), compared to a height velocity of 8.8 cm/y (5.3) in the hCG group ($P = .28$).

Only 6 of 52 patient charts showed documentation of a pre-therapy discussion about various treatment options, including testosterone versus gonadotropin therapies, with full disclosure about the advantages and disadvantages of each (testosterone = 2; hCG = 4). A total of 46 patients had no documentation of a discussion regarding treatment options and were all started on testosterone therapy. Four out of the 6 patients that had a documented discussion, chose to be on hCG therapy.

We had a total of 42 patients with grade 0 disability and 10 patients with grade 1 disability. Of the 6 patients (testosterone group = 2; hCG = 4) whose charts documented a discussion of treatment options, all had grade 0 disability. Of the remaining 46 patients whose charts lacked documentation of such a discussion, 10 patients had grade 1 disability and 36 patients had no or grade 0 disability.

Of the 4 patients in the hCG group, 3 were being managed by Urology and only one by Endocrinology. All 48 patients in the testosterone group were being managed by Endocrinology.

Provider Survey Results

The provider surveys elicited 21 responses (Figures 3 and 4). Most providers (17/21; 81%) reported seeing 1 to 5 male patients with HH whom they start on therapy for pubertal induction every year; some (3/21; 14%) reported seeing 5 to 10 patients per year, whereas one of the providers reported not seeing any of these patients (1/21; 5%). Most providers (20/21; 95%) initiate therapy for pubertal induction when patients are between ages 14 and 17 years, whereas one provider reported starting patients before 14 years of age. The majority of providers (19/21) reported having >80% of their patients on testosterone therapy. This was despite the perceived greater benefits with gonadotropin therapies in nearly half of the providers (11/21; 52.4%), whereas 6 of 21 (29%) were not sure about its benefits and none perceived gonadotropins to have worse outcomes.

When asked about a discussion of treatment options with patients and families, only 7 out of 21 providers (33%) reported always discussing both treatment options with families. Most providers (15/21; 71%) reported referring patients who were interested in gonadotropin therapies to Urology or other specialties. Few providers were absolutely comfortable using gonadotropin therapy (2/21; 10%), some were partially comfortable (7/21; 33%), and most were not comfortable (12/21; 57%) inducing puberty with gonadotropins, monitoring its effects, and titrating its doses. The reported barriers against using gonadotropins (Figure 4) were inexperience/ lack of guidelines (13/21; 62%), cost and insurance issues (11/21; 52%), lack of conviction about its benefits (10/21; 48%), and parent difficulties with injection administration (8/21; 38%).

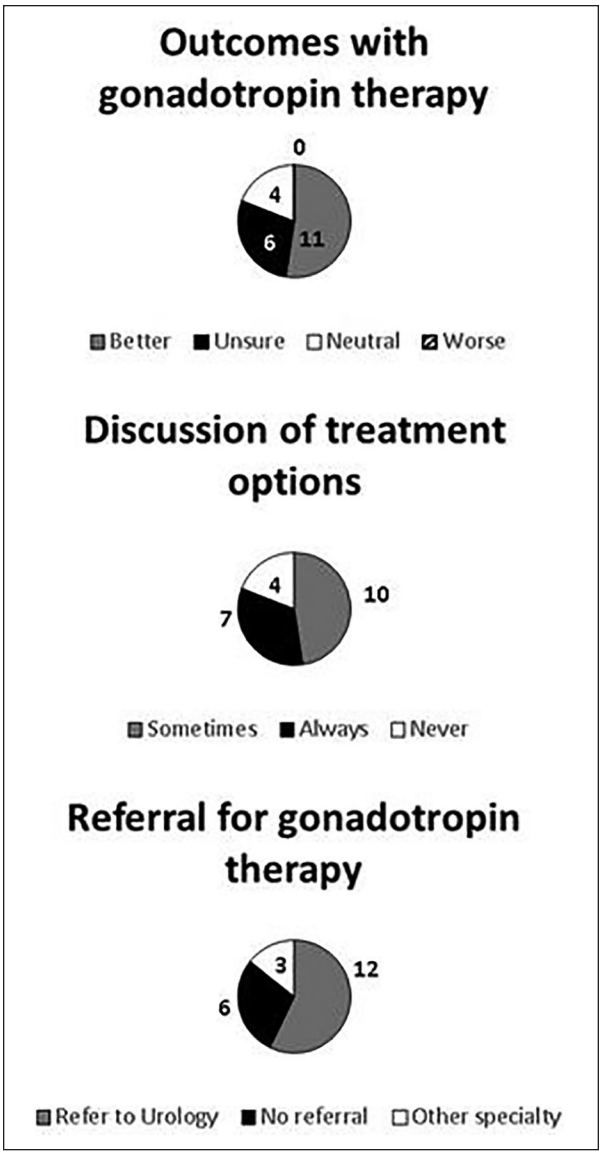

Figure 3. Provider survey results – Awareness and use of gonadotropins.

Discussion

Our results show that in adolescent pre-pubertal males with HH, pubertal induction with hCG therapy yields significantly better outcomes for testicular size when

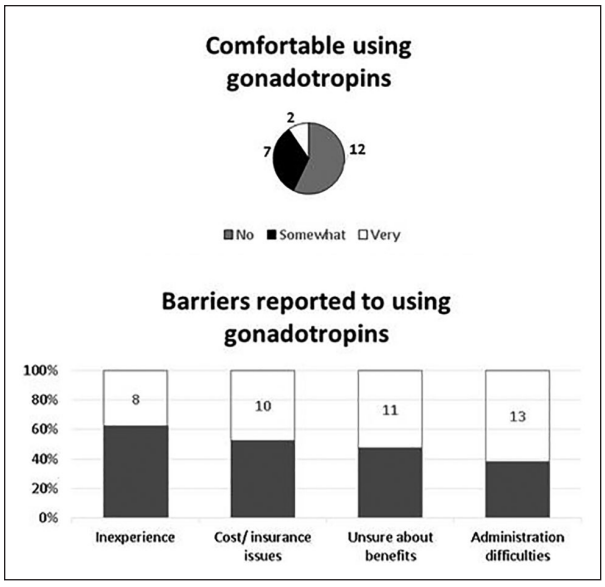

Figure 4. Provider survey results – Comfort and barriers to using gonadotropins.

compared to testosterone therapy after about 12 months of therapy, with no difference in testosterone levels between the 2 groups. Based on our results with the secondary outcomes – penile length, growth velocity, and Tanner stage, the 2 therapies did not differ for these outcomes. Studies have reported similar increases in final testicular volume, compared to baseline, with hCG monotherapy treatment among pre-pubertal adolescent patients with HH.[7,19-21] Additionally, other groups have reported similar findings indirect comparisons of these 2 treatment modalities in adolescent males with HH.[15,16]

In men with HH, all gonadotropin therapies, including hCG monotherapy or hCG in combination with HMG and rFSH, showed similar results with respect to testicular growth and virilization, in addition to promising results with spermatogenesis and conception.[8,22-25] Cryptorchidism and pre-therapy testicular volume in adult men may be confounding factors impacting testicular growth and spermatogenesis in response to gonadotropins.[8,19,26-28] Although hCG monotherapy has been reported to be less efficacious in final spermatogenesis as compared to combination therapies with rFSH or HMG,[24,29] the evidence is limited showing superiority of any of these therapies for the sole purpose of androgenization, virilization, and testicular growth.[8,24] If pubertal induction is the near-term goal, complicated treatment regimens involving multiple agents may not be needed. A valid limitation of using hCG in combination with HMG and rFSH therapies includes the need for more frequent injections at a potentially greater cost. Finally, hCG therapy can be administered subcutaneously or intramuscularly, and although there exists the possibility of differential clinical effects using these different routes, this has not been reported.[30]

It is necessary to discuss treatment options with the patient and family before starting any therapy. Discussions between the patient/family and provider should include full disclosure about the advantages and disadvantages of both testosterone and gonadotropin therapies. Our results showed that most patients (46 out of 52) had no documentation of a pre-therapy discussion about various treatment options. These 46 patients with no documented discussion were started on testosterone therapy per the physician's discretion. Only 6 patients had a documented discussion about various treatment options out of which 4 patients chose to be on hCG therapy. The presence of significant disability in a patient could bias a physician toward the use of testosterone therapy on the assumption of limited interest in future fertility preservation and therefore lead clinicians to not discuss options – and so we evaluated the patients with no or grade 0 disability (42 patients). However, out of the 42 patients with grade 0 disability, 36 had no documented discussion.

Despite the apparent benefit of hCG, the results from our provider survey show a gap in practice among pediatric endocrinologists. Most pediatric endocrinologists at our center reported using testosterone therapy for pubertal induction. About half were aware of the benefits of gonadotropin therapies over testosterone, and 30% of the providers were unsure about its benefits. Only about a third of the providers reported discussing the option of gonadotropin treatments with patients and families, and most (70%) said that they would refer to Urology and other specialties for gonadotropin therapies. Inexperience among pediatric endocrinologists and lack of guidelines was the major barrier to using gonadotropin therapies, followed by the cost of medication.

Strengths and Limitations

We compared the effect of testicular growth under gonadotropin versus testosterone therapy during the peri-pubertal ages and identified a gap in clinical practice among pediatric endocrine providers. The results highlight the discrepant use of gonadotropins and testosterone for pubertal induction despite the apparent benefits of gonadotropins and reflect the current state of practice among pediatric endocrinologists. Our findings also identify the barriers to using gonadotropin therapy.

Currently, there is little longitudinal evidence in the pediatric literature for gonadotropin use in the management of adolescent males with HH, and much is extrapolated from the adult literature. Based on adult evidence

regarding fertility predictors, we used testicular growth as a surrogate marker for future fertility potential. Prospective, longitudinal studies are necessary to confirm paternity rates, the true measure of fertility, in these adolescent patients, who are diagnosed and treated at a time where future fertility is of a relatively low priority to them. This tilt of focus toward pubertal development and away from fertility is precisely why studies evaluating for future fertility in this patient population remains difficult.

The major limitation of our study is the low number of patients who received hCG therapy at our institution, which was only 8% of eligible males during our study time period. Additionally, since this was a retrospective chart review study, we were reliant on physician documentation, which resulted in some missing outcome data. For these reasons, we were limited in our ability to draw statistical conclusions from this cohort. Also, the results from the provider survey results cannot be generalized, as this represents responses from a single center and may potentially be biased by institutional management protocols and insurance policies. These data do provide initial evidence to support our hypothesis of the beneficial effects of hCG therapy. However, larger multi-institutional studies are needed to confirm this finding.

Conclusion

This study highlights the benefits of gonadotropin use over testosterone in terms of testicular growth and, potentially, later fertility outcomes. However, practice gaps exist among pediatric endocrinologists. Testosterone therapy is still widely used for pubertal induction in adolescent males with HH, primarily because of inexperience with gonadotropin treatments and lack of guidelines.

Treatment of HH from the adolescent phase itself should be directed toward both androgenization and fertility. Testosterone therapy appears to fall short with regards to preserving fertility. In contrast, gonadotropin replacement not only promotes androgenization, but could potentially prevent infertility, oligo-spermatogenesis, and testicular atrophy from prolonged exogenous androgen exposure. The use of gonadotropins among pediatric endocrinologists is limited primarily because of inexperience with independently managing and monitoring hCG regimens. Establishing management strategies based on the available literature and expert recommendations will provide clinicians with guidance on gonadotropin use in adolescent males with HH. This will facilitate larger scale comparison studies to allow for more evidence-based guidelines for their use, potentially resulting in improved outcomes and improving the quality of care provided to these patients.

Author Contributions

S.A, L.K, P.A, and D.T contributed to the conception and design of the project. S.A, M.S, and L.K were involved with data acquisition, interpretation, and analysis. S.A drafted the initial manuscript which was subsequently reviewed, revised, and finally approved by all other authors before final submission.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr. Austin serves as a consultant for Allergan Pharmaceuticals and Urovant. Drs. Agarwal, Tu, Scheurer, and Karaviti have indicated that they have no potential conflicts of interest.

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