Puberty Induction in Adolescent Males: Current Practice

Mohammed S. Alenazi 1, 2, Ali M. Alqahtani 2, Mohammad M. Ahmad 2, Eyad M. Almalki 3, Angham AlMutair 4, 5, Mussa Almalki 2, 6

1. Diabetes and Endocrine Treatment Center, Prince Sultan Military Medical City, Riyadh, SAU
2. Obesity, Endocrine, and Metabolism Center, King Fahad Medical City, Riyadh, SAU
3. Medicine, Shaqra University, Shaqra, SAU
4. Pediatrics, Division of Endocrinology, King Abdulaziz Medical City, King Abdullah Specialist Children’s Hospital, Ministry of National Guard-Health Affairs, Riyadh, SAU
5. Medicine, King Abdulaziz Medical City, King Saud Bin Abdulaziz University for Health Sciences, Ministry of National Guard-Health Affairs, Riyadh, SAU
6. Medicine, King Fahad Medical City, King Saud bin Abdul Aziz University for Health Sciences, Riyadh, SAU

Corresponding author: Mussa Almalki, m2malk@yahoo.com

Abstract

Puberty is a developmental stage characterized by the appearance of secondary sexual characteristics which leads to complete physical, psychosocial, and sexual maturation. The current practice of hormonal therapy to induce puberty in adolescent males is based on published consensus and expert opinion. Evidence-based guidelines on optimal timing and regimen in puberty induction in males are lacking, and this reflects some discrepancies in practice among endocrinologists. It is worth mentioning that the availability of various hormonal products in markets, their different routes of administration, and patients/parents’ preference also have an impact on clinical decisions. This review outlines the current clinical approach to delayed puberty in boys with an emphasis on puberty induction.

Introduction And Background

Delayed puberty in males is defined as the absence of testicular growth at an age that is 2 to 2.5 SD later than the population means (traditionally, the age of 14 years). However the onset of puberty varies by country, race, and ethnicity [1], and it is delayed in around 2%-3% of boys [2]. Normal pubertal development is the result of the increasing release of gonadotropin-releasing hormone (GnRH) by the hypothalamus, which in turn stimulates the pituitary gland to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Transient activation of the hypothalamus-pituitary-gonadal axis starts from intrauterine life to the first few months of life, a process that has been described as “mini-puberty.” Subsequently, the hypothalamus-pituitary-gonadal (HPG) axis is inactivated by gamma-aminobutyric acid (GABA) until the beginning of pubertal maturation [3]. The exact trigger that initiates pulsatile GnRH secretion is not fully known but is thought to be influenced by multiple factors including genetics, nutrition, neurotransmitters, and hormones. It has been demonstrated that the major neurotransmitter responsible for activating the GnRH pulse generator are glutamate, neuropeptide Y, endorphins, opioids, and melatonin [4]. Furthermore, kisspeptin and its receptor regulate GnRH secretion [4]. Inactivating mutations in the genes encoding the human kisspeptin receptor leads to failure of puberty progression [5]. The gonadotropins stimulate the development of gonads and result in synthesis as well as the release of sex steroids estrogens and androgens, and this process leads to the physical and hormonal changes of puberty: gonadarche indicates pubertal onset and it is provoked by the GnRH release in a pulsatile fashion, which activates the HPG axis. In males, LH stimulates the Leydig cells to produce testosterone and maintain spermatogenesis, while FSH stimulates the Sertoli cells and initiates spermatogenesis [6, 7]. Adrenarche (i.e., androgen production by adrenal glands leading to the development of the pubic and axillary hairs, the sebaceous and the apocrine glands) is a separate but usually parallel process and does not in itself indicate genuine puberty [7]. Premature adrenarche is the presence of secondary sexual hairs in boys younger than nine years old [8]. The normal physiology of puberty is illustrated in Figure 1.
When to suspect delayed puberty in boys?

Puberty is considered delayed when there are no signs of testicular enlargement by 14 years of age. The earliest indicator of genuine puberty in boys is a testicular enlargement of at least 4 mL in volume or 2.5 cm in length, which occurs at an average age of 11.6 years (range: 9.5 to 14 years) [9,10]. Any disruption of the normal physiology as described above may result in delayed puberty and under-virilization. And can also result in malformation of the external genitalia if the disruption occurs early in intrauterine life. In boys, once puberty has begun, a period of 3.2±1.8 years is necessary to achieve an adult testicular volume [11]. The earliest stage of maturation is an increase in testicular volume (more than 3 mL), followed by thinning of the scrotum, penile growth, pubic hair development, and, lastly, a linear growth spurt [9]. Pathological changes may be present when pubertal changes have started but fail to get completed within approximately four
years of its onset, a condition considered stalled puberty [11]. Hypogonadism is classified as either primary or secondary, primary hypogonadism, also known as hypergonadotropic hypogonadism is caused by testicular failure and is associated with elevated gonadotropin levels. Secondary hypogonadism, also known as hypogonadotropic hypogonadism (HH), is characterized by low or inappropriately normal gonadotropin levels, as well as low testosterone concentrations, and is caused by a hypothalamic or pituitary defect or damage [12]. HH can be transient due to an underlying medical condition or persistent due to a congenital, acquired pituitary disorder or idiopathic in origin [7,12]. Constitutional delay of growth and puberty (CDGP) is the most common cause and is a nonpathological condition where the affected subjects achieve complete sexual maturation later than their peer. There is often a strong family history of CDGP in the parents or siblings, which suggests that there may be an underlying genetic cause [13,14].

**When and how to evaluate the patient with delayed puberty?**

The initial evaluation aims to rule out underlying disorders causing delayed puberty. Table 1 summarizes the commonest causes of delayed puberty [1,14-16].

| Constitutional Delayed Growth and Puberty (CDGP) 60%-65% |
|----------------------------------------------------------|
| Gonadotropin deficiency (hypogonadotropic hypogonadism) 10% |
| Isolated gonadotropin deficiency |
| Idiopathic |
| Kallmann syndrome (with anosmia) |
| Genetic (e.g., GNRHR, GNRH1, GPR54, FGFR1, FGF8, PROK2, PROK) |
| Obesity syndromes: (LEP, LEPR, and PCSK1 mutations), Prader-Willi Syndrome, and Bardet-Biedl syndrome. |
| Multiple pituitary hormone deficiencies |
| Congenital (Commonest Prop1 gene mutation) |
| Acquired due to central nervous system lesion (e.g., Craniopharyngioma) |
| Primary gonadal failure (hypergonadotropic hypogonadism) 5%-10% |
| Radiation to the testes |
| Following surgery for cryptorchidism |
| Vanishing testes syndrome |
| Klinefelter syndrome (small testes but adequate androgen production) |
| Functional hypogonadotropic hypogonadism 20% |
| Inflammatory bowel disease |
| Anorexia nervosa |
| Celiac disease |
| Cystic fibrosis |
| Thalassemia and sickle cell disease |
| Juvenile rheumatoid arthritis (JRA) |
| Hypothyroidism |
| Excessive exercise |

**Clinical history**

Questions about the initiation and evolution of body odor, acne, testicular growth, and pubic and axillary...
Hair should be asked of patients and their parents. Also, it is important to inquire about the psychosocial impact and emotional stress affecting the patient. A family history should be retrieved, including childhood growth patterns and the parents’ age at pubertal onset. It has been estimated that 80% of patients with CDGP have first-degree family members with delayed puberty [17,18]. Underlying secondary disorders can cause temporary delay of puberty (functional HH) if they are of sufficient intensity and duration. Therefore, it is essential to inquire about chronic disease symptoms, with a focus on certain disorders (e.g., poorly controlled type 1 diabetes, celiac disease, severe asthma, thyroid disease, Thalassemia, sickle cell disease, and anorexia) as well as medication use, nutritional status, and psychosocial functioning. Bilateral cryptorchidism or small penis at birth may suggest HH [19]. Also, hyposmia or anosmia may suggest Kallmann syndrome. History of chemotherapy or radiotherapy may indicate primary gonadal failure or HH. Hypogonadism in pediatric cancer patients is linked to the patient’s age, treatment dose, and duration. Hypogonadism affects between 11% and 56% of juvenile cancer survivors, according to current estimates [20-22].

Physical examination

Tanner scale, growth chart, and orchidometer are the tools needed to document and track the development of secondary sexual characteristics and puberty. Generally looking for any dysmorphic features, midline defects, along with obtaining height and weight and plotting the measurements for comparing it with previous ones to assess longitudinal growth is the main part of the examination [1,15,16,23]. The Prader orchidometer is widely used in clinical settings to estimate the testicular volume and is inexpensive, usually correlates well with ultrasonography for testicular size and volume [24]. The clinical findings associated with delayed puberty are summarized in Tables 2, 3.

### TABLE 2: Genitalia’s findings associated with delayed puberty.

| Genitalia                                      |
|-----------------------------------------------|
| Testes <2.5 cm in length (volume < 4 mL) are prepubertal. |
| Penis <7 cm stretched is prepubertal          |
| Penis <5 cm is small and may suggest congenital hypogonadotropic hypogonadism [18]. |
| Bilateral cryptorchidism may suggest congenital hypogonadotropic hypogonadism [18,22]. |
| Pubarche may or may not be present and does not impact a diagnosis of delayed puberty. |

### TABLE 3: Growth and body proportion findings associated with delayed puberty.

| Growth and body proportions                                      |
|------------------------------------------------------------------|
| Most boys who have CDGP are <10th percentile in height.         |
| A linear growth curve that is below but parallels to the third percentile, with a drop off after the age of 13 years, is suggestive of CDGP. |
| Growth rate < 3 cm/year during adolescence may suggest hypogonadotropic hypogonadism, hypopituitarism, growth hormone deficiency, or hypothyroidism but can also occur with CDGP. |
| Normal weight or being overweight for height is suggestive of CDGP. |
| Morbid early childhood obesity with normal development suggests leptin pathway gene mutation (LEP, LEPR, and PCSK1 mutations), if delayed development consider Prader-Willi syndrome or Bardet-Biedl syndrome. |
| Low weight for height is common in boys with an underlying disorder that causes a delay in puberty. |
| Boys with delayed puberty due to Klinefelter syndrome are usually tall [25]. |
| Boys with persistent hypogonadotropic hypogonadism may have eunuchoid body proportions characterized by arm span greater than height due to late epiphyseal closure [25]. |

### Investigations

Initial screening tests to confirm the diagnosis and to distinguish between primary and secondary hypogonadism include serum LH, FSH, and testosterone. Thyroid function tests, prolactin, and insulin-like
growth factor (IGF-1) are often needed to exclude any underlying disorders that have an impact on the onset of puberty and can delay it. If height velocity does not rise on testosterone therapy or short stature is a feature at the presentation, a diagnosis of growth hormone deficiency must be ruled out. Other labs include complete blood count, erythrocyte sedimentation rate, blood urea nitrogen, creatinine, tissue transglutaminase-immunoglobulin A antibodies (TTG-IgA), and liver function tests should be done to evaluate for the possibility of nutritional disorders, celiac disease, or occult chronic illnesses. A radiograph of the left hand and wrist to evaluate bone age should be obtained at the initial visit to assess skeletal maturation and then repeated over time if needed. Testicular ultrasonography can be used to determine testicular volume, omitting the contribution of the epididymis and overlying skin and providing a more precise estimate, particularly for smaller testicular volumes [24]. Additional tests have been proposed to help in distinguishing between CDGP and congenital HH (CCH) which include inhibin B, antimullerian hormone, basal gonadotropin (LH and FSH) levels, GnRH stimulation, or GnRH-agonist stimulation tests, and human chorionic gonadotropin stimulation tests [26,27]. Depending upon the clinical presentations MRI brain to rule out intracranial tumors or genetic testing may be indicated. In this review we seek to discuss puberty induction in boys, however, a detailed review of diagnostic workup is beyond the scope of this review, and the main diagnostic approach is illustrated in Figure 2.

**FIGURE 2: Diagnostic approach to a boy with suspected delayed puberty.**

### Puberty induction

**Goals**

The current practice of hormonal therapy to induce puberty in adolescent males is based on published consensus and expert opinion. Evidence-based guidelines on optimal timing and regimen in puberty induction in males are lacking, and this reflects some discrepancy in practice among endocrinologists which was reflected in surveys done in 2004 and 2020 [28,29]. Delayed puberty can result in significant psychological distress as well as low self-esteem for the adolescent male [30-32]. Additionally, it has a negative impact not only on metabolic profile, fat distribution, muscle mass, and bone mass but also on growth velocity [33,34]. Sex steroids are vital therapeutically in attaining mid-parenteral height and play an important role in numerous aspects of growth regulation [33,34]. Boys with CDGP typically tend to have short stature and delayed bone maturation. Multiple observational studies including 97 boys with self-limited delayed puberty found near-adult heights that are comparable to expected adult heights or mid-
parental heights [35-37]. On the other hand, other studies with a total of 218 boys, suggest that these boys may not reach their genetic height potential [38-40]. Several studies have evaluated the effects of testosterone therapy and reported that it does not adversely affect adult height and that there is no significant difference in adult height between treated and untreated boys [41-43]. Boys with HH who are treated later in life have aberrant body proportions and are taller than average [44]. The principal motivation for treating adolescents with CDGP is the severe psychological suffering they experience as a result of being shorter and less physically developed than their peers. The purpose of managing puberty in CDGP is to improve well-being and optimize growth and final height. In the case of persistent HH maintenance, hormonal replacement therapy is required after puberty induction to prevent adverse effects of delayed puberty on body proportions, to improve peak bone mass, and to avoid metabolic and psychosocial adverse effects associated with delayed puberty and hypogonadism.

**Optimal Timing**

Adolescents with pubertal delay should begin puberty induction therapy around the age of normal average puberty (12 years), but boys with CDGP might present later and begin treatment closer to 14 or 15 years of age [45]. Nonetheless, some endocrinologists tend to wait until the patient’s bone age is at least 10.5 years old because they are concerned about adult height implications if treatment is started too early [45].

**Treatment options for adolescent boys with delayed puberty**

To induce puberty, testosterone injections are the most widely used therapy in adolescent males with CDGP or hypogonadism. When compared to other regimens, testosterone is an effective, practical, safe, well-tolerated, and low-cost option. However, the effect of testosterone on the initiation of spermatogenesis and testicular growth is an unresolved issue. However, in adolescent males with hypogonadism, hCG with or without FSH appears to be more physiologic and potentially safer than testosterone in initiating spermatogenesis and testicular growth. In this review, various treatment options will be briefly explored to improve the management of this condition.

**Testosterone**

In most cases, testosterone is used to induce puberty in boys with hypogonadism and CDGP due to the flexibility in dose administration. A lower dose of testosterone is usually required at first to induce puberty in patients with hypogonadism and CDGP. For those who require long-term treatment, the dose is gradually increased [46,47].

In boys with permanent hypogonadism, testosterone therapy should be started at an appropriate age usually around the chronological age of 12 for physiological induction of puberty [46], while it is around 14 years for patients of CDGP [48]. For patients with concomitant severe short stature, growth hormone deficiency, and delayed bone age, testosterone therapy is usually delayed to allow increasing the final adult height [48]. Most of the clinical data for use in the management of pubertal development has been with the testosterone esters such as T enanthate and cypionate or with a mixture of very short and short-acting esters [46]. There is a paucity of published clinical data in respect to other testosterone formulations in adolescent populations (Table 4). The long-acting intramuscular preparation of T undecanoate for puberty induction and maturation is usually indicated for boys with permanent hypogonadism [49] and is unsuitable for cases with CDGP. A randomized cross-over study of oral vs. intramuscular testosterone did not show any significant difference in terms of efficacy for linear growth between the two agents [50]. Lawaetz et al. showed oral T undecanoate formulations were found to be effective in promoting height, inducing secondary sexual characteristics but without affecting bone age advancement [51]. Moreover, a three-month therapy resulted in a significant increase in fat-free mass along with increased height velocity [52]. Transdermal testosterone was found to be effective in promoting growth and virilization in patients with secondary hypogonadism affected by beta-thalassemia [53]. Similarly, 1% testosterone gel was effective in promoting secondary sexual characteristics in boys affected with Klinefelter’s syndrome [54]. Recently, testosterone transdermal gel preparations in strengths of 1% and 2% were found to be safe and effective on adolescent hypogonadal boys with concomitant hypertransaminasemia [55]. Another recent study on boys affected with CDGP has reported equal efficacy of testosterone transdermal gel 2% and intramuscular testosterone in comparison to untreated subjects in increasing height velocity [56]. For patients with partial androgen insensitivity syndrome (PAIS) and 5-alfa reductase deficiency, Dihydrotestosterone gel 2.5% has resulted in increased penile length [57,58]. Furthermore, a randomized, open-label trial on boys with CDGP compared efficacy of intramuscular testosterone (1 mg/kg/4 weeks) to oral letrozole (2.5 mg/day), for promoting puberty, reported a greater rise in gonadotrophins and testicular growth with letrozole although linear growth and bone age advancement did not differ [59]. The testosterone treatment options for the induction of puberty in boys with CDGP and hypogonadism are presented in Table 4.
| Testosterone Preparation | CDGP | Hypogonadism |
|--------------------------|------|--------------|
| T. Enanthate, Cypionate or a mixture of T. esters, IM injections | Starting dose: 50 mg monthly, for 3-6 months [46,60] | Starting dose: 25-50mg monthly. Increase by 50 mg every 6-12 months [46,60] |
| | May increase the dosage by 25-50 mg. Maximum Dose 100 mg [46,60] | Adult dosage: 150-200 mg every 2 weeks [61] |
| T. Undecanoate IM Injection | No data available | For puberty induction, only in young men [62] |
| T. Transdermal gels | 10 mg daily for 3 months [56] | Gel 1%: 0.5 g/day, increased up to 5 g/day as needed [54]. Adult dosage: 5-10 g/day [61] |
| T. Transdermal gels | Initial dose 40 mg daily, Maximum dose 80 mg twice daily [51] | Gel 2%: Initial dose 10 mg/day [55]. Adult dosage: 40-70 mg/day [61] |
| T. Undecanoate Oral tablets | 40 mg daily for 4 weeks [50] | Adolescent Population: No data |
| T. Undecanoate Oral tablets | 40 mg daily for 3 months [52] | |
| | 20 mg daily for 6 months [63] | Adult with hypogonadism, maximum dose is 80 mg twice daily [51] |
| | 40 mg daily for mean of 3.5 months [64] | |
| T. Transdermal patches | Age 12.5 to 15 years: 5 mg over 8-12 hours for 8 weeks [65] | Pre-pubertal 14-16 years: 2.5 mg over 12 hours overnight [65] |
| | | Partially virilized 17-19 years: 2.5 mg daily [65] |
| | | Virilized men above 20 years: 5 mg daily [53] |
| T. Pellets Subcutaneous | No Data Available | 13.9 to 17.5 years: 8-10 mg/Kg every 6 months for three doses [53] |
| T. Nasal gel | No Data Available | No Data Available for the adolescent population |
| T. Transbuccal Bio-adhesive tablet | No Data Available | No Data Available for the adolescent population |

TABLE 4: Summary of the studies done in puberty induction.

Testosterone therapy should be increased gradually to mimic normal pubertal physiology and can be stopped once the HPG axis has been significantly activated, as indicated by an increase in the testicular volume of 6 to 8 mL. Adolescents with permanent hypogonadism, on the other hand, require gradual increases in testosterone dose over two to three years until adult doses are reached to allow for optimal growth [45]. For evaluation of the effectiveness of testosterone therapy in clinical practice, regular follow-up every three to six months is needed along with an assessment of progression of pubertal maturation, height velocity, and changes in body composition [46]. Along with clinical assessment, other imaging, and laboratory workups such as bone mineral density assessment by DXA and hand-wrist radiograph for bone age are useful monitoring tools for both therapeutic benefits and side effects of testosterone therapy. Monitoring is highly recommended and has been standardized for testosterone therapy in hypogonadal men in the recent guideline [61], but such clear guidance is lacking for adolescents [46,66] and studies have shown that these adolescents on testosterone therapy undergo insufficient and incomplete biochemical monitoring [67]. Such wide variations in monitoring can be explained based on many diverse conditions and clinical indications in adolescents necessitating testosterone therapy. It is to be acknowledged that guidelines for clinical and hormonal monitoring for patients undergoing testosterone therapy and targeted approaches based on the etiology of hypogonadism are lacking due to the paucity of studies. With the availability of various newer testosterone formulations and the increasing knowledge of its therapeutic effects, careful monitoring and structured guidelines are needed more than ever. In this regard, Stancampiano et al. proposed a practical approach in a recent article [68]. Based on the temporary or permanent need for ongoing testosterone therapy, they proposed two different schemes for monitoring of replacement therapy and recommended complete blood count, liver function tests, bone age assessment...
with full clinical evaluation before starting testosterone therapy. This will provide us with not only a baseline, but also the ability to identify underlying diseases such as polycythemia or hypertransaminasemia when testosterone therapy is contraindicated. It will also alert the physician to additional diagnostic work-up for an underlying condition and the selection of preparations with a lower side effect profile, paving the way for individualized monitoring for each patient. Boys with CDGP usually have induction of puberty with a six-month course of testosterone therapy and once the therapy is initiated, full clinical evaluation alone at three- and six-month intervals is usually sufficient. Patients with a strong suspicion of CDGP but who are requiring therapy for more than six months need to be managed differently. They will need thorough evaluation for the underlying etiology and are likely to do better with the monitoring protocol for patients with hypogonadism which includes assessment of bone mineral density along with the metabolic and gonadal profile. Monitoring in cases with permanent hypogonadism requires the bone mineral density assessment by DXA scan using validated methods with adjustment for age, size, and sex along with bone age assessment and serum lipid profiles at baseline, one year, and then every one to two years. Through clinical evaluation and laboratory assessment such as serum total testosterone and complete blood counts needs to be done at baseline and at three, six, and 12 months followed by periodic assessment every 6–12 months has been suggested while liver function tests and serum level of FSH and LH is to be obtained at baseline [67-69]. The psychosocial impact can be assessed with a standardized QoL tool such as the EQ-5D-Y [70]. The assessment of the effectiveness of testosterone therapy in clinical practice should be based mainly on the clinical response observed such as an increase in testicular volume and a change in pubic hair growth. However, biochemically, keeping serum total testosterone level in the mid-normal reference range during treatment is much safer for the pubertal stage [46] forming the basis of the recommendation for its laboratory assessment which needs to be done periodically as mentioned above. For testosterone therapy, depending upon the type of preparation used and the timing of its administration, variability is observed in the level of serum testosterone obtained. For intramuscular testosterone enanthate or cypionate, the sample should be collected between the injections, whereas for testosterone undecanoate, it should be collected before the next dose. The level of testosterone is usually checked two weeks after starting therapy and 3–12 hours after application of transdermal testosterone patch while for transdermal gel preparations, it should be tested two hours after application, two weeks after starting treatment. In case of oral testosterone undecanoate, the level can be checked in a non-fasting state 5-5 hours after ingestion and at least two weeks of starting therapy.

**Potential adverse effects of testosterone replacement**

Adverse effects of testosterone therapy are uncommon in the short-term therapy of three to six months usually indicated for induction of puberty; however, they can occur in those with hypogonadism where long-term therapy is indicated. Erythrocytosis, acne and oily skin, Detection of subclinical prostate cancer, growth of metastatic prostate cancer, and reduced sperm production and fertility are some of the effects for which there is evidence of association with testosterone therapy, while gynecomastia, male pattern balding, growth of breast cancer and induction or worsening of obstructive sleep apnea are few of the uncommon adverse events having weak evidence of association with testosterone therapy [61].

**Gonadotropin**

The stimulation of testicular growth and spermatogenesis with improvement in potential fertility is an additional benefit of gonadotropin treatment over testosterone treatment [71]. Although it is commonly used to treat infertility in adults with CHH, it can also be used to induce puberty in adolescent males with CHH. On the other hand, for an inpatient with CHH, testosterone therapy alone is not a feasible treatment option for stimulating testicular growth.

To induce puberty in adolescent boys with CHH, various treatment protocols have been used, including hCG alone or in combination with FSH. The treatment regimen varies between 1,000-1,500 IU for hCG and 75–150 IU for FSH administered intramuscularly three times per week [72]. The hCG dose is to be titrated based on testosterone levels, whereas the FSH dose is usually adjusted based on clinical signs [72]. In a retrospective study of boys with CHH, treatment with 5,000 in weekly hCG injections and monthly testosterone injections had a comparable virilizing effect but the final testicular volume was significantly greater in patients treated with hCG [73]. Nonetheless, a prospective study including adolescents with delayed puberty, the majority of them with absent puberty, the use of hCG and rFSH led to significant testicular growth and induced spermatogenesis in 91% of patients [74].

Using FSH alone may be considered in adolescents with severe GnRH deficiency where the goal of priming with FSH alone is to stimulate the proliferation of immature Sertoli cells before seminiferous tubule maturation [75,76]. Raivo et al. [77] studied a small group of boys aged 9.9–17.7 years with gonadotropin deficiency who were initially treated with FSH alone (two mo-2.8 years) that induced testis growth and increasing circulating inhibin B levels, followed by successful pubertal induction with a combination of hCG and r-hFSH. Furthermore, a randomized controlled study of 18 adolescents GnRH-deficient men (CHH) with prepubertal testes (<4 mL) and no cryptorchidism or prior gonadotropin therapy showed FSH pre-treatment followed by GnRH was successful in inducing testicular growth, normalizing inhibin B levels, and promoting fertility [78].
Pre-treatment with FSH prior to testicular maturation appears to compensate for suboptimal testicular development during late fetal life and mini puberty, and thus may be beneficial for optimizing testicular growth and future fertility in adolescent males. It was previously noted that the initial testis size in men with CHH reflects the degree of gonadotropin deficiency and predicts treatment response [79]. Thus, boys with complete gonadotropin deficiency as determined by initial mean testicular volume < 4 mL require both hCG and FSH to achieve full testicular maturation, whereas boys with partial gonadotropin deficiency with initial mean testicular volume, 7 mL usually require only hCG [80].

Gonadotropin-releasing hormone

Throughout puberty, the LH and FSH response increases with the progression of puberty, GnRH stimulates the release of both LH and FSH [81]. Pulsatile GnRH treatment may be an option for patients with CHH who have GnRH deficiency but normal pituitary function. The most physiological approach is to use GnRH infused in a pulsatile fashion, with pulse intervals of 90–120 minutes. I.V. infusion results in the most effective pulsatile stimulation and thus the pulsatile release of gonadotropin, whereas sc administration results in more flattened gonadotropin levels, which can also result in adequate gonadal stimulation [82]. For hypogonadotropic males, GnRH treatment will result in a complete development with testicular growth including spermatogenesis and virilization [83]. For optimal testicular growth and spermatogenesis, the individual dose of GnRH and the time required to achieve maximum effectiveness are variable, ranging from 25–600 ng/kg and requiring a minimum of two years [84]. According to Liu et al. [80], pulsatile sc GnRH therapy for two years in adolescents with the complete form of CHH does not significantly accelerate or enhance testicular growth, hasten the onset of sperm production, or increase sperm output compared to hCG/hMG therapy. Thus, whether pulsatile GnRH administration, a more time-consuming treatment modality, does not offer any practical advantages over conventional hCG/hMG therapy in men with idiopathic HH (IHH), especially given the latter’s extremely high fertility rate, remains to be seen [85].

Our suggested approach to patient delayed puberty

There has been significant variation in the induction of puberty of adolescent males with central hypogonadism, and there is little agreement on proper treatment. A small number of studies, primarily in those with permanent hypogonadism, support our practice. We used a variety of treatment regimens for pubertal induction and completion, all of which were based on our experience rather than evidence provided by carefully designed studies. After several years of clinical practice, these regimens appear to be largely successful in achieving full virilization.

The initial testicular size usually reflects the severity of gonadotropin deficiency and predicts the increase in testicular volume in response to treatment in patients with delayed puberty and hypogonadism, so we use it as a guide for selecting the initial treatment option. We use both hCG and FSH in an adolescent boy with a previous history of absent puberty and small testicular size. Although hCG alone can increase testicular volume, combined treatment with hCG and FSH have been shown to result in a better response in terms of final testicular size, because normal levels of both gonadotropins appear to be necessary for appropriate spermatogenesis induction during puberty. If the patient’s pubertal development occurs spontaneously and the testicular size is greater than 4 mL, hCG can be started as a monotherapy. When a patient lacks pubertal development and has a testicular size of fewer than 4 mL, the optimal treatment regimen to optimize testicular growth and maximize the potentiality for fertility is unknown; however, we usually begin with FSH as monotherapy; hCG can be added if the patient achieves better testicular growth. Subsequently, we switch to testosterone in both groups when the testicular volume reaches the normal adult range or no further increase in testicular size was obtained. Figure 3 summarized the treatment approach for patients with delayed puberty due to HH (complete or stalled puberty).
However, the treatment is usually easier for older boys with delayed puberty and adult testicular size. Expectant observation or low-dose testosterone therapy are the two treatment options for CDGP patients. Figure 4 summarized the treatment approach for patients with delayed puberty due to CDGP. For patients with delayed puberty due to hypergonadotropic hypogonadism, our approach is to start testosterone at the age of 11-12 years old and gradually increase. Figure 5 summarized the treatment approach for patients with delayed puberty due to hypergonadotropic hypogonadism.

FIGURE 3: Suggested treatment approach for patients with delayed puberty due to HH (complete or stalled puberty).
FIGURE 4: Suggested treatment approach for patients with delayed puberty due to CDGP.

CDGP - Constitutional delay of growth and puberty
Conclusions

Adolescence is a critical period in human life, marking the transition from childhood to emerging adulthood and characterized by numerous challenges and developments in both the physical and social domains. Testosterone therapy in adolescent boys is primarily intended to increase linear growth and pubertal progression, but it may also improve bone mineral content, muscle function, metabolic profile, and psychological well-being. Some people may only need testosterone therapy for a short time, while others may need it for the rest of their lives, and therapy monitoring will thus depend on the underlying condition. Gonadotropin treatment can also be used to induce puberty in an adolescent male with...
hypo gonadism. The stimulation of testicular growth and spermatogenesis with improvement in potential fertility is an additional benefit of gonadotropin treatment over testosterone treatment.

**Additional Information**

**Disclosures**

**Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

**Acknowledgements**

The authors would like to thank the Research Centre at King Fahad Medical City for their valuable support in the preparation of this manuscript.

**References**

1. Kaplowitz PB: Delayed puberty. Pediatr Rev. 2010, 31:189-95. 10.1542/pir.31-5-189
2. Howard S, Dunkel L: Sex steroid and gonadotropin treatment in male delayed puberty. Endocr Dev. 2016, 29:185-97. 10.1159/000435891
3. Nebesio TD, Eugster EA: Current concepts in normal and abnormal puberty. Curr Probl Pediatric Adolesc Health Care. 2007, 37:50-72. 10.1016/j.cppeds.2006.10.005
4. Farello G, Al-tieri C, Cutini M, Pozzobon G, Verrotti A: Review of the literature on current changes in the timing of pubertal development and the incomplete forms of early puberty. Front Pediatr. 2019, 7:147. 10.3389/fped.2019.00147
5. Topaloglu AK, Tello JA, Kotan LD, et al.: Inactivating KISS1 mutation and hypogonadotropic hypogonadism. N Engl J Med. 2012, 366:629-35. 10.1056/NEJMoa1111884
6. Bordini B, Rosenfield RL: Normal pubertal development: Part I: the endocrine basis of puberty. Pediatr Rev. 2011, 32:223-9. 10.1542/pir.32-6-223
7. Bordini B, Rosenfield RL: Normal pubertal development: part II: clinical aspects of puberty. Pediatr Rev. 2011, 32:281-92. 10.1542/pir.32-7-281
8. Williams RM, Ward CE, Hughes IA: Premature adrenarche. Arch Dis Child. 2012, 97:250-4. 10.1136/archdischild-2011-300111
9. Marshall WA, Tanner JM: Variations in the pattern of pubertal changes in boys. Arch Dis Child. 1970, 45:15-23. 10.1136/adc.45.2.15
10. Herman-Giddens ME, Wang L, Koch G: Secondary sexual characteristics in boys: estimates from the national health and nutrition examination survey III, 1988-1994. Arch Pediatr Adolesc Med. 2001, 155:1022-8. 10.1001/archpedi.155.9.1022
11. Argente J: Diagnosis of late puberty. Horm Res. 1999, 51 Suppl 3:95-100. 10.1159/000053168
12. Klein DA, Emerick JE, Sylvester JE, Vogt RS: Disorders of puberty: an approach to diagnosis and management. Am Fam Physician. 2017, 96:590-9.
13. Palmert MR, Boepple PA: Commentary: variation in the timing of puberty: clinical spectrum and genetic investigation. J Clin Endocrinol Metab. 2001, 86:2564-8. 10.1210/jcem.86.6.7603
14. Sedlmeier IL, Pal mert MR, Hospital CNS: Delayed puberty: analysis of a large case series from an academic center. J Clin Endocrinol Metab. 2002, 87:1613-20. 10.1210/jcem.87.4.84383
15. Watson SE, Lee PA, Houk CP: Delayed puberty. Pract Pediatr Adolesc Gynecol. 2013, 91:6. 10.1002/9781118588555.ch10
16. Wei C, Crowne EC: Recent advances in the understanding and management of delayed puberty. Arch Dis Child. 2016, 101:481-8. 10.1136/archdischild-2014-307963
17. Sedlmeier IL, Hirschhorn JN, Pal mert MR: Pedigree analysis of constitutional delay of growth and maturation: determination of familial aggregation and inheritance patterns. J Clin Endocrinol Metab. 2002, 87:5581-6. 10.1210/jcem.2002-020862
18. Wehkalampi K, Widen E, Laine T, Palotie A, Dunkel L: Patterns of inheritance of constitutional delay of growth and puberty in families of adolescent girls and boys referred to specialist pediatric care. J Clin Endocrinol Metab. 2008, 93:723-8. 10.1210/jcem.2007-1786
19. Boas M, Boinen KA, Virtanen HE, et al.: Postnatal penile length and growth rate correlate to serum testosterone levels: a longitudinal study of 1962 normal boys. Eur J Endocrinol. 2006, 154:125-9. 10.1530/eje.1.02066
20. Rose SR, Horne VE, Howell J, Lawson SA, Rutter MM, Trotman GE, Corahners SD: Late endocrine effects of childhood cancer. Nat Rev Endocrinol. 2016, 12:319-36. 10.1038/nrendo.2016.45
21. Greenfield DM, Walters SJ, Coleman RE, et al.: Prevalence and consequences of androgen deficiency in young male cancer survivors in a controlled cross-sectional study. J Clin Endocrinol Metab. 2007, 92:5476-82. 10.1210/jc.2006-2744
22. Lehmann V, Chemaitilly W, Lu L, et al.: Gonadal functioning and perceptions of infertility risk among adult survivors of childhood cancer: a report From the St Jude Lifetime Cohort Study. J Clin Oncol. 2019, 37:893-902. 10.1200/JCO.18.01065
23. Abitbol L, Zborovski S, Pal mert MR: Evaluation of delayed puberty: what diagnostic tests should be performed in the seemingly otherwise well adolescent?. Arch Dis Child. 2016, 101:767-71. 10.1136/archdischild-2015-310575
system in hypogonadal adolescents and young men with beta-thalassemia major
De Sanctis V, Vullo C, Urso L, et al.: 1992, 37:207-13.

on growth, body composition, strength and energy expenditure of adolescent boys
Gregory JW, Greene SA, Thompson J, Scrimgeour CM, Rennie MJ: 2015, 100:1376-85.

with delayed puberty: diagnostic use of a new puberty nomogram and effects of oral testosterone therapy
Pazderska A, Mamoojee Y, Artham S, Miller M, Ball SG, Cheetham T, Quinton R: 2020, 35:1197-202. 10.1515/jpem-2020-0105

Graber JA, Seeley JR, Brooks-Gunn J, Lewinsohn PM: Is pubertal timing associated with psychopathology in young adulthood? J Am Acad Child Adolesc Psychiatry. 2004, 43:718-26. 10.1097/01.chi.0000120022.14101.11

Conley CS, Rudolph KD: The emerging sex difference in adolescent depression: interacting contributions of puberty and peer stress. Dev Psychopathol. 2009, 21:593-620. 10.1093/devpsych/pan046

Gross RT, Duke PM: The effect of early versus late physical maturation on adolescent behavior. Pediatr Clin North Am. 1980, 27:71-7. 10.1016/S0009-9141(18)33820-2

Tanner M, Whitehouse IH, Marshall, E, Resende LF: The adolescent growth spurt of boys and girls of the Harpenden growth study. Ann Hum Biol. 1976, 3:109-26. 10.1080/03014467600001231

Perry RJ, Farquharson C, Ahmed SF: The role of sex steroids in controlling pubertal growth. Clin Endocrinol (Oxf). 2008, 68:4-15. 10.1111/j.1365-2267.2007.02960.x

Cools BL, Rooman R, Op De Beeck L, Du Caju MV: Boys with a simple delayed puberty reach their target height. Horm Res. 2008, 70:209-14. 10.1159/000157665

Butenandt O, Bechtold S, Medert A: Final height in patients with constitutional delay of growth and development from tall statured families. J Pediatr Endocrinol Metab. 2005, 18:165-9. 10.1515/jpem.2005.18.2.165

Sperlich M, Butenandt O, Schwarz HP: Final height and predicted height in boys with untreated constitutional growth delay. Eur J Pediatr. 1995, 154:627-32. 10.1007/BF02079065

Rohani F, Alai MR, Moradi S, Amidkhanian D: Evaluation of near final height in boys with constitutional delay in growth and puberty. Endocr Connect. 2018, 7:456-9. 10.1530/EC-18-0045

Poyrazoglu S, Gunoz H, Darendeliler F, Saka N, Bundak R, Bay F: Constitutional delay of growth and puberty: from presentation to final height. J Pediatr Endocrinol Metab. 2005, 18:171-9. 10.1515/jpem.2005.18.2.171

Albanese A, Stanhope R: Does constitutional delayed puberty cause segmental disproportion and short stature?. Eur J Pediatr. 1995, 152:293-6. 10.1007/BF01956736

Kelly BP, Paterson WF, Donaldson MD: Final height outcome and value of height prediction in boys with constitutional delay in growth and adolescence treated with intramuscular testosterone 125 mg per month for 3 months. Clin Endocrinol (Oxf). 2005, 58:267-72. 10.1046/j.1365-2267.2005.01692.x

Zucchiini S, Wasniewska M, Cistermino M, et al.: Adult height in children with short stature and idiopathic delayed puberty after different management. Eur J Pediatr. 2008, 167:677-81. 10.1007/s00431-007-0576-y

Richman RA, Kirsch LR: Testosterone treatment in adolescent boys with constitutional delay in growth and development. N Engl J Med. 1986, 315:1565-7. 10.1056/NEJM198612113151902

Balsevich BB, Baron J, Garcia HB, Barnes KM, Loriaux DL, Cutler GB, Jr: The effect of pubertal delay on adult height in men with isolated hypogonadotropic hypogonadism. J Clin Endocrinol Metab. 1992, 74:436-40. 10.1210/elenet.74.2.1449545

Mason KA, Schoelwer MJ, Rogol AD: Androgens during infancy, childhood, and adolescence: physiology and use in clinical practice. Endocr Rev. 2020, 41:bnaa003. 10.1210/edrv/bnaa003

Bertelloni S, Baronecelli GI, Garofalo P, Gianferrari S: Androgen therapy in hypogonadal adolescent males. Horm Res Paediatr. 2010, 74:292-6. 10.1159/000320090

Dunkel L, Quinton R: Transition in endocrinology: induction of puberty. Eur J Endocrinol. 2014, 170:R229-39. 10.1530/EJE-13-0894

Zhu J, Chan YM: Adult consequences of self-limited delayed puberty. Pediatrics. 2017, 139:e20163177. 10.1542/peds.2016-3177

Pazderska A, Mamoojee Y, Artham S, Miller M, Ball SG, Cheetham T, Quinton R: Safety and tolerability of one-year intramuscular testosterone regime to induce puberty in older men with CHH. Endocr Connect. 2018, 7:153-8. 10.1530/EC-17-0241

Ahmed SF, Tucker P, Mayo A, Wallace AM, Hughes IA: Randomized, crossover comparison study of the short-term effect of oral testosterone undecanoate and intramuscular testosterone depot on linear growth and serum bone alkaline phosphatase. J Pediatr Endocrinol Metab. 2004, 17:941-50. 10.1515/jpem.2004.17.7.941

Lawertz JG, Hagen CP, Mieritz MG, Blomberg Jensen M, Petersen JH, Juul A: Evaluation of 451 Danish boys with delayed puberty: diagnostic use of a new pubertal nomogram and effects of oral testosterone therapy. J Clin Endocrinol Metab. 2015, 100:1576-85. 10.1210/jc.2014-3651

Gregory JW, Greene SA, Thompson J, Scrimgour CM, Rennie MJ: Effects of oral testosterone undecanoate on growth, body composition, strength and energy expenditure of adolescent boys. Clin Endocrinol (Oxf). 1992, 37:207-15. 10.1111/j.1365-2265.1992.tb02312.x

De Sanctis V, Vullo C, Urso L, et al.: Clinical experience using the androderm testosterone transdermal system in hypogonadal adolescents and young men with beta-thalassemia major. J Pediatr Endocrinol
80
79
78
77
76
75
74
73
72
71
70
69
68
67
66
65
64
63
62
61
60
59
58
57
56
55
54
53
52
51
50
49
48
47
46
45
44
43
42
41
40
39
38
37
36
35
34
33
32
31
30
29
28
27
26
25
24
23
22
21
20
19
18
17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1

80
dysfunction? J Pediatr Endocrinol Metab. 2017, 30:105-9. 10.1515/jped-2016-0201

55. Conners MF, Raisinghani M, Prasad K, Franklin B, Shah B: Transdermal testosterone gel for induction and
 continuation of puberty in adolescent boys with hypothalamic dysfunction. J Pediatr Endocrinol Metab. 2017,
 30:105-9. 10.1515/jped-2016-0201

54. Rogol AD, Swerdloff RS, Reiter EO, et al.: A multicenter, open-label, observational study of testosterone gel
 (1%) in the treatment of adolescent boys with klinefelter syndrome or anorchia. J Adolesc Health. 2014, 54:20-5. 10.1016/j.jadohealth.2013.07.021

53. Becker D, Wain LM, Chong YH, et al.: Topical dihydrotestosterone to treat micropenis secondary to partial
 androgen insensitivity syndrome (PAIS) before, during, and after puberty - a case series. J Pediatr Endocrinol
 Metab. 2016, 29:175-7. 10.1515/jped-2015-0175

52. O dame I, Donaldson MD, Wallace AM, Cochran W, Smith PJ: Early diagnosis and management of 5 alpha-
 reductase deficiency. Arch Dis Child. 1992, 67:720-3. 10.1136/adc.67.6.720

51. Varino T, Huoio H, Karila I, et al.: Letrozole versus testosterone for promotion of endogenous puberty in
 boys with constitutional delay of growth and puberty: a randomised controlled phase 3 trial. Lancet Child
 Adolesc Heal. 2019, 3:1006-10. 10.1016/S2352-4642(18)30377-8

50. Palmert MR, Dunkel L: Clinical practice. Delayed puberty. N Engl J Med. 2012, 366:443-53. 10.1056/NEJMcp1109290

49. Bhasin S, Brito JP, Cunningham GR, et al.: Testosterone therapy in men with hypogonadism: an Endocrine
 Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2018, 103:1715-44. 10.1210/jc.2018-00229

48. Giagulli VA, Trigiani V, Carbone MD, Corona G, Tafaro E, Licchelli B, Guastamacchia E: The role of long-
 acting parenteral testosterone undecanoate compound in the induction of secondary sexual characteristics
 in males with hypogonadotropic hypogonadism. J Sex Med. 2011, 8:3471-8. 10.1111/j.1745-6109.2011.02497.x

47. Brown DC, Butler GE, Kelnar CJ, Wu FC: A double blind, placebo controlled study of the effects of low dose
 testosterone undecanoate on growth of small for age, prepubertal boys. Arch Dis Child. 1995, 73:131-5. 10.1136/adc.73.2.131

46. Albanese A, Kewley GD, Long A, Pearl KN, Robins DG, Stanhope R: Selective hypogonadotropic hypogonadism
 and the instrument's characteristics, development, current use, and challenges of developing its value set
 J Sex Med. 2019, 16:2509-16. 10.1016/j.jsxm.2019.03.010

45. Bertelloni S, Dati E, Baroncelli GI: Clinical practice. Delayed puberty n 2012. 10.1210/jc.2003-031086

44. Nahata L, Yu RN, Bhasin S, Cohen LE: Management of testosterone therapy in adolescent boys: the need for a
 structured approach. Horm Res Pediatr. 2019, 92:215-28. 10.1002/hrp.2802

43. Crabtree NJ, Shaw NJ, Bishop NJ, et al.: Alagamgated reference data for size-adjusted bone densitometry
 measurements in 5598 children and young adults-the ALPHABET study. J Bone Miner Res. 2017, 32:172-80.
 10.1002/jbmr.2935

42. Creimeier S, Greiner W: EQ-5D-Y as a health-related quality of life instrument for children and adolescents:
 the instrument's characteristics, development, current use, and challenges of developing its value set. Value
 Health. 2019, 22:51-7. 10.1016/j.val.2018.11.001

41. Young J, Xu C, Papadakis GE, et al.: Clinical management of congenital hypogonadotropic hypogonadism.
 Endocr Rev. 2019, 40:669-710. 10.1210/endo-2018-00116

40. Barrio R, de Luis D, Alonso M, Lamas A, Moreno JC: Induction of puberty with human chorionic
 gonadotropin and follicle-stimulating hormone in adolescent males with hypogonadotropic hypogonadism.
 Fertil Steril. 1999, 71:244-8. 10.1016/S0015-0282(98)00450-6

39. Bistrizter T, Lunenfeld B, Passwell JH, Theodor R: Hormonal therapy and pubertal development in boys
 with selective hypogonadotropic hypogonadism. Fertil Steril. 1989, 52:502-6. 10.1016/s0015-0282(99)00688-9

38. Rohayem J, Haufla BP, Zacharin M, Klescich S, Zitzmann M: Testicular growth and spermatogenesis: new
 goals for pubertal hormone replacement in boys with hypogonadotropic hypogonadism? - a multicentre
 prospective study of hCG/hFSH treatment outcomes during adolescence. Clin Endocrinol (Oxf). 2017, 86:75-87.
 10.1111/cen.13164

37. Arslan M, Weinbauer GF, Schlatt S, Shahab M, Nieschlag E: FSH and testosterone, alone or in combination,
 initiate testicular growth and increase the number of spermatogonia and Sertoli cells in a juvenile non-
 human primate (Macaca mulatta). J Endocrinol. 1993, 136:225-35. 10.1677/joe.0.1360235

36. Raivio T, Toppaari J, Perheentupa A, McNellis AS, Dunkel L: Treatment of prepuberal gonadotropin-
 deficient boys with recombinant human follicle-stimulating hormone. Lancet (London, England). 1997, 350:263-4. 10.1016/s0140-6736(05)62227-1

35. Raivio T, Wikström AM, Dunkel L: Treatment of gonadotropin-deficient boys with recombinant human
 FSH: long-term observation and outcome. Eur J Endocrinol. 2007, 156:105-11. 10.1530/eje.1.02515

34. Dewyer AA, Sykriotis GP, Hayes FJ, et al.: Trial of recombinant follicle-stimulating hormone pretreatment
 for GnRH-induced fertility in patients with congenital hypogonadotropic hypogonadism. J Clin Endocrinol
 Metab. 2013, 98:11790-5. 10.1210/jc.2013-2518

33. Burris AS, Rodbard HW, Winters SJ, Sherins RJ: Gonadotropin therapy in men with isolated
 hypogonadotropic hypogonadism: the response to human chorionic gonadotropin is predicted by initial
 testicular size. J Clin Endocrinol Metab. 1988, 66:1144-51. 10.1210/jcem-66-6-1144

32. Liu L, Banks SM, Barnes KM, Sherins RJ: Two-year comparison of testicular responses to pulsatile

2022 Alenazi et al. Cureus 14(4): e23864. DOI 10.7759/cureus.23864
15 of 16
gonadotropin-releasing hormone and exogenous gonadotropins from the inception of therapy in men with isolated hypogonadotropic hypogonadism. J Clin Endocrinol Metab. 1988, 67:1140-5. 10.1210/jcem-67-6-1140

81. Karten MJ, Rivier JE: Gonadotropin-releasing hormone analog design. Structure-function studies toward the development of agonists and antagonists: rationale and perspective. Endocr Rev. 1986, 7:44-66. 10.1210/edrv-7-1-44

82. Delemarre EM, Felius B, Delemarre-van de Waal HA: Inducing puberty. Eur J Endocrinol. 2008, 159 Suppl 1:S9-15. 10.1530/EJE-08-0514

83. Delemarre-Van de Waal HA: Induction of testicular growth and spermatogenesis by pulsatile, intravenous administration of gonadotrophin-releasing hormone in patients with hypogonadotrophic hypogonadism. Clin Endocrinol (Oxf). 1995, 58:473-80. 10.1111/j.1365-2265.1995.tb00342.x

84. Whitcomb RW, Crowley WF Jr: Clinical review 4: diagnosis and treatment of isolated gonadotropin-releasing hormone deficiency in men. J Clin Endocrinol Metab. 1990, 70:3-7. 10.1210/jcem-70-1-3

85. Burris AS, Clark RV, Vantman DJ, Sherins RJ: A low sperm concentration does not preclude fertility in men with isolated hypogonadotropic hypogonadism after gonadotropin therapy. Fertil Steril. 1988, 50:543-7. 10.1016/s0015-0282(16)60084-5