BRIEFING BOOK
FOR
Pediatric Advisory Committee (PAC)

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Prepared for Consortium of Sponsors

Meeting Date: April 8th, 2019

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. INTRODUCTION AND BACKGROUND FOR THE MEETING

1.1. INDICATION AND USAGE

Currently, testosterone replacement products all share a class indication of

> PRODUCT is an androgen indicated for testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone:
>
> - Primary hypogonadism (congenital or acquired): testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (follicle-stimulating hormone [FSH], luteinizing hormone [LH]) above the normal range.
> - Hypogonadotropic hypogonadism (congenital or acquired): gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum concentrations but have gonadotropins in the normal or low range.
>
> **Limitations of use:**
>
> - Safety and efficacy of [Product Name] in males less than 18 years old have not been established

2. SPONSOR CONSORTIUM PARTICIPANTS

- Acerus Pharmaceuticals Corp.
- Clarus Therapeutics, Inc.
- Ferring Pharmaceuticals, Inc.
- Lipocine Inc.
- Viramal Limited

2.1. TIMELINE FOR SPONSOR ENGAGEMENT FOR PEDIATRIC ADVISORY COMMITTEE (PAC):

On March 1, 2019, the FDA had a teleconference to inform all potential sponsors about this meeting. The list of sponsors which chose to collaborate for the PAC meeting was distributed by the FDA on March 11, 2019. The final PAC briefing book was due to the FDA on April 1, 2019. Because the sponsors only had about 3 weeks to prepare the PAC briefing book, there was not adequate time to fully research some of the questions posed to industry by the FDA. The collaborating industry sponsors engaged Dr. Alan Rogol, an expert in the area of testosterone use in the pediatric population, who will share information about the use of testosterone replacement in male children.

3. BACKGROUND AND RATIONALE

3.1. INTRODUCTION

Puberty may be defined as the physiologic process resulting in the attainment of sexual maturity and reproductive capacity. Puberty is an integral component of the evaluation and treatment of endocrine disorders in children and adolescents. Not only does it impact sexual maturation, but it has other effects with lifelong consequences, including linear growth, changes in body composition, and skeletal mineralization. Patients with disorders of puberty, including precocious and delayed puberty, make up a large percentage of the children and adolescents who consult pediatric endocrinologists. An understanding of delayed or absent puberty requires a foundation in the normal processes regulating the onset of puberty and factors essential for its progression and completion. In this chapter, we will first review the mechanisms of normal growth and puberty, particularly with regard to their interdependence. We shall then discuss the differential diagnosis of delayed or absent puberty and present diagnostic algorithms for hypergonadotropic and hypogonadotropic hypogonadism, emphasizing some gender-specific aspects.

3.2. PHYSICAL CHANGES OF PUBERTY

Concurrent with the secretion of sex steroids during puberty, major physical changes, physiologic adaptations, and social and emotional challenges occur. The measurement and assessment of these changes are critical for determining when pubertal development is progressing normally or not and to monitor the efficacy of treatment.

3.2.1. Boys

In boys, the earliest physical change associated with puberty is testicular enlargement, although a subset of boys have pubic hair growth due to adrenal androgens prior to testicular enlargement. Testicular size is commonly assessed by using a series of calibrated, testis-shaped ellipsoids (beads) called the Prader orchidometer. If this is not available, the long axis of the testis can be measured using simple calipers or an ordinary tape measure. Prepubertal testes are <4 mL in volume and less than 2.5 cm in length. As puberty ensues, the testes gradually enlarge, mainly due to increases in volume of the seminiferous tubule content, and eventually reach the adult volume of 15-25 mL or length of 4-5 cm. Physical changes accompanying testicular enlargement include thinning of the scrotal skin, apocrine sweating and adult body odor, and the growth of sexual hair. Additional changes present in boys include an increase in muscular size and strength and body hair growth in a typical adult male pattern. Deepening of the voice occurs during the second half of pubertal development.

Genital development in boys is often assessed using the method of Tanner. Two rating scales are used in males: one for pubic hair growth and another for enlargement of the testes, penis, and scrotum. Tanner stages for boys are reviewed in **Table 1**. Briefly, pubic hair growth starts as fine, straight, lightly pigmented hairs generally located on the pubic symphysis at the base of the penis. As puberty progresses, the hair becomes coarser and curly, with darker pigmentation. At Tanner stage 5, the growth extends down the medial thighs and up the lower abdomen. Genital Tanner stages are somewhat more subjective. The early stage of puberty consists of testicular

enlargement only, followed by gradual enlargement of the penis, first in length and then in circumference, and enlargement of the testes to reach full adult development. [1]

Table 1 Pubertal Development in Males

Pubic Hair in Males	
Stage	**Physical characteristics**
1	Prepubertal
2	Sparse growth of long, slightly pigmented hairs at the base of the penis (males) or mons veneris/labia majora (females)
3	Further darkening and coarsening of hair, with spread over the symphysis pubis
4	Hair is adult in character but not in distribution, has not spread to the lower abdomen (males) or to the medial surface of the thighs (males and females)
5	Hair is adult in distribution, with extension to the lower abdomen (males) and/or the medial surface of the thighs (males and females)
Genital Development in Males	
1	Prepubertal
2	Enlargement of the testes and scrotum, thinning and reddening of the scrotal skin, penis remains prepubertal
3	Further growth of testes and scrotum; enlargement of the penis, predominantly in length
4	Further growth of testes and scrotum with pigmentation of the scrotal skin; further enlargement of the penis, especially in circumference, and development of the glans
5	Testes, scrotum, and penis are adult in size and shape

Modified from [2]

3.2.2. Growth and Pubertal Development

The clinical hallmark of puberty as it relates to body size is the pubertal growth spurt. In boys, the peak of the growth spurt is timed to Tanner stage III-IV, whereas in girls the peak occurs earlier in puberty, typically at Tanner stages II-III. The average peak growth velocity in boys is 9.5 cm/year, and in girls it is somewhat less, 8.3 cm/year. The later onset of puberty, the later occurrence of the growth spurt within puberty in boys, and the greater magnitude of the growth spurt result in an average height difference between the sexes of 13 cm. Children with advanced bone ages typically enter puberty earlier than their peers, while those with delayed bone ages

enter puberty later. Factors that alter the bone age also alter the timing of puberty, and these may include sex steroids and the GH/IGF-1 system. [3]

3.3. AGE AT ONSET OF PUBERTY

There is a great deal of disagreement about the age at which pubertal development is normal. Most of this disagreement relates to the lower age limit of normal. There is evidence that the age of onset of puberty has decreased in the last several decades in both girls and boys. For boys, data show that the average age at Tanner stage 2 development is between 11.2 and 12.4 years. The normal range of attainment of stage 2 puberty in boys is commonly considered to extend from 9 years up to 13.5 years.

3.4. HYPOTHALAMIC-PITUITARY-GONADAL (HPG) AXIS DEVELOPMENT

3.4.1. Physiologic maturation of the HPG axis

The hypothalamic-pituitary-gonadal axis is active in utero, with peak secretion of gonadotropin releasing hormone (GnRH), luteinizing hormone (LH), and follicle stimulating hormone (FSH) occurring between 20 and 24 weeks gestation. During later pregnancy, levels drop as the negative feedback effects of gonadal hormones intensify. In both males and females, there is a "minipuberty of infancy" that occurs during the first few months after birth. Beginning at birth, gonadotropin levels begin to increase under the influence of GnRH, possibly stimulated by withdrawal of placental estrogens. In girls, the increase in FSH is particularly robust. Sex steroid levels also increase, and the serum testosterone in boys often reaches 150 ng/dL or greater during the minipuberty of infancy. [4] Testosterone peaks at 2-3 months of age in males, while estradiol peaks at about 4 months in females. By 5-6 months of age, the negative feedback effects of sex steroids are beginning to be reestablished, and GnRH secretion, LH and FSH levels, and gonadal steroid levels fall to their prepubertal levels. This cessation of activity is known as the juvenile pause. It may be related to increases in hypothalamic estrogen receptors, allowing negative feedback to intensify. The suppression of HPG activity may be incomplete in some females, and this may result in transient estrogen secretion, giving rise to the clinical picture of premature thelarche. Over the course of the next several years, the juvenile pause persists, reaching the greatest degree of axis suppression in females at about age 6 years.

GnRH is released from the hypothalamus in a pulsatile fashion, with the pulses in prepubertal children being small in amplitude and somewhat irregular. The frequency of the pulses is roughly once every 1-2 hours. In males, as the age of clinical puberty approaches, the amplitude of the pulses begins to increase. The average age for this to occur is 9-12 years of age. Hence, before clinical signs of puberty are noted, early endocrine changes have begun. Initially, this increase in GnRH pulse amplitude occurs during the night, and daytime pulse amplitude remains low. The pulsatile GnRH secretion is reflected in gonadotropin secretion. The pulses in LH secretion can be detected by careful serial measurement of LH concentrations using sensitive assays. Although FSH is also released in a pulsatile manner in response to pulsatile GnRH, variations in the serum FSH are not apparent, perhaps due to the longer circulating half-life of FSH. Higher overnight gonadotropin concentrations result in higher testosterone levels in boys and an increase in estradiol levels in girls. In early pubertal boys, testosterone levels are highest

overnight and in the early morning hours. In early pubertal girls, estradiol levels peak in the mid-morning, about 12 hours after the peak of LH secretion.

Using current standard immunoassays for testosterone and estradiol, which lack sensitivity at low concentrations, the morning increases in sex steroid levels may be difficult to detect during the very earliest stages of puberty. However, more modern techniques, especially liquid chromatography/tandem mass spectrometry (MS) can usually detect even the lower prepubertal levels. In early puberty, gonadotropin levels also may be difficult to distinguish from normal prepubertal levels in part due to the pulsatile nature of their secretion and in part due to the low amplitude of secretion during the daytime. These factors make the routine laboratory evaluation of delayed puberty difficult, because casual gonadotropin and sex steroid levels do not differentiate a patient who is nearing a normal but delayed puberty from one who will never enter puberty due to a pathological condition. However, as GnRH pulsatility increases in early puberty, pituitary stores of LH also increase. These stores may be released following acute stimulation by GnRH. This is the basis for the GnRH stimulation test, which may be positive even before physical changes of puberty become clinically apparent.

With progressing pubertal development, there is a further expansion of pulsatile GnRH secretion, with the amplitude and the frequency of the pulses increasing. Instead of being confined to the night, larger amplitude pulses are now also produced during the daytime. The pulse frequency becomes more tightly regulated, occurring virtually hourly. Gonadotropins continue to be released in a pulsatile fashion, but the baseline levels are also increased above prepubertal concentrations. Additionally, there is a shift in the glycosylation pattern of LH toward forms that are more biologically active. As GnRH, LH, and FSH secretion expand, sex steroid secretion also increases, and the marked diurnal variation in testosterone and estradiol levels is damped. Testosterone concentrations in prepubertal males generally are below 10 ng/dL, and in young adults they are above 300 ng/dL.

3.4.2. Control of Pubertal Timing

The timing of puberty is a complex trait, and in the general population, it has a Gaussian distribution. There are many influences on the regulation of pubertal timing, including nutritional factors, environmental influences, and activity of genetic input. Complex traits often demonstrate a high degree of genetic regulation, and it is estimated that between 50-80% of the variance of normal pubertal timing is explained by genetic factors. Efforts to understand the genetics of pubertal timing have led to the discovery of many genes that are clearly necessary for pubertal development. Many of these genes, when mutated, lead to specific syndromes of delayed or absent puberty, which are discussed below. These include defects in GnRHR, KAL1, FGFR1, LEP, LEPR, KISS1, GPR54, PROK2, and PROK2R. However, it is not clear that these genes individually or as a group explain much of the variability of the onset of normal puberty. The onset of puberty is almost certainly controlled by a polygenic mechanism. Genome-wide association studies and other high throughput technologies have shown promise in elucidating regulatory systems for complex traits. Such studies are likely to reveal a large number of involved genes, each playing only a small role, but collectively explaining much of the variance. These techniques, though, may be limited by statistical issues that affect their reproducibility.

3.5. DELAYED PUBERTY AND HYPOGONADISM

The causes of delayed puberty and hypogonadism can be divided into those involving delays or defects in hypothalamic regulation of the initiation of puberty and those involving primary defects of the gonads. These groups of conditions are best differentiated by the serum concentrations of gonadotropins after the age when puberty is expected. Hypothalamic and pituitary deficiencies are termed hypogonadotropic hypogonadism or central hypogonadism, and primary gonadal disorders are termed hypergonadotropic hypogonadism or primary hypogonadism.

3.5.1. Hypogonadotropic hypogonadism

3.5.1.1. Constitutional delay of growth and puberty (transient hypogonadotropic hypogonadism)

Constitutional delay of growth and puberty (CDGP) is a common variant of physiologic (normal) maturation. Its major outward characteristics include a slowing of the growth rate as well as a delay in the timing (and perhaps tempo) of puberty. The typical patient is a boy (or his parents) who seeks endocrinological evaluation in the early teenage years because the discrepancy in growth and adolescent development between the patient and his/her age peers causes significant concern. [**Figure 1** and **Figure 2**]

Clinically, the height age (the age for which the patient's height is the 50th centile) is delayed with respect to the calendar age but is concordant with the "biological age" as indexed by the bone age. Sexual development is either prepubertal or lagging behind that of their peers, although it is often appropriate for the bone age. The height velocity is normal for a prepubertal child, although it may decline to subnormal values if the delay is more than 2-3 years (pre-pubertal "dip). When the height is plotted on the standard growth curve, the height gain appears to be "falling off" the previously defined height centile, since the standard growth curve incorporates the pubertal growth spurt at an "average" age. This discrepancy in growth between the normal adolescent and the one with CDGP only accentuates the difference between these age peers. This discrepancy, as well as the delay in pubertal maturation, is often a compelling concern of the patient or the family and brings the adolescent to medical consultation. Tanner has devised longitudinal growth curves that account for the later growth and adolescent development, because this pattern is so common. The large majority of those with CDGP follows this "custom" curve, emphasizing that the standard growth curves based upon cross-sectional data, although adequate for the population "averages," do not necessarily describe the growth of an individual.

Biochemically, adolescents with CDGP resemble their peers with comparable biological (bone) ages. Thus, the pubertal increases in hemoglobin, hematocrit, creatinine, and alkaline phosphatase will not be present. Serum levels of growth hormone (pulsatile pattern), IGF-I, IGFBP-3, LH, FSH, and the sex steroids may be diminished for chronological age, but normal when compared to younger adolescents of the same stage of sexual development. The suppressed HPG axis found in adolescents with CDGP represents an extension of the physiologic hypogonadotropic hypogonadism (the "juvenile pause") noted since infancy.

Without intervention with sex steroids, most adolescents with CDGP will undergo spontaneous pubertal development and will reach their target height range as calculated from parental stature.

Development occurs as much as several years after that of their peers. Many adolescents find that intolerable and suffer significant emotional distress because they differ in their appearance from their peers during these years. That is often the rationale for the short-term use of gonadal steroid therapy. Linear growth and a more mature “appearance” are more objective outcomes of gonadal steroid administration.

Figure 1: Growth chart of patient with CDGP. Birth to 36 months: Boys. Length-for-age and weight-for-age percentiles.

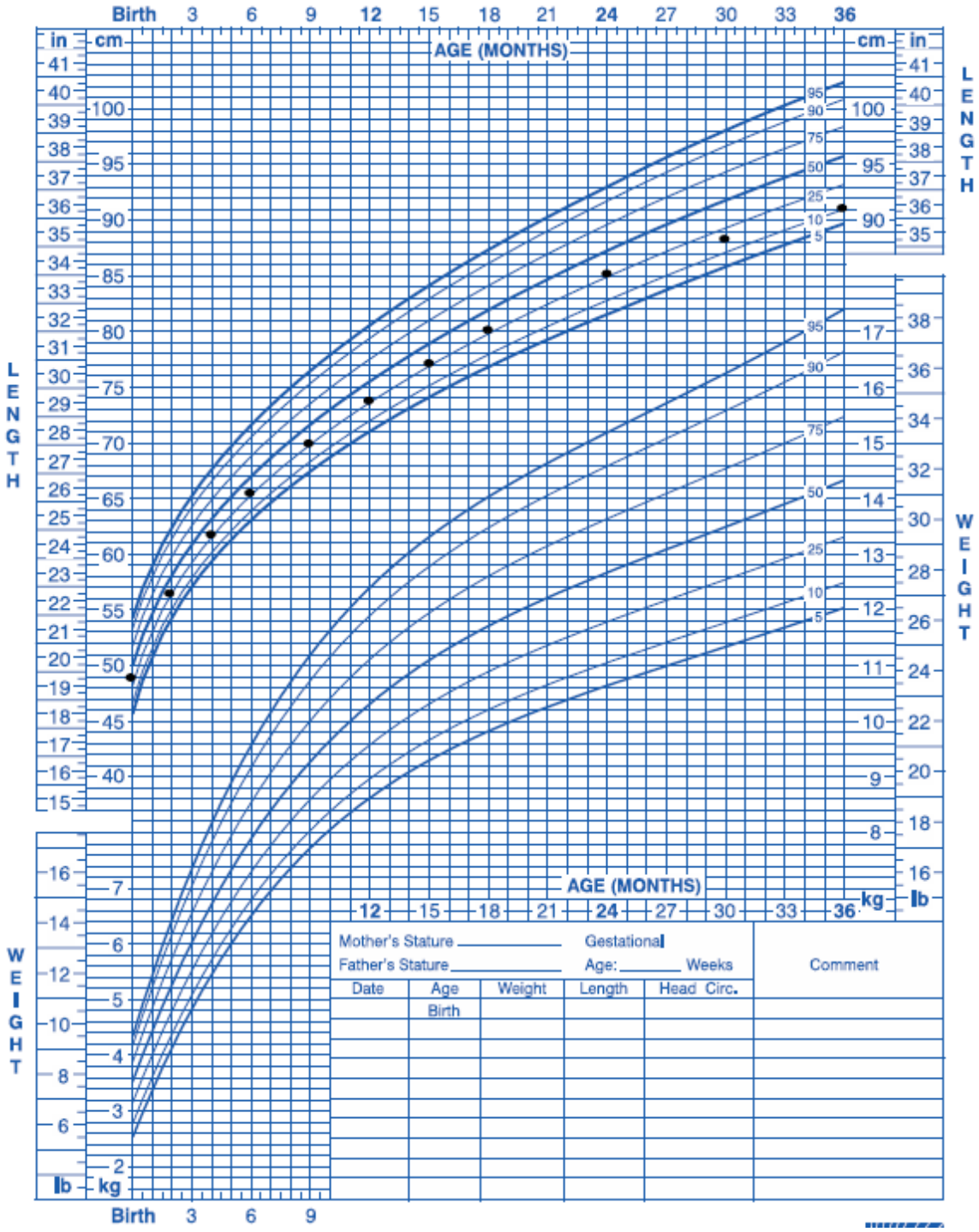
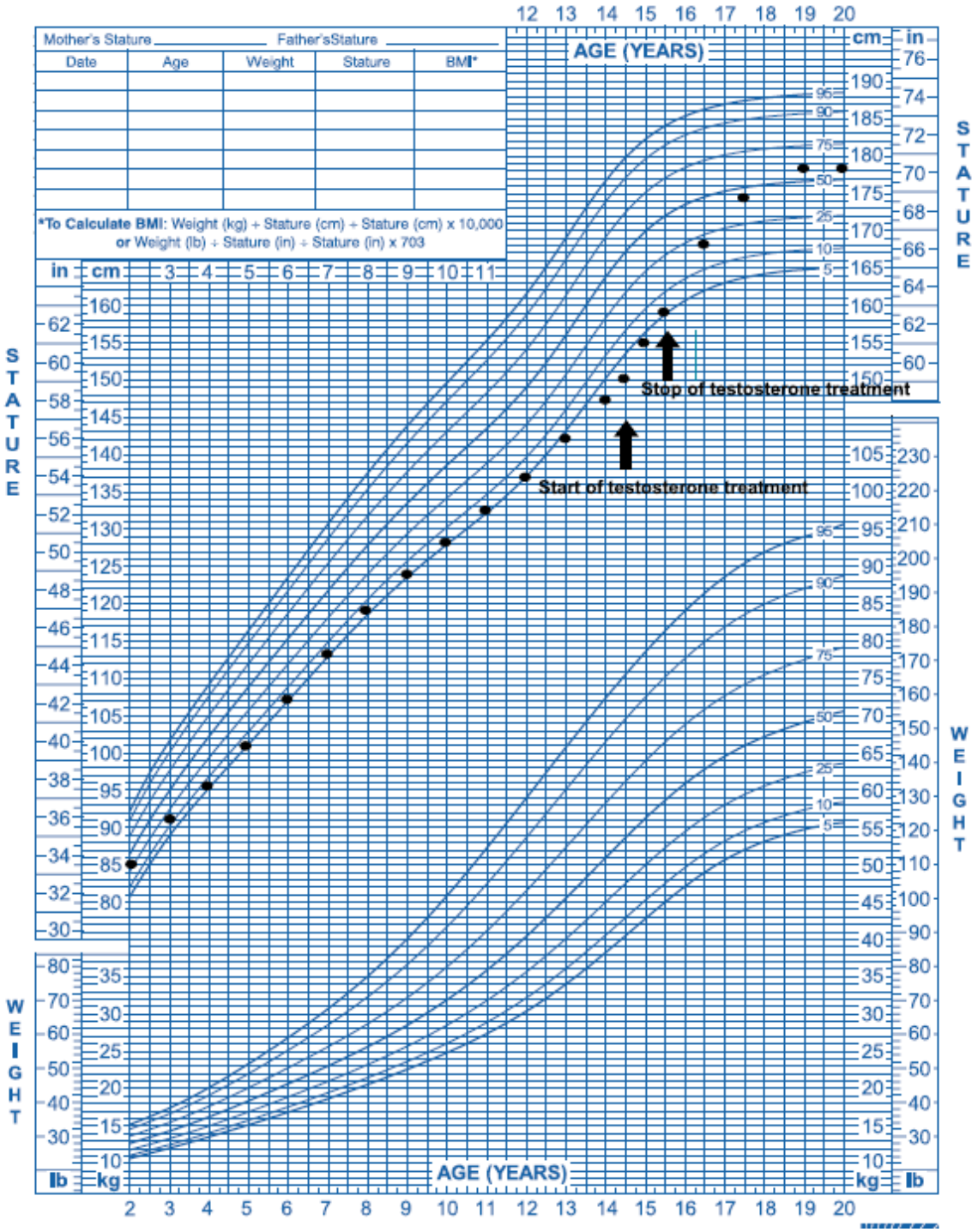


Figure 2: Growth chart of patient with CDGP. 2 to 20 years: Boys. Stature-for-age and weight-for-age percentiles.



3.5.1.2. Combined pituitary hormone deficiencies (with gonadotropin deficiency)

There are many causes of combined pituitary hormone deficiency, both congenital and acquired, that may include deficiency of GnRH or gonadotropins.

3.5.1.3. Isolated hormone abnormalities

The neuroendocrine control in mammalian reproduction is governed by a single gene coding for gonadotropin-releasing hormone (GnRH). A neural network of approximately 1,500 to 2,000 neurons integrates various upstream genes that are responsive to environmental cues such as food (energy) availability, stress and perhaps light-dark cycles (at least in seasonally breeding mammals).

A cascade of signaling molecules and transcription factors plays a crucial role in pituitary development, cell proliferation, patterning and terminal differentiation. [10] Genes are expressed in an orderly sequence to activate or inhibit downstream processes (target genes) that have specific roles in the terminal differentiation of pluripotential precursor cells. Mutations involved specifically in human hypothalamic-pituitary disease are listed in **Table 2**. It should be noted however, that there is increasing evidence that disorders of puberty may result from multiple genetic mutations, with some disorders presenting from the accumulative burden of mutations in genes such as FGFR1 and GnRHR (see below). These likely broaden (synergize) the phenotypic spectrum and the endocrine profiles of the subjects.

Table 2 Genetic defects associated with hypogonadotropic hypogonadism

Gene	Condition/phenotype	Locus	Inheritance	Site ofdefect	OMIM number
Isolated hormone abnormalities					
KAL1	KS, renal agenesis, synkinesia	Xp22.3	X-linked recessive	Hypothalamus	308700
NELF	KS	9q34.3		Hypothalamus, olfactory apparatus	608137
GPR54	nIHH	19p13.3	AR	Hypothalamus	604161
KISS-1	nIHH	1q32	AR	Hypothalamus	603286
FGFR-1	nIHH and KS, cleft lip and palate, facial dysmorphism	8p11.2-11.1	AD, AR, ?dosage effect	Hypothalamus	136350
GNRH1	nIHH	8p21–11.2	AR	Hypothalamus	152760
GnRHR	nIHH	4q21.2	AR	Pituitary	138850
PROK2	KS and nIHH, severe sleep disorder, obesity	3p21.1	AD	Hypothalamus, olfactory bulb	607002
PROKR2	KS and nIHH	20p13	AD, AR	Hypothalamus, olfactory bulb	607123
TAC3	nIHH	12q13-21	AR	Hypothalamus	162330/
TACR3	nIHH	4q25	AR/AD	Hypothalamus	162332

Gene	Condition/phenotype	Locus	Inheritance	Site ofdefect	OMIM number
Leptin	HH and obesity	7q31.3	AR	Hypothalamus	164160
Leptin R	HH and obesity	1q31	AR	Hypothalamus	601007
DAX-1	AHC and HH	Xp21	X-linked	Hypothalamus, pituitary	300200
PC-1	Obesity and HH, ACTH deficiency, hypoglycemia, gastrointestinal sx	5q15-21	AR	Widespread, including hypothalamus	162150
LHβ	Isolated LH deficiency, delayed puberty	19q13.32	AR	Pituitary	152780
FSHβ	Isolated FSH deficiency, primary amenorrhea, defective spermatogenesis	11p13	AR	Pituitary	136530
Combined pituitary hormone deficiency					
PROP1	GH, TSH, LH, FSH, prolactin, and evolving ACTH deficiencies	5q	AR	Pituitary	601538
Gene	Condition/ phenotype	Locus	Inheritance	Site of defect	OMIM number
Specific syndrome					
HESX1	SOD and other pituitary deficits including HH	3q21.1-21.2	AR, AD	Pituitary	601802

Gene	Condition/phenotype	Locus	Inheritance	Site ofdefect	OMIM number
SOX3	Pituitary hormone deficits including HH, mental retardation	Xq26.3	X-linked	Hypothalamus, pituitary	313430
SOX2	An/micro-ophthalmia, anterior pituitary hypoplasia, HH, esophageal atresia	3q26.3-27	X-linked	Hypothalamus, pituitary	184429
GLI2	Holoprosencephaly with MPHD including HH, multiple midline defects	2q14	AD, AR	Hypothalamus, pituitary	165230
LHX3	Variable CPHD including HH, limited neck rotation	9q34.3	AR	Pituitary	600577
CHD7	CHARGE syndrome, may have Kallmann syndrome as primary feature	8q12.1	AD, de novo	Hypothalamus	608892

ACTH, adrenocorticotropic hormone; AD, autosomal dominant; AHC, adrenal hypoplasia congenita; AR, autosomal recessive; CRH, corticotropin-releasing hormone; FSH, follicle-stimulating hormone; GH, growth hormone; HH, hypogonadotropic hypogonadism; KS, Kallmann syndrome; LH, luteinizing hormone; MPHD, multiple pituitary hormone deficiency; nIHH, normosmic idiopathic hypogonadotropic hypogonadism; OMIM, Online Medelian Inheritance in Man; R, receptor; SOD, septo-optic dysplasia; TSH, thyroid stimulating hormone; XL, X-linked; Adapted from Reference [10]

3.5.1.4. Kallmann syndrome (KS) and normosmic idiopathic hypogonadotropic hypogonadism (nIHH)

Kallmann syndrome is the combination of hypogonadotropic hypogonadism (HH) and a diminished sense of smell—hyposmia or anosmia. It has many genetic causes and the more common genes altered are listed in **Table 2**.

3.5.1.5. Distinguishing Between CDGP and IHH {*from ref [5]}*

The following patient scenarios provide insight to the difficulty in making a differential diagnosis between CDGP and IHH. We present 2 boys, both in excellent health at presentation. We provide typical observations and measures, as well as a treatment scenarios.

3.5.1.5.1. Patient 1: CDGP

A 14 6/12-year-old male presents for evaluation of short stature and lack of pubertal maturation.

Patient was born at term, birthweight 3.69 kg (8 lbs. 2 oz), appropriate for gestational age (AGA). Pregnancy and delivery were uncomplicated. No medical problems were noted after birth, or during infancy/early childhood. He reached all developmental milestones within the appropriate age ranges. There is no concern for intellectual or learning disabilities and does well in school. His parents describe him as an active adolescent who loves to play basketball and run. He has a robust appetite. No history of chronic fatigue, headache, changes in vision, abdominal pain, vomiting, constipation, diarrhea, polyuria, polydipsia, heat or cold intolerance, joint pain or rash. He is very much bothered by his height, stating that it puts him at a disadvantage when playing basketball. He is also bothered by the fact that he has not “gone through puberty” while most of his friends and co-athletes have.

PMH: No significant medical problems
Medications: none
Allergies: none
Family history:
- Mother’s height 165 cm (5 ft 5 in.)
- Father’s height 178 cm (5 ft 10 in.)
- Mid-parental height 178 cm (5 ft 10 in.), which is approximately 50-60th percentile
- Mother had menarche at age 14 years
- Father notes that he continued to grow after completing high school

Social history:
- Is currently in 9th grade, average student

Exam:
- Weight 40 kg (8th percentile, Z-score _ 1.37)
- BMI-for-age is at the 28th percentile
- Vital signs: Heart rate 65, Respiratory rate 15, Blood pressure 105/65 mm/Hg
- Please refer to Error! Reference source not found. and Error! Reference source not found. for growth charts

Genitourinary exam:
- Normal male external genitalia, testes 4 mL bilaterally, early tanner stage 2 pubic hair.

Exam otherwise unremarkable.

Laboratory data:

All within normal ranges: including CBC, CMP, IGF1, IGFBP3, TSH, Free T4, ESR, celiac screen

LH 0.3 mIU/mL and FSH 2.0 mIU/mL, testosterone 25 ng/dL (0.9 nmol/L)

Bone age: At chronological age of 14 6/12 years, bone age is 12 years. This delay in bone age allows one to predict that his Adult height will be approximately that of his mid-parental target.

Patient was started on testosterone therapy, 50 mg intramuscular monthly. After 6 months of treatment, testicular size increased to 6 mL bilaterally. His dose was then increased to 100 mg monthly with a further testicular size increase to 10 mL bilaterally after an additional 6 months of treatment. He was very happy with his interval height increase of 4.5 cm (annualized height velocity 9 cm/year), along with secondary sex characteristics such as a small amount of facial hair and deepening of his voice. Given excellent response, testosterone therapy was discontinued at age 15 6/12 years, and testicular growth continued to 15 mL bilaterally in addition to 9 cm gain in height at his follow-up visit 1 year after cessation of testosterone. He continued to grow until age 19 years when he reached his mid-parental target of 178 cm.

3.5.1.5.2. Patient 2: IHH

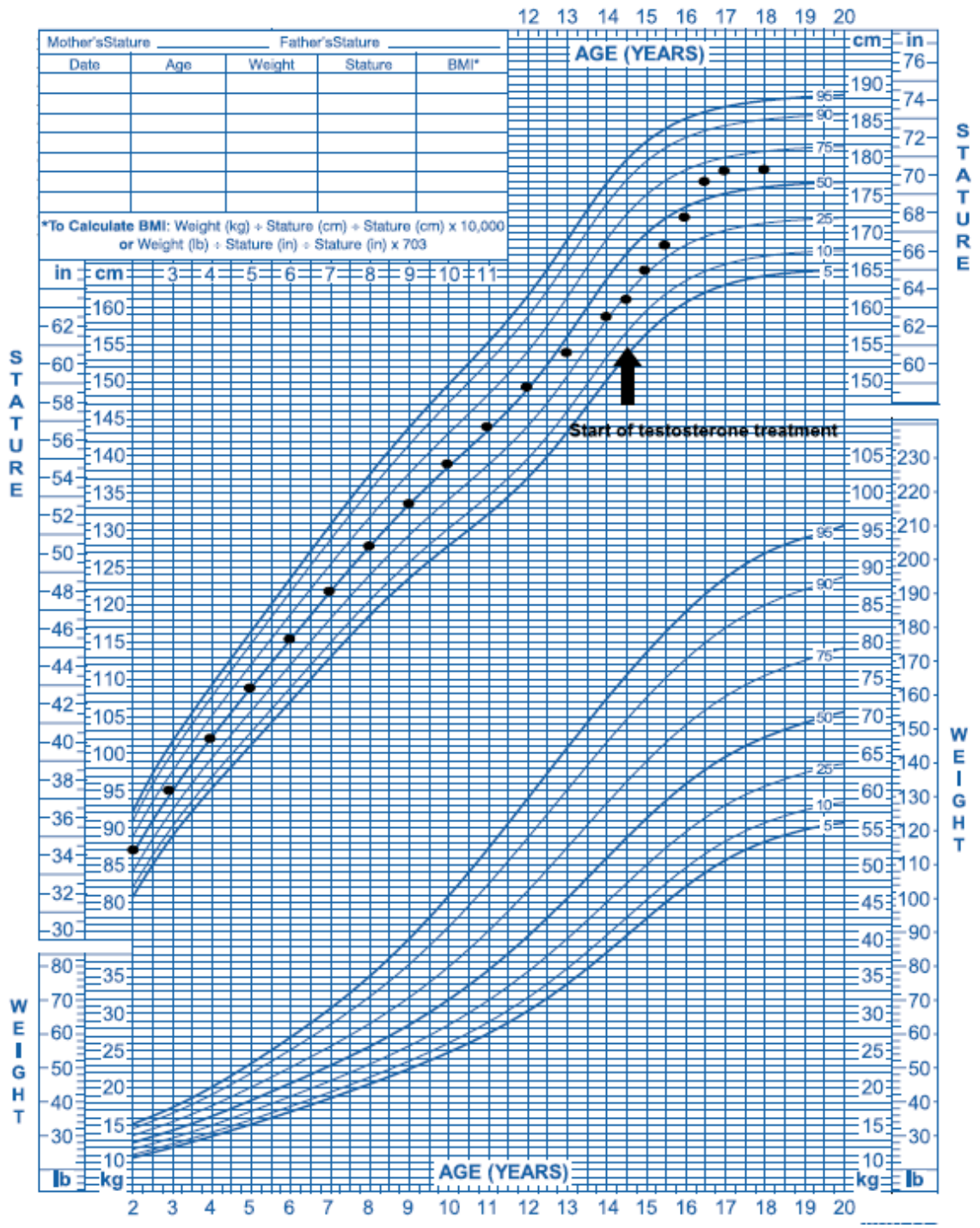
A 14 6/12-year male presents for evaluation of delayed pubertal maturation.

Patient was born at term, birthweight 3.60 kg (7 lbs. 15 oz) (AGA). Pregnancy and delivery were uncomplicated. He denies any medical problems other than simple repair (descent) of undescended testicles during infancy. His parents had no concerns for delayed developmental milestones or intellectual or learning disability. He has always been an excellent student. He is on the school's football team and it bothers him that he has not had any signs of puberty while most of his teammates have. He has not been particularly concerned about his height, but notes that "many of the guys who play (football) are much bigger than me." There is no history of chronic fatigue, headache, changes in vision, abdominal pain, vomiting, constipation, diarrhea, polyuria, polydipsia, heat or cold intolerance, joint pain or rash. By history, he has a sense of smell noting that he can smell coffee and flowers.

PMH: uncomplicated repair of undescended testicles during infancy
Medications: none
Allergies: none
Family history:
Mother's height 168 cm (5 ft 6 in.)
Father's height 175 cm (5 ft 9 in.)
Mid-parental height 178 cm (5 ft 10 in.) (approximately 50–60th percentile)
Mother had menarche when she was 11 6/12 years old
Father does not note growing after high school
Social history:
Is currently in 9th grade, excellent student
Exam:
Height 158 cm (24th percentile, Z-score 0.72)
Weight 50 kg (46th percentile, Z-score 0.10)
BMI-for-age is at the 62nd percentile
Vitals: Heart rate 70, Respiratory rate 14, Blood pressure 110/70
Please refer to **Error! Reference source not found.** for growth chart
Genitourinary exam: normal male external genitalia, testes 1–2 mL bilaterally, no pubic hair (Tanner stage 1)
Exam otherwise unremarkable
Laboratory data:
All within normal ranges; including CBC, CMP, IGF1, IGFBP3, TSH, Free T4, ESR, celiac screen
LH 0.1 mIU/mL and FSH 0.3 mIU/mL, testosterone 8 ng/dL (0.3 nmol/L).
Bone age: At chronological age of 14 6/12 years, bone age is read as 13 6/12 years. This bone age puts him at his midparental target, or approx. 178 cm (50–60th percentile).

Patient was started on testosterone 50 mg intramuscular monthly. At his six-month follow-up, he had no interval testicular growth. Despite a dose increase to 100 mg monthly for 6 months, bilateral testes remained at prepubertal size. He noted a small amount of facial hair, but had a robust response with axillary and pubic hair growth, in addition to increased muscle mass with weight training. He continued to follow-up in endocrine clinic at 6-month intervals with gradual increases in his testosterone dose. After 2 years of treatment, he reached the adult testosterone replacement dose of 200 mg every 2 weeks. At his 2.5-year follow-up, at the age of 17 years his testes remained at prepubertal size but he had reached his mid-parental target of 178 cm.

Figure 3: Growth chart of patient with IHH. 2-20 years: Boys. Stature-for-age and weight-for-age percentiles.



3.5.1.5.3. Commentary

The above two patient scenarios are very similar upon presentation; both have excellent health and negative review of systems. The boy with CDGP has a family history of delayed puberty, evidence of early puberty on exam (note that many children with CDGP may not have any signs of puberty upon presentation), and a delayed bone age which predicts his adult height at approximately his mid-parental target. Upon treatment with testosterone, he shows evidence of central activation of the HPG axis with testicular growth, and endogenous testosterone secretion. He continues to progress in pubertal development after the cessation of testosterone, and reaches his near adult height at age 19 years, significantly later than the average adolescent male. On the other hand, the patient with IHH has a history of undescended testes in infancy, presents to the clinic with very small testes (1–2 mL bilaterally), and does not show evidence of testicular growth upon treatment with testosterone, indicating a lack of HPG axis activation. Although he develops secondary sex characteristics with testosterone treatment, his testes remain prepubertal size.

Although there are features that help distinguish IHH from CDGP (refer to

Table 3), the two diagnoses are often indistinguishable upon presentation in the clinical setting. Therefore, it is pertinent to follow patients over time. Patients with CDGP will have normal, yet delayed progression of puberty, while patients with IHH will have either no pubertal progression, or in some cases may have initial signs of puberty with subsequent "plateauing," meaning lack of further progression. IHH is diagnosed if endogenous puberty has not begun by the age of 18 years [6]. Approximately 10%–20% of patients with IHH will have "recovery" of the HPG axis upon treatment, even if years later. [7-9]

Table 3 Distinguishing features of CDGP and IHH

Clinical/lab test	CDGP	IHH
Presence of endogenous progressive pubertal development by age18 years	+	-
Puberty pattern	Delayed adrenarche, pubarche, gonadal development	More likely to have absent/arrested gonadal development alone
History of undescended testicles	_	+/-
Anosmia/hyposmia	_	+ (30%–50% of patients)
Family history of delayed puberty	+	+/-
Height for age	Usually short	Usually normal
Genitourinary exam	Delayed pubertal exam; normal testes and penile size for bone age.	Small testes (1–2 mL) +/- small phallus
General physical exam	Normal physical exam	Usually normal but can be associated with: unilateral renal agenesis, synkinesia (mirror movements), cleft lip and/or palate, sensorineural hearing loss, dental agenesis, and skeletal malformations
Laboratory evaluation	No test reliably distinguishes between CDGP and IHH, although efforts have been made to establish these tests	

Table data obtained from Palmert, M. R., Dunkel, L. (2012). Delayed puberty. New England Journal of Medicine 366 (5), 443–453; Dwyer, A. A., Phan-Hug, F., Hauschild, M., Elowe-Gruau, E., Pitteloud, N. (2015). Transition in endocrinology: Hypogonadism in adolescence. European Journal of Endocrinology 173 (1), R15–24.

3.5.2. Hypergonadotropic Hypogonadism

3.5.2.1. Congenital hypergonadotropic hypogonadism

3.5.2.1.1. Disorders of sex chromosome number

3.5.2.1.1.1. Klinefelter Syndrome (47,XXY and its Variants)

The karyotypic abnormality consisting of two or more X chromosomes and one or more Y chromosomes is known as Klinefelter syndrome. Klinefelter syndrome is the most common defect of chromosome number, with a prevalence of 1:500 – 1:1000 in the general population. It is thought that many males are undiagnosed, even in adulthood. Infants and young children often have problems with expressive language development, and school aged children may have difficulty with reading. Psychological testing often shows disorders of executive function as well. Physically, the testes appear normal during infancy and childhood, and levels of FSH and LH are normal before puberty. As pubertal development unfolds, the testes do not increase in size normally, and the seminiferous tubules gradually become hyalinized, with loss of germ cells and Sertoli cells. Clinically, the testes remain small and may become very firm to palpation. In one study, the mean bitesticular volume was 5.5 mL. [11] LH and FSH levels begin to rise into the upper portion of the normal adult range early in puberty. By mid-puberty, LH and FSH concentrations are often abnormal. Although the onset of puberty is typically normally timed, 80% of affected individuals do not achieve normal adult concentrations of testosterone. The abnormal testosterone secretion results in a slow tempo of physical changes and lack of attainment of normal pubic hair and other sexual hair growth, as well as small penis size and lack of muscular development. The relatively low levels of testosterone and high concentrations of estradiol predispose adolescents and adults to gynecomastia, which occurs in about 40% of affected individuals.

Essentially all affected men with Klinefelter syndrome have azoospermia or severe oligospermia and are infertile. However, intracytoplasmic germ cell injection (ICSI) has proven to be a feasible approach for those who have viable spermatozoa isolated from ejaculates or after testicular sperm extraction (TESE).

3.5.2.1.2.

3.5.2.1.2.1. Vanishing Testis Syndrome

The term vanishing testis syndrome refers to the case of the phenotypically normal male born with bilaterally absent testes. Normally functioning testicular tissue is presumably present in early gestation, as the external and internal genitalia are normally formed and there are typically no Mullerian remnants, implying normal secretion of testosterone and MIS in utero. This condition is thought to be due to antenatal bilateral torsion of the testes or other vascular events. This condition is uncommon, occurring in approximately 1:20,000 males. Careful physical examinations at birth and during childhood will reveal apparent bilateral undescended testes, and further evaluation by measuring MIS, inhibin b, or human chorionic gonadotropin (hCG)-stimulated testosterone will show the absence of functioning testicular tissue. However, if a good physical examination is not performed in childhood, this condition may remain undetected

and present with delayed pubertal development. In some cases, the vascular insult may occur near the time of delivery, and bilateral testicular necrosis may be identified. [12]

3.5.2.1.3. Acquired Hypergonadotropic Hypogonadism

3.5.2.1.3.1. Infection

Viral orchitis is an uncommon problem that usually affects adult men. Infection with the mumps virus causes orchitis in 15-30% of postpubertal males, although orchitis is rare in children. In 15-30% of cases, orchitis is bilateral. Symptoms include pain, edema, and erythema of the scrotum. After resolution, approximately half of affected men have decreases in testicular volume. [13] Some patients will have minor alterations in endocrine function, but sterility is rare.

3.5.2.1.3.2. Radiation exposure

Gonadal tissue is very radiosensitive. Germ cells are particularly prone to radiation injury. In the male, loss of germ cells leads to infertility, but Leydig cells are more resistant to radiation-induced damage. Hence, at lower doses of radiation, there may be loss of fertility with preservation of endocrine function, diagnosed by elevation of FSH with normal LH and testosterone levels. At higher doses of radiation, both fertility and hormone secretion are affected, with elevation of both FSH and LH and low testosterone concentration. With any degree of radiation exposure in the male child or adolescent, germ cell loss can occur, while Leydig cell injury does not usually occur until doses exceed 20-30 Gy.

3.5.2.1.3.3. Chemotherapy

Chemotherapeutic medications, especially alkylating agents, commonly cause gonadal injury in both prepubertal and pubertal patients. Higher dose protocols are more likely to cause gonadal dysfunction. This group of medications includes cyclophosphamide, ifosfamide, procarbazine, busulfan, chlorambucil, and others. Defects in testosterone secretion in males exposed to alkylating agents are uncommon. Overall, males who have survived cancer in childhood have a 24% decrease in fertility.

3.6. DIAGNOSIS OF DELAYED PUBERTY AND HYPOGONADISM

The evaluation starts with a careful history and physical examination. Important historical features include the presence or absence of any signs of puberty, including the age at onset and the tempo of progression. Inquiry about the patient's sense of smell is important, because patients and families will not volunteer this information in this setting. The growth pattern of the patient must be assessed by examination of a standard growth chart. Finally, the timing of puberty in the parents, siblings, and other relatives is critical, as many of the possible conditions are heritable.

Important physical features include the patient's height and weight, the presence or absence of any signs of puberty, and the quantification of these signs if possible. Quantification of pubertal development includes assessment of Tanner stages, measurement of testicular volume and penile length in males, and measurement of breast size in females or gynecomastia in males.

The laboratory diagnosis begins with determinations of LH and FSH concentrations. Normal or low gonadotropin levels direct the evaluation along the hypogonadotropic hypogonadism

pathway, while elevations of gonadotropins suggest a diagnosis involving primary testicular or ovarian failure.

3.7. ESTIMATE OF PREVALENCE OF DELAYED PUBERTY AND HYPOGONADISM

Based on demographic data and estimated prevalence, we have made some rough estimates of population sizes for certain causes of delayed puberty.

3.7.1. Number of children in the United States with delayed puberty and and CDGP

The ***US census from the year 2017*** notes the following population statistics for Boys—[total census at that age divided by 2]:

Age 14 = 2.06×10^6

Age 15 = 2.06×10^6

Age 16 = 2.11×10^6

Age 17 = 2.15×10^6

The 97th percentile [above 2 SD, and thus "abnormal"] for starting puberty in boys is 13.7 years from a proper population study (Belgian boys in 2009) [C]

a) Assumptions for calculations:
   i. For this calculation will use the least parsimonious number, 2.3 %
   ii. That number relates to the 14 year olds and is clearly less for the older age bands for CDGP.
   iii. I have arbitrarily halved the percentage each additional year, although clinical experience over more than 4 decades would note that number to be high
   iv. Two large single center studies from academic centers noting differing referral patterns show approximately 65% of the boys with delayed puberty have CDGP

b) CDGP
   Thus, for the 14 year old boys, 2.3 % have delayed puberty, 65% have CDGP
   i. $2.06 \times 10^6 \times 0.023 \times 0.65 = 3.08 \times 10^4$
   ii. Clearly those with delayed puberty diminish as the age nears 18 years, especially those with CDGP. Conservatively, diminish that by 50 % each year, yielding 1.54, 0.77 and 0.39 for the ensuing years for a total of $\underline{5.78 \times 10^4}$

c) Primary Hypogonadism
   Kleinfelter syndrome estimated to be ~1:500-600 males and that is the most prevalent form. However only about 10% present before age 18.
   -Boys 14 to 18 y = $8.38 \times 10^6 / 6 \times 10^2 = 1.4 \times 10^4$ but only `10 % carry the diagnosis leaving approximately 1.4×10^3 adolescents with the diagnosis of Kleinefelter syndrome.

d) Hypogonadotropic Hypogonadism
   Kallmann syndrome estimated to be ~1:10,000 males and that is the most prevalent form of hypogonadotropic hypogonadism.

-Boys 14 to 18 y = $8.38 \times 10^6 / 1 \times 10^4 = 8.38 \times 10^2$ Once again not all will have a diagnosis but these adolescents will likely not have started any pubertal development and more will be captured than those with the Kleinfelter syndrome where most do start pubertal maturation

3.8. TREATMENT OF DELAYED PUBERTY AND HYPOGONADISM

The principle goal of treatment of delayed or absent puberty is the attainment of sex steroid levels and physical development that are appropriate for the stage of adolescent development (see **Table 4**). Replacement may be temporary in cases of transient delayed puberty, such as constitutional delay of growth and puberty (CDGP), or long-term in cases of permanent absence of pubertal development. Subsequent goals of sex steroid therapy in the adolescent are to promote physiological linear growth and development of secondary sexual characteristics and to permit the acquisition of normal body composition, including muscle mass and skeletal bone mineral content, with the purpose of mimicking the normal physiologic process. Regardless of whether the patient has hyper- or hypogonadotropic hypogonadism, long-term sex steroid replacement is accomplished similarly.

One should not lose sight of other benefits, including amelioration or low self-esteem, distorted body image, impaired psychosocial development, and perhaps increased anxiety and depression.

Table 4 Goals of Testosterone Therapy in Adolescents with Hypogonadism

1. To induce sex-specific secondary sexual characteristics, and then maintain them in adulthood.
2. To optimize pubertal growth spurt and have physiologic body proportions (not to be eunuchoid).
3. To obtain adequate lean muscle mass, fat mass, and optimal bone mineral mass accretion.
4. To develop adequate external genital appearance (penile size and scrotum) and internal genitalia growth.
5. Ro reduce cardio-vascular and metabolic syndrome risk by optimization of lipid profile.
6. To induce sex-specific psychosocial and psychsexual maturation, and assure normal soial/sexual life and well-being.

Modified from Soliman [14]

3.8.1. Androgen therapy in delayed pubertal development

The primary clinical uses for androgen therapy in adolescent males are to induce pubertal development and as replacement therapy in those with permanent hypogonadism of either the hypogonadotropic or hypergonadotropic variety. The most common cause, although its precise incidence is unknown, is constitutional delay of growth and puberty (CDGP).

Without intervention, most patients with CDGP will undergo normal pubertal development spontaneously and most, but not all, will reach their genetically determined mid-parental height range. Many adolescents suffer significant emotional distress because they differ in their appearance from their peers during these years. Androgen therapy was initially proposed for boys with CDGP to alleviate their psychological discomfort, in addition to the beneficial effects on bone mineral accrual, lean body mass (protein metabolism) and the regional distribution of body fat. **Table 5** shows the available androgens in the US and abroad.

Table 5 Therapy for delayed puberty/male hypogonadism

Medication	Formulation	Trade name	Dosage units supplied	Induction of puberty dose	Dose range and frequency	Application site	Disadvantages, common adverse effects	Advantages
Testosterone (Stanhope et al., 1988)							Serum testosterone levels fluctuate, Erythrocytosis, weight gain, prostate hyperplasia; high doses can cause premature epiphyseal closure; not for use in boys with a bone age of <10 year	
	Intramuscular Injections	Testosterone enanthate (Delatestryl) Testosterone cypionate (Depo-Testosterone)	200 mg/mL 100, 200mg/mL	50–100 mg IM every 4 weeks for 3 months (Richmond and Rogol, 2007; Snyder, 2012)	1. CDGP: If no physiologic changes are apparent after 3 months, the dose can be increased by 25-50mg administered every rv 4–6 months. Treatment is usually continued at 3 months intervals with evaluation. Treatment is continued 6–12 months 2. IHH: Increase dose at 6 month intervals by 25–50 mg per month gradually to adult replacement dose of 200 mg every 2–3 weeks	Thighs, buttocks	Local side effects: pain, erythema, inflammatory reaction, and sterile abscess; priapism can occur in patients with sickle cell disease; longer duration of effect for testosterone enanthate than propionate (Palmert and Dunkel, 2012); gynecomastia, mood disturbances, peaks and troughs in circulating testosterone (Bertelloni et al. 2010)	Many studies and clinical experience in treating adolescents
		Mixture of testosterone esters of propionate, phenylpropionate, isocaproate, and decanoate (Sustanon) not available in United States	250 mg every three weeks, or 100–200 mg every two weeks, or 50–100 mg weekly	Increasing dose schedule every 6 months:25 mg/m^2 per 2 weeks IM50 mg/m^2 per 2 weeks IM75 mg/m2 per 2 weeks IM100 mg/m^2 per 2 weeks IM (Delemarre, et al., 2008)	Adult dose: 250 mg per 3–4 weeks (Delemarre, et al., 2008)			
		Testosterone undecanoate	250 mg/mL	No available data in children	Optimal adult dose: 1000 mg/12 weeks (Range 10–14 weeks)	Gluteal medius only	Lack of experience in adolescents; local pain; Injection-associated pulmonary oil microembolism (POME), restricted access in United States, trochar needed for extra-long acting esters	Stable testosterone levels
	Transdermal patch	Testosterone transdermal 24-hour patch (Androderm)	2 mg/24-hour patch, 4 mg/24-hour patch	14–16 years: 2.5 mg/12 night h; 17–19 years: 2.5 mg/day; >20 years: 5.0 mg/day; 12.5–15 years: 5 mg/8–12 h	Adult dose: 2.5–5 mg/day	Dry intact skin of back, abdomen, upper thighs, or arm	Skin rash, poor adherence, little data in adolescents	Mimics circadian variations
	Transdermal gels, pumps, solutions	Testogel 1 percent gel	50 mg in 5 gram packet	20 mg daily or every other day for the first year, increase by one-	50 mg daily	Dry intact skin of back, abdomen,	Normal serum testosterone levels not achieved in all hypogonadal males, potential for skin	Mimics circadian variations,

Medication	Formulation	Trade name	Dosage units supplied	Induction of puberty dose	Dose range and frequency	Application site	Disadvantages, common adverse effects	Advantages
				third of sachet (20 mg) every year to final dose of 50 mg daily in third year (El-Khairi et al., 2017)		upper thighs, or arm	transfer, therefore avoid skin contact with others; little data in adolescents	good clinical response, no visible patch, gel dries quickly
		Testim 1 percent gel	50 mg in 5 gram packet	No data available in children				
		AndroGel 1 percent gel (Rogol, 2005)	25 mg in 2.5 g packet, 50 mg in 5 g packet	0.5g/day, increasing dose based on testosterone levels	Increase dose in step-wise fashion to increased in stepwise fashion to 1.0, 1.5, 2.5, 3.0, or 5.0 g/day. Adult dose: 5–10 mg/day			
		AndroGel 1.62 percent gel	20.25 mg in 1.25 g packet, 40.5 mg in 2.5 g packet, metered dose pump (20.25 mg per actuation)	No data available in children	No data available in children			
		Fortesta 2 percent gel	Metered dose pump (10 mg per actuation)					
		Axiron 2 percent solution	Metered dose pump (30 mg per actuation)					
	Oral testosterone	Testosterone undecanoate (Andriol, Restandol), not available in United States	40 mg capsules	Start at 40 mg once daily, gradually titrate up every 6 months to max dose of 80 mg twice daily after 2–3 years (El-Khairi et al., 2017)	Max dose 80 mg twice daily (El-Khairi et al., 2017)	Oral	Short half life, must be taken with food for satisfactory absorption	Oral administration
	Testosterone subcutaneous implants (pellets)	Testosterone implant pellets (Testopel)	75 mg pellets	No data available in children	No data available in children	Subcutaneous implant under hips	Incision required for insertion, pellet extrusion, infection, fibrosis, no information available on optimal dosing	
	Buccal testosterone	Buccal testosterone system (Striant)	30 mg per buccal system		Adult dose: 1–2 cps per day	Buccal	Poor adherence, gum irritation	
Aromatase inhibitors (Palmert and Dunkel, 2012)							Not currently approved for CDGP; after onset of puberty, may increase gonadotropin secretion and circulating testosterone levels	
	Oral letrozole	Femara	2.5 mg oral tablets	May use in conjunction with testosterone	2.5 mg orally once daily	Oral	Decreased level of high-density lipoprotein cholesterol, erythrocytosis, vertebral deformities. Muscle, joint pain in adults	Oral administration

Medication	Formulation	Trade name	Dosage units supplied	Induction of puberty dose	Dose range and frequency	Application site	Disadvantages, common adverse effects	Advantages
	Oral anastozole	Arimidex	1.0 mg oral tablets		1.0 mg orally once daily	Oral	Less potent than letrozole	Oral administration
Anabolic steroid 28)	Oral oxandrolone	Oxandrin	2.5 mg, 10 mg tablets	No data available in children	2.5 mg orally once daily	Oral	Premature epiphyseal closure, increases low-density lipoprotein and decreases high-density lipoprotein	Oral administration
hCG (Zacharin, 2015)	Subcutaneous injection	Novarel, Ovidrel, Pregnyl, A.P.L., Profasi, Chorex, Gonic, HCG, Chorigon, Choron-10	5000 units; 10000 units; 20000 units; recombinant 250 mcg; recombinant 250 mcg/0.5 mL	Not applicable	Dose range: 500IU subcutaneous twice weekly to 1500 IU twice weekly. May consider addition of FSH[a]	Dry intact skin of upper outer arm, abdomen, thigh	Local side effects: pain, erythema, inflammatory reaction, and sterile abscess; costly; no guidelines available	

Source: Reference 5

4. CLINICAL TRIALS IN CHILDREN/ADOLESCENTS WITH HYPOGONADISM

What seems to be requested of industry for testosterone replacement trials?

Based on documents that are in the public domain, the FDA appears to have defined the indications and age-range of the boys who will be studied in testosterone replacement trials. The class indication for testosterone replacement products for adult males that the FDA refers to as "classical hypogonadism" is on the package insert of all testosterone replacement products and is

"Conditions associated with a deficiency or absence of endogenous testosterone":

- *Primary hypogonadism (congenital or acquired): testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (follicle-stimulating hormone [FSH], luteinizing hormone [LH]) above the normal range.*
- *Hypogonadotropic hypogonadism (congenital or acquired): gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum concentrations but have gonadotropins in the normal or low range.*

The package inserts have a "Limitation of Use" that indicates that these products have not been studied in a pediatric population. Specifically, the "Limitation of Use" states:

> *Safety and efficacy of [Product Name] in males less than 18 years old have not been established.*

However, it appears that the FDA does not intend to ask for studies in all male adolescents with "classical hypogonadism". In the approval letter of Xyosted™ (available on FDA website), a recently approved injectable T-enanthate, and that of JATENZO®, an oral testosterone undecanoate, there is a Pediatric Study requirement which has a lower age cutoff of 14 years. The Pediatric Study Requirement in the approval letter states:

> *We (*the FDA*) are waiving the pediatric study requirement for all […] males from birth to < 14 years old, because studies are impossible or highly impracticable.*

Subsequently it states

> *A trial of testosterone replacement therapy in pediatric males ages 14 years and older for conditions associated with a deficiency or absence of endogenous testosterone due to primary hypogonadism or hypogonadotropic hypogonadism.*

The design, including patient populations and endpoints, of any such trial(s) is not provided.

4.1. CHALLENGES IN PERFORMING T REPLACEMENT TRIALS IN BOYS WITH "PRIMARY OR HYPOGONADAL HYPOGONADISM:

Thus the FDA has placed some significant constraints on the pediatric studies based on both indication and age that may adversely affect the feasibility of conducting such trials. The impact of some of these constraints is listed below:

4.1.1. Differentiation of IHH and CDGP-

Although IHH is a cause of "classical hypogonadism" and thus is on indication, CDGP is not. IHH and CDGP can be distinguished, eventually; however, this often happens after the adolescent has received T treatment. At presentation, there are no clinical observations, analytical tools or laboratory measures that can definitely distinguish IHH from CDGP at presentation or prior to TRT treatment. This can make it extremely impossible to be sure that only the appropriate children are recruited into trials. This was a problem that occurred when AndroGel was studied in a pediatric population. [Rogol 2014] The investigators had no difficulty diagnosing anorchia or Klinefelter syndrome, but the larger recruited population also included IHH and CDGP. After careful review of approximately 50 subjects the investigators were unable to unequivocally place them in either the IHH or CDGP categories and did not have sufficient longitudinal data to know eventually to which category they belonged (ADR personal communication).

4.1.2. Presentation of Kleinfelter syndrome patients

Kleinfelter syndrome is the most common genetic cause of hypogonadism,which is readily diagnosed by genotyping. However, these patients overwhelmingly have a natural progression into pubertal maturation, but fail to progress through all of the stages. As such, less than 10% Kleinfelter syndrome patients present before 18 years of age, as the phenotype is predominantly behavioral and psychosocial.

4.1.3. Patients presenting before 14 years of age

Psychosocial challenges faced by young, under-developed patients is impetus for children under age 14 to present for TRT treatment. These adolescents "want something done NOW" to stay apace of their peers and present because of themselves, their families or their primary care givers. Very few pediatricians are comfortable prescribing testosterone to any adolescent at this age.

4.1.4. TRT off-label use

TRT is readily available "off label" and is prescribed to adolescent boys with psychosocial needs. It is often impossible to convince a patient/parents that they should participate in a clinical trial when a well-accepted therapy can be prescribed by their health care provider. This is especially relevant since the clinical trials will not offer a new therapeutic option, but rather an already approved therapy. The trial adds burden for the patient/family without offering anything that is not already available.

4.1.5. TRT in adolescent males – anecdotal example (Rogol AD)

This is not to say that it is impossible to study T replacement in 14-18 year old boys with "classical hypogonadism", it is just very challenging even to find the numbers of subjects to propose being in a trial when some many not receive active drug right away. Those that come to a pediatric endocrinologist have already overcome the barrier to treatment.

I have been involved in a trial of testosterone replacement in adolescent males [**Rogol AD**, Swerdloff RS, Reiter EO, Ross JL, ZumBrunnen TL, Pratt GA, Brennan JJ, Benesh J, Kan-Dobrosky, Miller MG. A multicenter, Open-Label, Observational Study of Testosterone Gel (1%) in the Treatment of Adolescent Boys with Klinefelter syndrome or Anorchia. *J Adoles Health 2014; 54:20-25*]. In that trial, the effect of AndroGel 1% on boys with Kleinfelter syndrome or anorchia was examined with the objective to evaluate the clinical response to Testosterone-gel 1% for the treatment of delayed puberty in boys of adolescent age. The trial recruited 86 patients at 18 clinical sites[1] but took more than 3 years to complete (August 2002 – June 2006). In the study proper dosing became an issue given the variable responses in individual adolescents and the difficulties in determining the diagnosis of IHH versus CDGP as noted above. Please note that this was an open label trial and all received active drug at the start.

4.2. OVERALL CONCLUSIONS - RUNNING CLINICAL TRIALS IN ADOLESCENTS

In summary, conducting pediatric trials for testosterone replacement therapy may not be feasible in any reasonable timeframe due to the inability to unequivocally distinguish between IHH and CDGP, the low rate of presentation of Kleinfelter syndrome prior to 18 years of age, and the well-accepted therapy options already available to patients.

[1] Site recruitment statistics – 2 sites recruited 10 patients each; 2 sites recruited 9 patients; 1 site recruited 7 patients; 4 sites recruited 5 patients; 1 site recruited 4 patients; 3 sites recruited 3 patients; 3 sites recruited 2 patients; and 2 sites recruited 1 patient each.

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