'Management of Hypogonadism From Birth to Adolescence'
for *Best Practice and Research Clinical Endocrinology and Metabolism*.

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Abstract:

Management of patients with hypogonadism is dependent on the underlying cause. Whilst functional hypogonadism presenting as delayed puberty in adolescence is relatively common, permanent hypogonadism presenting in infancy or adolescence is unusual. The main differential diagnoses of delayed puberty include self-limited delayed puberty (DP), idiopathic hypogonadotropic hypogonadism (IHH) and hypergonadotropic hypogonadism. Treatment of self-limited DP involves expectant observation or short courses of low dose sex steroid supplementation. More complex and involved management is required in permanent hypogonadism to achieve both development of secondary sexual characteristics and to maximize the potential for fertility. This review will cover the options for management involving sex steroid or

gonadotropin therapy, with discussion of benefits, limitations and specific considerations of the different treatment options.

Key words: Puberty, hypogonadism, gonadotropin therapy, rFSH, testosterone, estradiol

Practice Points

1. The mini-puberty is an important window of opportunity for the evaluation of suspected hypogonadism in an infant, and diagnosis during the mini-puberty may aid management and future outcomes.
2. It is very important to diagnose the underlying cause of delayed puberty, especially to distinguish between self-limited DP and IHH in adolescents, as treatment aims, options and duration are very different in these two patient groups.
3. The consideration of fertility in hypogonadic males, even in adolescence, should be paramount for clinicians, as appropriate treatment may optimize future fertility potential in these patients in a time-sensitive manner that may not be possible later in life.
4. We have highlighted the need for an awareness of the clinical spectrum in IHH, and the differing requirements of patients with severe congenital HH versus partial or indeed reversible HH.

Research Agenda

1. Because of the secular change in the timing of puberty, traditional limits which define delayed puberty may need moderating in particular environments and ethnic groups
2. Because of the lack of controlled trials, it remains unclear what the optimal management of males with severe hypogonadotropic hypogonadism (cryptorchidism, micropenis and lack of spontaneous increase in testicular size in puberty) should entail. Whether such patients would benefit from prepubertal (or even neonatal) FSH treatment to improve potential for future fertility is an unanswered question.
3. The genetic and environmental basis for both DP and IHH is an area of research where there is still much to be discovered, and one that may bring future benefits for informed management of these patients. Our understanding of the key controllers of

pubertal onset and its timing is advancing, but it is still a complex puzzle to be unlocked.

4. In self-limited DP low dose sex steroid treatment is adequate for the majority of patients who require intervention. However, a proportion of young men will remain adversely affected by their delayed pubertal development and/or short stature in adolescence, which may have long-term consequences. It is not known whether pubertal delay has a negative impact on adult bone mass and whether potentially compromised bone health is a reason to initiate sex-steroid replacement.

Introduction

The hypothalamic-pituitary-gonadal (HPG) axis is measurably active in fetal life, and then undergoes a process of reactivation twice between birth and adulthood. The first is in early infant life, during the so-called 'mini-puberty', and the second after a period of dormancy between the age of one and eight-to-nine years, during the onset of puberty (1). While puberty is recognised as the maturational process of the reproductive endocrine system that results in achievement of adult height and body proportion, in addition to development of the genital organs and the capacity to reproduce, mini-puberty has also been increasingly recognised as vital for normal fertility development (2).

Development of the clinical features of puberty is initiated by the reactivation of the HPG axis after this relative quiescence, but the nature of the puberty 'brake' that acts on the axis after the mini-puberty, and how and when this brake is released, is not well understood. Whilst the timing of pubertal onset varies within and between different populations, it is a highly heritable trait with estimates of up to 80% of individual variation being under genetic regulation (3). However despite strong heritability, the key genetic factors that determine human pubertal timing in the normal population and in cases of disturbed pubertal timing remain mostly unknown.

In healthy boys the normal age limits for Tanner genital stage 2 (G2) development are between 9 and 14 years (4). Similarly, the great majority of Caucasian girls have at least early signs of breast development (Tanner breast stage 2, B2) by 13 years of age (Figure 1). Whilst a large variability in the timing of pubertal onset exists in both

genders, clear age cut-offs for normal pubertal development have been drawn. However, for both genders the age limits for identifying children who need evaluation for delayed puberty (DP) may vary in different ethnic groups.

Diagnosis of hypogonadism, infants

Mini-puberty provides a window of opportunity for evaluation of the functionality of the HPG axis before puberty. However, even at birth a suspicion of hypogonadism may be raised by the assessment of genital appearance. In conditions of congenital gonadotropin-releasing hormone (GnRH) deficiency, such as in idiopathic hypogonadotropic hypogonadism (IHH), both fetal and postnatal pituitary gonadotropin secretion is low. In males during fetal life, placental human chorionic gonadotropin (hCG) stimulates the testis, resulting in masculinization of the external genitalia. However, later in fetal life, when hCG concentration in fetal circulation falls, luteinizing hormone (LH) stimulates further penile growth and testicular descent. Consequently, boys with IHH often have micropenis and cryptorchidism at birth. It is important to consider the diagnosis of IHH in isolated congenital undescended testes (2). Primary hypogonadism may also present at birth with under-developed genitalia in male infants if the condition is gonadotropin dependent, or alternatively as ambiguous or female genitalia if the defect is of early-fetal onset due a disorder of sex development (DSD) (5). A full review of the diagnosis and management of DSD is beyond the scope of this review, and has been comprehensively addressed elsewhere (6).

If a suspicion of hypogonadism arises in the first 3-4 months of life it can be investigated on the basis of sex steroid and gonadotropin levels without the need for stimulation tests. Gonadotropin levels in healthy infants start to increase during the 1st week of life and then decrease towards the age of 6 months, except for FSH levels in girls that remain elevated until 3–4 years of age (7) (Figure 2). Testosterone levels in boys increase in response to LH levels and peak at 1–3 months of age, but in girls estradiol levels fluctuate, probably reflecting ovarian follicular growth and atrophy. Estradiol levels in girls decline in the 2nd year of life. Postnatal HPG axis activation during the mini-puberty has important roles in both sexes: in males, for penile and testicular growth (8) and in girls, for maturation of ovarian follicles and development of estrogen-sensitive target tissues (mammary gland and uterus) (9). However, most studies on hormone levels during mini-puberty have had cross-sectional design, and hence the inter-individual differences in timing, duration, and magnitude of the mini-puberty have remained largely unexplored. Serial blood sampling from healthy infants is problematic because of its invasiveness and non-invasive urine or salivary sampling are a way around this problem; however, urine and saliva assays are not widely used in clinical routine.

Recently, longitudinal data has provided new information about the hormonal patterns including the timing of the peak hormone levels and the decrease in hormonal activity according to developmental age (8-11). Because of the large variability in reported estradiol levels during infancy, profiling of longitudinal hormone levels is particularly important to gain a better understanding of the nature of ovarian activity in infant girls. Consequently, these data may aid in

defining aberrant HPG axis activity in infancy and facilitate early diagnosis of HPG axis disorders.

Newer markers of gonadal function are useful, particularly in males, for diagnosis of hypogonadism, both soon after birth and after the mini-puberty is completed. In healthy newborn boys, inhibin A levels are undetectable (12), but rise from day 2 onwards to robust levels by the end of the first month (13), reflecting Sertoli cell activity. Inhibin B levels peak in boys at three months of age to levels higher than in adult men, but then decrease by 15 months of age (14), although remain detectable at the lower limit of the adult range through into mid-childhood (12). In girls, inhibin B levels are low at birth but increase during the first months of life and then decrease again towards one year of age (14). Thus, inhibin B is a useful marker of Sertoli cell function from the neonatal period into early childhood and can be used to assess males infants with micropenis and/or cryptorchism, both due to central and primary hypogonadism (5). Its use in female infants is less clear.

Anti-mullerian hormone (AMH) is strongly expressed by Sertoli cells from the time of testicular differentiation to puberty and at much lower levels in females by the granulosa cells from birth until menopause. In boys, AMH levels increase after birth to peak levels around two months of age and then decrease by the age of one year (15). Undetectable AMH and inhibin B are diagnostic of anorchia. In infant girls, a similar pattern in AMH levels during the first months of life has also been reported, but the levels in girls are significantly lower (16).

In primary hypogonadism with gonadal dysgenesis, anorchia or testicular regression, gonadotropin levels in the mini-puberty are generally raised, but may fall to normal levels in later childhood (Table 1). However, in Turner syndrome, infant girls with the

45,X0 karyotype have higher FSH levels than healthy girls, and the levels remain elevated for several years. In contrast, Turner girls with other karyotypes than 45,X0 often have close to normal FSH levels, suggesting some ovarian feedback effects on pituitary FSH secretion in these patients (17). Often, infant boys with Klinefelter's syndrome (47,XXY karyotype) have normal levels of inhibin B, AMH, and INSL3, suggesting normal Sertoli and Leydig cell function in infancy, although they have elevated LH (18) and FSH levels (18, 19). Testosterone levels in these boys are either normal (or slightly elevated).

Thus, low sex steroid and gonadotropin levels in an infant less than 3 months of age indicate central hypogonadism with an absence of the normal 'mini-puberty'. In contrast, high gonadotropins associated with low/undetectable basal testosterone and INSL3 (in boys) are diagnostic of primary hypogonadism. Outside of the mini-puberty period, useful tests for the investigation of hypogonadism include Inhibin B and AMH (5).

Diagnosis of hypogonadism, adolescence

Etiology

The pathogenesis of delayed puberty (DP) encompasses several conditions, but is most commonly due to self-limited DP. There are three main groups of differential diagnoses of self-limited DP (Table 2): functional hypogonadism, disorders causing primary hypogonadism and GnRH deficiency leading to hypogonadotropic

hypogonadism (HH) (4, 20), although up to 30 different aetiologies underlying DP have been identified (21).

Self-limited DP, also known as constitutional delay of growth and puberty (CDGP), represents the commonest cause of DP in both sexes. Up to 83% of boys, and 30-55% of girls, with pubertal delay have self-limited DP (20-23). Individuals with self-limited DP lie at the extreme end of normal pubertal timing, with the absence of testicular enlargement in boys or breast development in girls at an age that is 2 to 2.5 standard deviations (SD) later than the population mean (4). In addition, self-limited DP may also encompass older children with delayed pubertal progression, a diagnosis that is aided by the use of puberty normograms (Figure 1) (23). Self-limited DP is associated with adverse health outcomes including short stature, reduced bone mineral density and compromised psychosocial health (24).

Self-limited DP segregates within families with complex patterns of inheritance including autosomal dominant, autosomal recessive, bilineal and X-linked (25), although sporadic cases are also observed. The majority of families display an autosomal dominant pattern of inheritance (with or without complete penetrance) (25, 26). 50 to 75% of subjects with self-limited DP have a family history of delayed pubertal onset (25).

The absence of pathological medical history, signs and symptoms, and a positive family history of pubertal delay in one or both of the parents suggests a diagnosis of self-limited DP; however, before making the diagnosis, significant pathological conditions must be excluded. These include the aforementioned differential diagnoses of DP (Table 2) (4, 20): functional hypogonadotropic hypogonadism, where late pubertal development is due to maturational delay in the HPG axis

secondary to chronic disease (found in approximately 20%), malnourishment, excessive exercise, psychological or emotional stress; hypergonadotropic hypogonadism, with primary gonadal failure leading to elevated gonadotropin levels due to lack of negative feedback (found in approximately 7% of male patients and 25% of female patients with DP); and permanent hypogonadotropic hypogonadism, characterized by low LH and FSH levels (9% of boys and up to 20% of girls).

A thorough history should note evidence of chronic disease, anorexia, the intensity of athletic training, and the timing of puberty of both parents (Figure 3). A history of chronic illnesses, such as coeliac disease and inflammatory bowel disease, will suggest a temporary or secondary delay of puberty.

Permanent GnRH deficiency is due to congenital hypothalamic or pituitary disorders, or an acquired central dysfunction secondary to irradiation, tumour or vascular lesion. A picture of IHH with no associated anatomical or functional defect in the HPG axis occurs in 1-10 cases per 100,000 births. Because of different causes and incomplete penetrance, there is a wide spectrum of phenotypes, ranging from complete HH with lack of pubertal development to a partial hypogonadism with an arrest of pubertal development, and even reversible HH in some patients post treatment (27). Despite recent advances, with over thirty genes linked to this disorder identified, the pathophysiological basis of HH in approximately 50% of individuals remains unclear. The condition may be due to failure of development of GnRH neurons, lack of activation of GnRH secretion or disrupted GnRH signaling. Kallmann Syndrome (KS, HH associated with anosmia) is the most common form of isolated HH, accounting for 60% of cases.

Assessment

It may be very difficult to distinguish clinically between the diagnosis of DP and congenital IHH in the teenage years. In the majority of subjects with constitutional delay there is delayed maturation during early childhood, and consequently they are shorter than their peers. It has been shown that those DP subjects who also have poor growth in childhood may not fully exploit their genetic height potential, resulting in an adult height below their mid-parental target height (28-31), with an average loss of 4.2cm if untreated (31). However, other studies showed only a negligible difference in final height, even in DP subjects who have received no intervention (32-38). This may imply a pathophysiological mechanism additional to lack of sex steroids contributing to the growth phenotype in some patients with DP, but not in others (38).

By contrast, patients with congenital IHH usually have steady linear growth during childhood and only become short for their age with absence of the pubertal growth spurt. However, hypogonadotropic states cannot be ruled out by short stature and slow growth rate. In DP adrenarche may also occur later than usual, in contrast to the normal age of adrenarche in patients with isolated HH (4). Bone age in DP (X-ray film of left hand and wrist) is behind chronological age, but the developmental milestones are achieved at a normal bone age; that is, onset of signs of pubertal development by the bone age of 13 years in girls and 13.5 years in boys. However, whilst bone age delay provides useful information in the growth analysis, it contributes little to the differential diagnosis. Gonadotropin and testosterone concentrations increase in concert with the development of the bone age. Thus, all stages of pubertal development occur at an age later than usual.

In congenital IHH the diagnosis is typically made during the second or third decade of life. Common presenting signs are delayed onset of puberty, poorly developed secondary sexual characteristics, eunuchoid body proportions, or infertility. In some cases the diagnosis can be suspected before the age of pubertal onset, as discussed above, during the mini-puberty. The presence or absence of "red flag" features remains the strongest discriminator between isolated DP and IHH. These red flags include microorchidism, cryptorchidism or micropenis, indicating a lack of prior 'mini-puberty', or the presence of other features of GnRH deficiency which include anosmia or hyposmia due to hypoplasia of the olfactory bulbs (in Kallmann Syndrome) and occasionally cleft lip and palate, unilateral renal agenesis, short metacarpals, sensorineural hearing loss, synkinesia and color-blindness (39). Evidence of other syndromic diagnoses linked to central hypogonadism may also be present, particularly with neurological phenotypes such as in the 4H syndrome (Hypomyelination, Hypodontia and Hypogonadotropic Hypogonadism) (40) or ataxia, as seen in Gordon-Holmes syndrome (41, 42).

Gonadotropin levels assessed by basal LH and FSH determination are often increased in adolescents with primary hypogonadism due to e.g. Klinefelter syndrome, but the basal gonadotropin values are not useful in the differential diagnosis of self-limited delay and HH (43). Investigation of the differential diagnosis of these latter two conditions may involve a number of physiological and stimulation tests, including assessment of LH pulsatility by frequent sampling (44), prolactin response to provocation (45), gonadotropin response to GnRH (46, 47), testosterone response to hCG (48-50) and first morning-voided urine FSH and LH (51). Most recently, a single measurement of inhibin B <35 pg/mL in prepubertal boys has been shown to

discriminate IHH from self-limited DP with high sensitivity (52), but this has not been demonstrated in girls. The trio of testicular volume (cut-off 1.1 ml), GnRH-induced maximal LH (cut-off 4.3 IU/L) and basal inhibin B level have been proposed as the most effective discriminators of IHH from DP in a new study (21). However, follow-up is often warranted before a definitive diagnosis can be made. An MRI pituitary with olfactory bulb views is warranted in cases of suspected hypogonadotropic hypogonadism.

With the major advances in the discovery of genes causing IHH that have taken place in the last two decades, increasing genetic diagnosis is likely to inform future management (53). However, variable penetrance and evidence for gene-gene interactions in the inheritance of IHH can make prediction of phenotype from genetic testing difficult. Family history and certain clinical features, such as cleft palate in FGFR1/FGF8, obesity or sleep disorder in PROK2 or PROKR2, and anosmia in KAL1 can be used to guide genetic testing.

In cases of primary hypogonadism a karyotype is important to confirm or exclude a diagnosis of Turner or Klinefelter's syndrome. Assessment of uterine development by ultrasound may aid diagnosis and response to treatment. Autoantibody screening may be informative in cases of female hypergonadotropic hypogonadism with premature ovarian insufficiency (POI). Measurement of AMH is valuable in POI to assess ovarian reserve.

Treatment of Hypogonadism – Males

Infancy

Postnatal HPG axis activation in boys, which results in testicular activation and proliferation of Sertoli cells during this period, has a role in the development of reproductive capacity. The association of testosterone levels at three months of age and early penile growth (54), and involution of the penis and scrotum in boys with IHH in infancy (55) suggests a role for postnatal testosterone in "stabilizing" male genitalia. Analogous to true puberty, androgens secreted early in life may also have effects on linear growth, skeletal development, body composition, and psychosexual development (56).

Hormone therapy has thus been advocated for penile growth and testicular descent in infant boys with IHH or Kallmann syndrome (57). In boys with primary hypogonadism, slightly higher FSH and LH levels and lower inhibin B as well as INSL-3 levels are seen at three months of age compared to healthy controls (58). Reported testosterone levels in cryptorchid boys are normal (59, 60) or subnormal (61). Decreased serum androgen bioactivity has also been reported in infant boys with at least one undescended testis (62).

Neonatal treatment with testosterone can be used to correct micropenis in both central and primary hypogonadism. Standard therapy is with either IM testosterone enanthate 25mg every 3 to 4 weeks for 3 months, or topical therapy with either 5% testosterone cream or DHT (63). Management of cryptorchidism is with surgical correction, with the use of hCG or GnRH therapy adjuncts only likely to provide a small additional benefit (64). However, these therapies will not address the microorchidism seen in a male infant with IHH. A small number of studies of infants with IHH have used recombinant LH and FSH treatment to increase both penile length and testicular volume (65, 66). Outcomes included improved testicular size

and function (measured with inhibin B and AMH), but it is not known if such therapy will improve the response to pubertal treatments or fertility outcomes in men with IHH. Concerns remain about the possible deleterious effects of hCG on germ cells in cryptorchid testes in infants, as its use has been associated with smaller testis volumes and higher FSH levels in adulthood (67, 68).

Adolescence

Induction or progression of puberty is commonly considered for adolescents who either have significantly delayed or arrested puberty, or have been diagnosed with hypogonadism. Appropriate treatment modalities are directed according to the underlying diagnosis.

A management strategy of 'watchful waiting' may be appropriate in isolated DP, where pubertal onset is late but expected to occur spontaneously. However, this decision should be taken in conjunction with the patient, taking into consideration their concerns and expectations. One major concern often raised by patients and their families is the effect of pubertal delay on both current and adult height. Patients with DP are often short compared with their peers, and this is often compounded by the fact that many have pubertal delay combined with familial short stature. However, reassurance can be given to such patients as usually in DP an adult height only slightly below the genetic height potential (target height) is reached; although there may be large individual variation (69, 70).

DP in adolescents can be associated with significant anxiety about body image in terms of physical size and pubertal immaturity, decreased self-esteem with social

isolation, withdrawal from sporting activities and psychosocial and peer relationship difficulties. In these circumstances, there is evidence that hormonal therapy can be beneficial (71, 72). The link between DP and reduced academic performance, substance misuse and behavioral difficulties is less well established.

In contrast, if "red flag" markers of hypogonadism are present or if endogenous gonadotropin-dependent puberty has not started after one year of treatment, then permanent HH and other diagnoses should be reconsidered. In such instances treatment should be initiated promptly in order to optimise skeletal growth and to induce secondary sexual characteristics and, therefore, minimise the psychosocial difficulties faced by adolescents with hypogonadism.

Self-limited DP Management:

The options for management of male patients with DP include monitoring with reassurance or therapy with low dose testosterone to augment growth rate and to induce secondary sexual characteristics (Table 3). There are a great number of published studies of treatment of DP in boys; these are mainly observational, with some small, randomized controlled trials (72-74). Most report treatment with short courses of low dose androgens with outcomes of increased height velocity without advanced bone age, advanced sexual maturation and often improvement in psychosocial parameters.

The most commonly used treatment regime with low dose testosterone for boys with DP is supplementation with intramuscular depot preparations of a testosterone ester (75), at a starting dose of 50mg each month for 3-6 months; a further 3-6

months of treatment may be given, with dose escalation as required (Table 3). Monitoring via serum testosterone increase (to mid-reference range one-week post injection), height velocity and virilisation is appropriate. The length of the polymorphism Cytosine-Adenine-Guanine (CAG) trinucleotide repeats present in the androgen receptor (AR) gene is associated with androgen receptor activity, which may in part modulate response to testosterone therapy (76). A diagnosis of GH deficiency must be ruled out if height velocity does not increase on testosterone therapy. Testosterone esters are to be avoided in hepatic impairment and hypercalcaemia and used with caution in renal impairment. Preparations are generally well tolerated but side effects may include headaches, depression and androgenic effects such as acne. Oral testosterone undecanoate can be prone to wide variations in serum testosterone because of its short half-life and thus requires careful monitoring, although has been successfully used for pubertal induction at a dose of 40-160mg daily (23). Although anabolic steroids such as oxandralone have been used historically for short-term improvement in height velocity, they are less effective in stimulating pubertal virilisation and therefore they are not recommended for the management of DP.

As discussed, DP is commonly seen in combination with idiopathic short stature (ISS) and such patients may present with concerns about short stature far out-weighing those about DP. After exclusion of those patients with GH deficiency, for example by the use of a primed GH-provocation test, the treatment of GH-replete DP patients with growth hormone remains controversial: it has been approved by the US FDA for the treatment of ISS and height SDS $\leq$ 2.25 for age, but leads to only a modest increase in adult height and its use is not recommended (77, 78).

A further potential pharmacological target in short boys with DP is inhibition of estrogen biosynthesis from androgens with aromatase inhibitors (79, 80). Epiphyseal closure is dependent on estrogens and thus aromatase inhibitors (AIs) can potentially act to extend the time period of long bone growth. Some published data supports this possible effect of AIs to delay bone maturation and to increase adult height in boys with short stature and/or DP (79, 80). However, despite recent data suggesting a good safety profile, there remains uncertainty about the efficacy and appropriateness of AI therapy in DP (81, 82).

Permanent Hypogonadism:

Although sex steroid replacement is used in nearly all conditions of hypogonadism for initiation of male puberty, more complex and involved management including gonadotropin treatment may be required in males with hypogonadism to achieve both the development of secondary sexual characteristics and to maximize the potential for fertility. Management of specific indications is discussed below.

Hypogonadotropic Hypogonadism:

In young men with a diagnosis of IHH, induction of puberty with sex steroid therapy is similar to that in self-limited DP; however, treatment can be initiated at a younger age (12yrs) if the condition is confirmed. In some patients, it may not be initially possible to distinguish between a diagnosis of IHH and DP and, therefore, commencement of testosterone therapy may be delayed until 14yrs. The starting dose of testosterone ester for IHH patients is also commonly 50mg, but doses are gradually increased to full adult replacement levels over approximately three years

(Table 3). Monitoring of response to treatment and for possible side effects is required, and therapy is likely to be required life-long. Maintenance therapy can be with IM testosterone, often as the longer acting testosterone undecanoate (Nebido), topical or oral therapy.

Importantly, testosterone therapy does not induce testicular growth or spermatogenesis in men with HH, as this is dependent on high intra-testicular concentrations of testosterone produced by LH-stimulated Leydig cells, in conjunction with FSH acting on Sertoli cells. Therefore, induction of fertility requires treatment with either pulsatile GnRH (83-85) or exogenous gonadotropins (85). Data from the last 5-10 years on a variety of regimens has been published, with treatments varying by indication, underlying diagnosis and severity of hypogonadism. Fertility outcomes also vary, with poorer responses in patients with signs of absent mini-puberty (prepubertal testes, cryptorchidism, and/or low inhibin B) (84, 86). Genetic diagnoses may also guide therapy: treatment of patients with KAL-1 mutations can be more difficult as they may have defects at several levels of the HPG axis (87), and patients with IHH due to GnRHR mutations may be better treated with hCG and FSH than pulsatile GnRH (88).

A sub-set of adolescent patients with IHH will have had a spontaneous onset of pubertal development that has then arrested. In such patients, monotherapy with hCG can be trialled for both completion of pubertal development and induction of fertility(89). FSH can then be added if there is persistent azoospermia after 6-12 months of treatment. In apubertal adolescent males, induction of puberty with either hCG monotherapy or with combinational therapy of hCG + rFSH leads to better testicular growth and fertility outcomes than treatment with testosterone

therapy (90). Furthermore, a combined regime of hCG + FSH has greater potential efficacy in the induction of spermatogenesis than monotherapy with hCG (90, 91). Additionally, timing of treatment is important, as FSH pre-treatment may theoretically optimise the Sertoli cell population prior to exposure to hCG or GnRH, and thus has the potential to improve fertility outcomes (92, 93). Although the optimal regimen in severe cases, i.e. those with testicular volume <4mL, is unknown, FSH pre-treatment followed by GnRH or combination hCG and FSH treatment may maximize the potential for fertility (94). Earlier age of treatment to induce spermatogenesis may also be beneficial in increasing the capacity for and speed of sperm production once fertility is desired; however, assisted reproductive technologies may still be required (95).

At the other end of the spectrum, patients can exhibit reversal of their phenotype during treatment. This phenomenon is being increasingly recognized in up to 20% of IHH cases (27). Awareness of this is important as a 'trial off treatment' can be utilized intermittently to assess requirements for maintenance therapy. However, these cases may also relapse off treatment and thus need ongoing monitoring. Patients with acquired HH, usually secondary to tumours or other structural lesions of the hypothalamic–pituitary axis or haemochromatosis, require treatment of their underlying condition with sex steroid or gonadotropin therapy depending on their specific requirements (93, 96).

Hypergonadotropic Hypogonadism:

The commonest condition underlying hypergonadotropic hypogonadism in males is Klinefelter's syndrome (47, XXY), with a prevalence of 1 in 667 live births. The

majority of those affected will enter puberty spontaneously at a normal age (97), although DP may be seen in those with a more complex karyotype (48, XXYY, 48, XXXY, 49, XXXXY). Sex steroid replacement is therefore not normally required for these patients at the start of puberty, but testosterone levels become increasingly deficient by Tanner stages 4-5, possibly as a result of secondary regression. However, only 10% of boys aged 10-14yrs with Klinefelter's syndrome have been diagnosed and many patients only come to the attention of an Endocrinologist in later adulthood (98). These patients present potentially difficult management decisions in terms of optimizing fertility outcomes, mainly relating to timing of interventions (99, 100). For patients with Klinefelter's syndrome requiring treatment due to falling testosterone levels, haematocrit, bone density, patient well-being or sexual function, low dose sex steroid replacement is the most commonly used therapy (Table 3). However, testicular sperm extraction and cryopreservation can be considered, even in adolescence prior to testosterone treatment, before the progressive seminiferous tubule degeneration that occurs in Klinefelter's syndrome has had an irreversible impact on sperm production (47). Unfortunately, the most invasive (& successful) sperm retrieval techniques have the potential to cause the most testicular damage, and so would ideally be reserved for those men actively desiring fertility. Balancing these opposing factors and giving clear information to young men who may not yet be concerned about their future fertility options, in order that they might make informed choices, is highly challenging.

The treatment of anorchic young men, secondary to congenital absence, vanishing testis syndrome or failed orchidopexy, for induction and maintenance of puberty is similar to that in boys with IHH. Androgen replacement should be commenced at a

low dose with incremental dose increases. IM testosterone esters administered monthly is the treatment of choice for pubertal induction, with testosterone gel via calibrated dispenser or 4-monthly intramuscular depot injections of Testosterone undecanoate 1g used for long-term maintenance therapy (Table 3).

Management of Hypogonadism - Females

Infancy

There is currently no evidence for therapy in hypogonadic female infants. These girls are less commonly diagnosed at birth or in infancy due to the lack of physical abnormalities (as compared to males with cryptorchidism or micropenis). However, in future pre- or postnatal genetic diagnosis may led to increased awareness and research in this area.

Adolescence

Self-Limited Delayed Puberty

Similarly to male patients with self-limited DP, the options for management of female patients with DP include monitoring with reassurance or therapy using low dose sex steroids to initiate pubertal development. Initial short-term therapy should be regularly reassessed and discontinued once puberty is progressing (Table 4).

Permanent Hypogonadism

As in boys, in cases of permanent hypogonadism more intensive and long-lasting therapy is required. Goals of treatment are induction of secondary sexual characteristics, development of reproductive capacity and increasing adult height. Once puberty is complete, ovulation and pregnancy can be achieved by pulsatile GnRH administration or combination gonadotropin therapy.

When estrogen therapy is required to induce pubertal development, the dosing and timing should be aimed at simulating the normal growth and development of secondary sex characteristics as closely as possible, taking account of the individual's desire to begin puberty and also of the family history of age at onset of puberty. Doses should be adjusted according to the needs and priorities of the individual. Response to therapy should be monitored in terms of the development of secondary sex characteristics, bone maturation, height velocity and uterine volume, with additional monitoring of blood pressure and bone density (101).

Both in young women with Turner syndrome and combined pituitary hormone deficiency, estrogen therapy should be coordinated with the use of GH. Previous practice in Turner syndrome tended towards delaying estrogen therapy until the mid-teens in order to optimize growth promotion with GH. However, more recent studies point to potential benefits from treatment with combined very low-dose estrogen and GH from an early age, in terms of final height and potentially other areas including cognitive development and uterine maturation (102, 103). Whilst it remains unclear as to the best timing to initiate estrogen therapy in young women with Turner syndrome, the current consensus is that induction of puberty should not be delayed in order to promote linear growth (104).

Additionally, whilst ethinylestradiol has traditionally been the estrogen of choice for pediatric patients, 17β-estradiol in transdermal, gel or oral form displays a better risk profile in terms of growth restriction, liver toxicity and vascular side-effects. Data from women with combined pituitary hormone deficiencies receiving combined estrogen and GH treatment indicate a markedly greater impairment of GH-mediated IGF1 synthesis with ethinylestradiol than with 17β-estradiol. Uterine development

may also be impaired with the use of ethinylestradiol as compared to 17β-estradiol (105, 106). Conjugated equine estrogens have been used, but formulations vary in biological potency and in view of reports of increased cardiovascular risks in postmenopausal women are best avoided.

Estrogen therapy should be initiated at a low dose (one-eighth to one-quarter of the adult dose) and increased gradually (at intervals of 6-12 months) (101). Doses can then be adjusted to the response (Tanner stage, bone age, and uterine growth), or if available, by ultrasensitive estradiol assay (107), with the aim of completing feminization gradually over a period of 2–3 years (Table 4).

A progestin such as oral medroxyprogesterone acetate should be added either if more than one episode of significant breakthrough bleeding occurs or after 24-36 months of estrogen therapy to establish menstrual cycles, with a frequency of at least every 2-3 months to prevent endometrial hypertrophy.

Individuals with Turner syndrome who have functioning ovaries and who progress through puberty spontaneously should receive contraceptive and genetic counseling. However, ovulatory function should be documented (FSH and LH measurements) because a peri-menopausal pattern of anovulation can lead to endometrial hyperplasia.

Conclusion

There are multiple genetic and environmental influences on the timing of puberty in the general population, and appropriate age cutoffs for delayed puberty in different ethnic groups may vary. DP is a frequent problem, and the most common underlying condition is self-limited (or constitutional) DP. However, the differential diagnoses

include hypogonadotropic hypogonadism and primary hypogonadism, and these conditions must be considered in young people with pubertal delay. Additionally, both of these forms of non-self-limiting hypogonadism may be diagnosed in infancy if the suspicion arises. Distinguishing between self-limited DP and permanent hypogonadotropic hypogonadism in adolescence remains difficult.

Management of adolescents with DP is dependent on the underlying cause. Treatment of isolated DP involves expectant observation or short courses of sex steroids in low doses, whilst more complex and involved management is required in patients with permanent hypogonadism. Achievement of fertility in patients with central hypogonadism requires therapy with gonadotropins. The management of infants diagnosed with permanent central hypogonadism is an area of future research.

Tables

Table 1: Upper limits for creatinine-corrected urinary gonadotropin levels before term, at term, and at 2–6 months of corrected age. Values above the limits suggest primary gonadal failure.

	Before term	At term	At 2–6 months corrected age
Girls			
FSH (IU/mmol Cr)	250	13	5
LH (IU/mmol Cr)	500	10	0.5
Boys			
FSH (IU/mmol Cr)	10	3	1.5
LH (IU/mmol Cr)	20	5	0.5

Values are based on original data published in Kuiri-Hänninen, T., Kallio, S., Seuri, R., et al., 2011a. Postnatal developmental changes in the pituitary-ovarian axis in preterm and term infant girls. J. Clin. Endocrinol. Metab. 96, 3432; Kuiri-Hänninen, T., Haanpää, M., Turpeinen, U., et al., 2013b. Postnatal ovarian activation has effects in estrogen target tissues in infant girls. J. Clin. Endocrinol. Metab. 98, 4709.

Table 2: Differential Diagnoses of Self-Limited Delayed Puberty

	Hypergonadotropic Hypogonadism	Hypogonadotropic Hypogonadism	Functional Hypogonadotropic Hypogonadism
:ommon :auses:	Male: Klinefelter's Syndrome Congenital anorchia/ testicular regression Female: Turner Syndrome Premature ovarian insufficiency Both: Gonadal dysgenesis Chemotherapy/Radiation Therapy	Isolated Hypogonadotropic Hypogonadism Kallmann syndrome Combined Pituitary Hormone Deficiency CNS Tumours/Infiltrative Diseases Chemotherapy/Radiation Therapy	Inflammatory Bowel Disease Coeliac Disease Anorexia Nervosa Hypothyroidism Excessive Exercise

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Table 3. Medications Used for the Treatment of Self-Limited Delay of Puberty and Permanent Hypogonadism – Males

Drug and formulation	Induction of Puberty in Boys		Side Effects and Cautions
	Isolated DP	Hypogonadism	
Testosterone (T)[i]			Erythrocytosis, weight gain, prostatic hyperplasia. High doses can cause premature epiphyseal closure. Not for use in boys with bone age < 10 yrs.
enanthate, ypionate, and ropionate. T nanthate has onger duration f effect than T ropionate. IM njection.	Not recommended before 13.5 yrs of age. Initial dose 50-100 mg every 4 weeks for 3 to 6 months. After review of response: repeated treatment with 25-50 mg increment in dose (not exceeding 100 mg)	Can initiate after age 12 yrs at 50 mg/month. Increase with 50 mg increments every 6 to 12 months. After reaching 100-150 mg monthly, decrease interval to every 2 weeks. Adult dose 200 mg every 2 weeks.	All IM preparations: local side effects (pain, erythema, inflammatory reaction and sterile abscess). Priapism can occur in patients with sickle cell disease.
undecanoate M injection	No data available.	Adult dose is 1000 mg every 10-14 weeks.	Very rarely, paroxysms of coughing and dyspnoea post-injection, ascribed to lipid embolism from the vehicle; hence not licensed in USA.
gel. ransdermal reparations, pplied topically t bedtime.	No data available.	Can be started when approximately 50% adult dose with IM T has been achieved. Adult dose 50-80 mg daily.	Local irritation. After applying, avoid close skin contact with others, especially females

Treatment of Fertility in Boys and Men**

	Isolated DP	Hypogonadism	
ulsatile GnRH .c. pump	Not recommended routinely	Initial: 5-25 ng/kg/pulse every 90-120 min; increase to 25-600 ng/kg/pulse	Requires extensive experience. Most physiological form of replacement.
CG (SC or IM) plus ecombinant FSH (SC).	Not recommended routinely	hCG: Dose 500 to 3000IU twice weekly, increased to every 2 days. Dose adjusted based on serum T levels. rhFSH: Dose 75 to 225 IU 2-3 times	hCG: Inflammation locally in the testis, may induce apoptosis of germ cells. In hypogonadotropic hypogonadism with prepubertal onset it is necessary to add FSH to induce testicular growth and spermatogenesis. No data on effects on future fertility.

		weekly***.	

*Testosterone undecanoate PO tablets or anabolic steroids are not recommended for the induction of secondary sexual characteristics.
**Induction of fertility may be less successful in men who have lower baseline testicular volumes, have received previously testosterone treatment, and have not previously received treatment with GnRH (83-86) or gonadotropins.
*****FSH pre-treatment for 4 months may be beneficial in men with prepubertal testes (92)**

Table modified and reprinted with permission from Palmert MR, Dunkel L. Clinical practice. Delayed puberty. N Engl J Med 2012;366:443-53 (4).

Table 4. Medications Used for the Treatment of Self-Limited Delay of Puberty and Permanent Hypogonadism – Females

Drug and Formulation	**Induction of Puberty in Girls**		**Side Effects and Cautions**
	Isolated DP	**Hypogonadism**	
Estrogens	Not recommended before 13 yrs of age.		
Transdermal 17b-estradiol e.g Evorel 25	Overnight patch: initial dose, 3.1–6.2µg per 24 hr (1/8-1/4 of 25-µg 24-hr patch); increase by 3.1–6.2 µg per 24 hr after 6 months*	Starting dose as for DP, increase by 3.1–6.2 µg per 24 hr until 1 full Evorel 25 patch continuously** Then maintenance with adult COCP or HRT	Patches may be difficult to use and fall off, especially if cutting whole patches into smaller fractions Reactions to adhesive Inter-individual variation in dose response
Oral 17b-estradiol (estradiol valerate)	0.5mg (1/2 tablet) alternate days or 5µg /kg of body weight daily; increase to 0.5mg (1/2 tablet) or 10µg/ kg daily after 6–12 months	Starting dose as for DP, increase by 5µg /kg of body weight every 6-12 months until dose of 1mg (1 tablet) daily Then maintenance with adult COCP or HRT	Inter-individual variation in dose response
Oral Ethinylestradiol (2µg tablets)	2µg daily, increase to 4µg after 6 months if required	2µg daily, increase by 2µg every 6 months until 10µg Then maintenance with adult COCP or HRT	High cost Liver toxicity, increased levels of some plasma-binding proteins Potential increased risk of hypertension and VTE Worse growth profile

Progestins	Not applicable	Introduced once breakthrough bleeding or 2+ yrs of continuous estrogen	
Norethisterone		5mg	More androgenic, increased risk of dysmenorrhoea
Utrogestan		200mg once daily	
Medroxyprogesterone acetate		5mg once daily	
Combination preparations		e.g. Evorel sequi, Elleste-Duet	

Treatment of Fertility in Women

Pulsatile GnRH s.c. pump	Not applicable		Requires extensive experience, treatment only within specialist centres. Most physiological form of replacement.
hCG (SC or IM) plus recombinant FSH (SC).	Not applicable		Requires extensive experience, treatment only within specialist fertility centres

* adjustments for body weight may be required, published advice on cutting patches available (107)

** once changed from overnight to all day use, patches to be changed twice weekly

COCP – combined oral contraceptive pill, HRT, hormone replacement therapy, VTE – venous thromboembolism.

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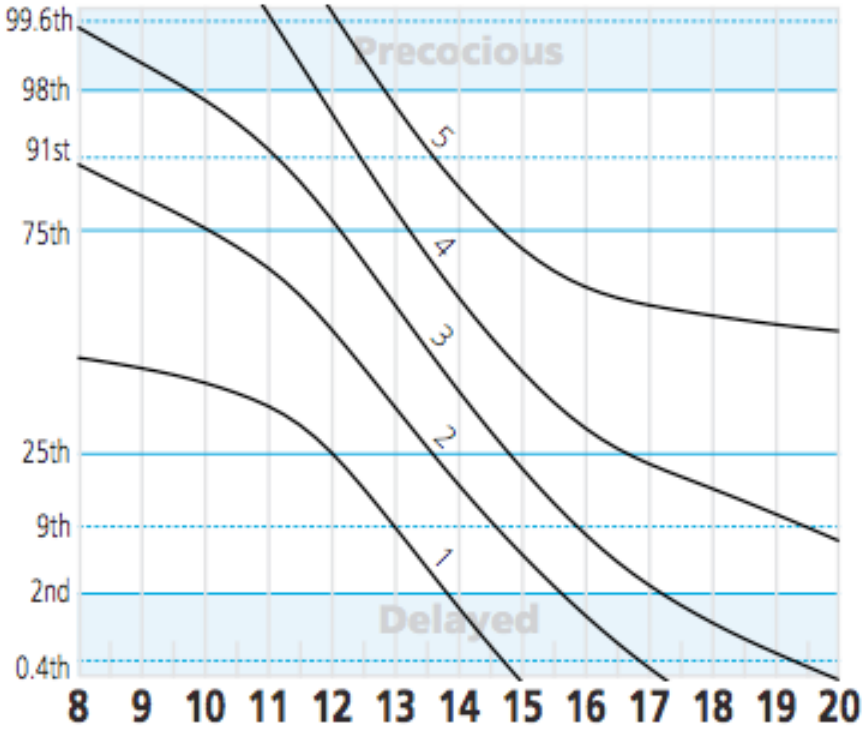
Genital stage



Breast stage

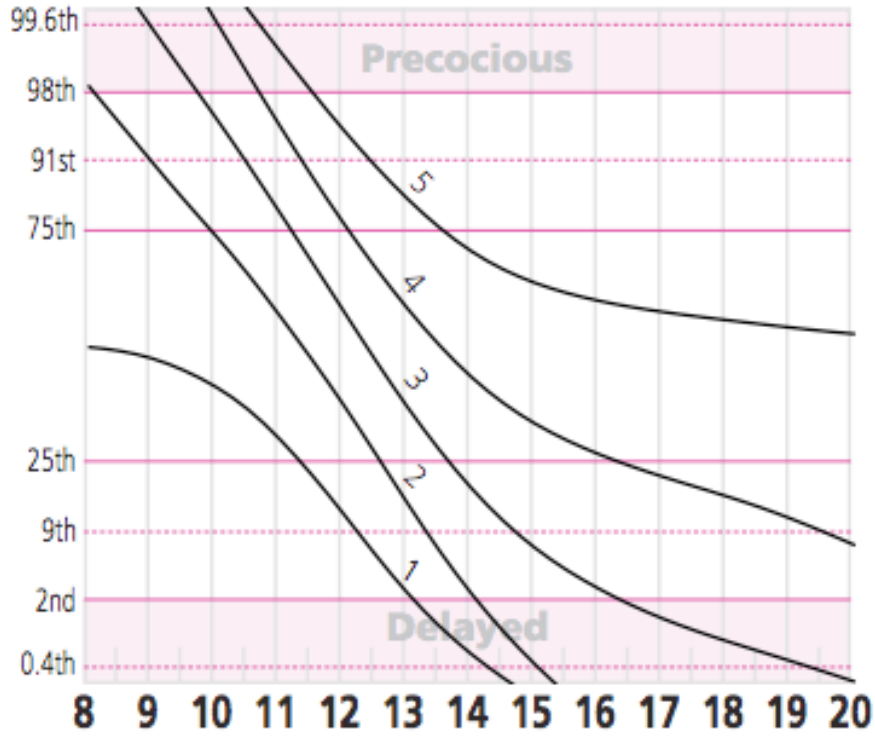


Figure 1 – The distribution of pubertal timing in healthy boys and girls. These data have been incorporated into UK growth charts and are available at www.growthcharts.rcpch.ac.uk. Original data from (108)

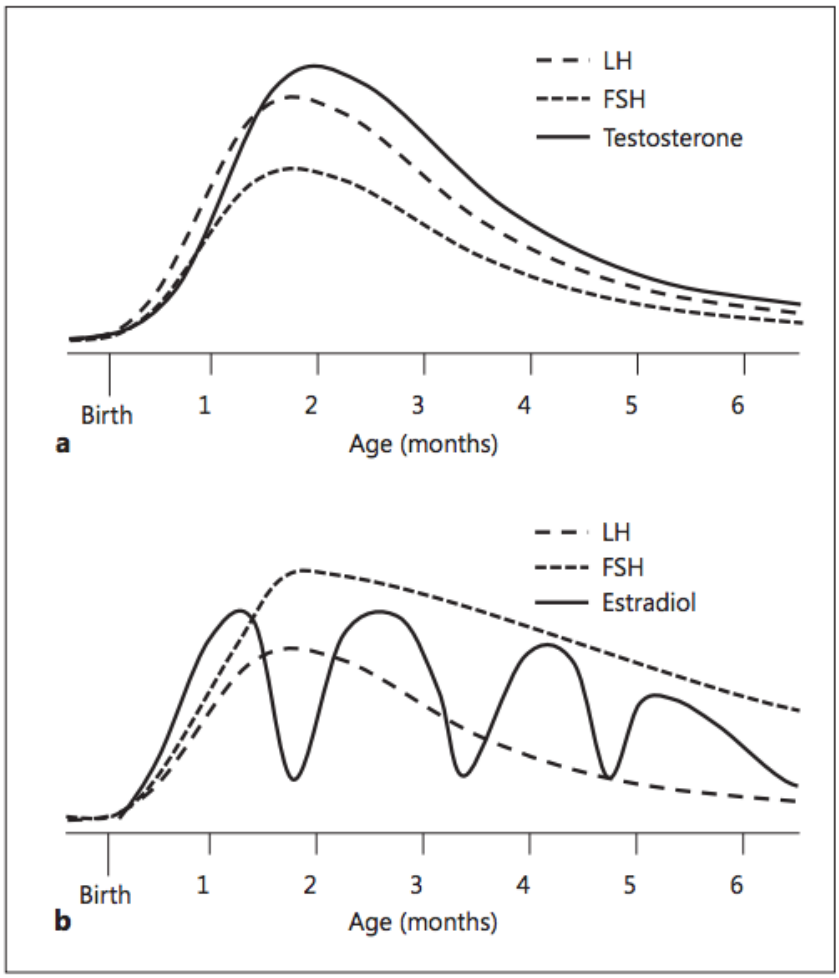


Figure 2 Patterns of postnatal gonadotropin and sex steroid secretion in boys (a) and girls (b). Gonadotropin levels start to increase during the 1st week of life, peak at 1–3 months, and then decline towards the age of 6 months. In boys, LH levels are higher than in girls, and in girls, FSH levels predominate and remain elevated until 3–4 years of age. Testosterone levels in boys increase following the LH levels and show a clear peak at 1–3 months of age, but in girls, estradiol levels fluctuate, probably reflecting ovarian follicular growth and atrophy. Estradiol levels in girls decline in the 2nd year of life. From (7); reproduced with author permission.

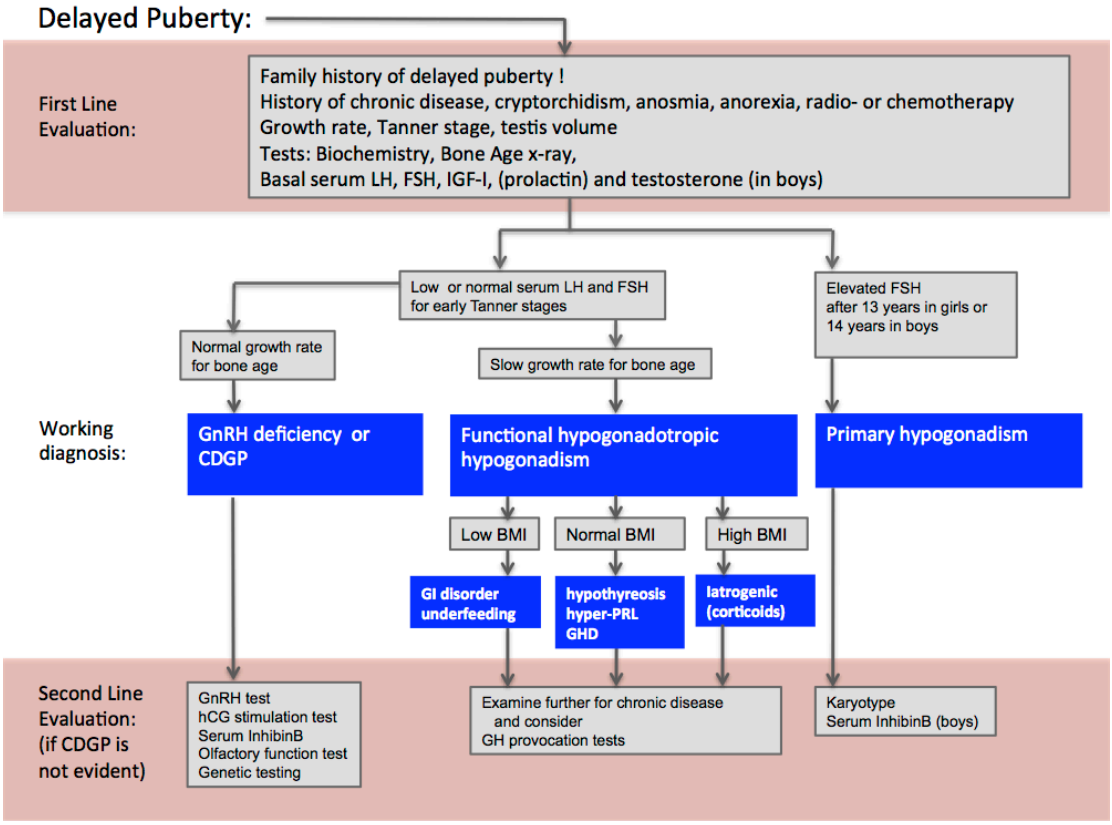


Figure 3. Differential diagnosis of delayed puberty.
Algorithm for the evaluation of a patient with delayed puberty. CDGP - constitutional delay of growth and puberty, GI - gastrointestinal, GH - growth hormone, GHD - GH deficiency, PRL - prolactin, IGF-1 - insulin-like growth factor 1. Reprinted with permission from Palmert MR, Dunkel L. Clinical practice. Delayed puberty. N Engl J Med 2012;366:443-53 (4).