



Disorders of Pubertal Development: From Hypogonadotropic Hypogonadism to Constitutional Delay of Puberty

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5.1 Background

Puberty is of paramount importance in the life of a young person. Puberty is the phase whereby secondary sexual characteristics develop, growth progresses towards final adult stature and reproductive ability is achieved. Rapid and complex changes involve physical, mental and social adjustments. Pubertal progression consists of specific sequential events. Disordered development can have adverse consequences, both physically and psychosocially [1]. Understanding the sequence of normal pubertal events is important in order to distinguish between normal, normal variants and pathological syndromes [2].

5.2 Normal Puberty

In order to have an understanding of disorders of pubertal development, it is first necessary to describe and comprehend normal puberty. Here, we focus exclusively on male development.

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5.2.1 Physiology

The hypothalamic-pituitary-gonadal (HPG) axis is active during early development in utero until the neonatal period. This neonatal phase is termed ‘mini-puberty’ and lasts up to age 6 months. The pubertal axis then becomes dormant after infancy and remains so during childhood, with very low levels of gonadotrophins and testosterone. The first stage in puberty is disinhibition of this axis, triggering reactivation. Gonadotrophin-releasing hormone (GnRH) is secreted in a pulsatile manner by neurosecretory cells of the hypothalamus into the hypothalamic-hypophyseal portal circulation [3]. This portal system serves as a direct vascular link between the hypothalamus and the anterior pituitary. GnRH stimulates gonadotropic cells in the anterior pituitary to synthesise and release luteinising hormone (LH) and follicle-stimulating hormone (FSH). LH stimulates testosterone synthesis in the testicular Leydig cells. FSH, in conjunction with testosterone, stimulates germ cell maturation, inducing spermatogenesis.

Adrenal androgens, secreted from the zona reticularis (ZR), also make an important contribution to the formation of secondary sexual characteristics, particularly pubic and axillary hair (pubarche). In normal puberty, adrenal and HPG axis maturation coincide; however, they are independent processes. Therefore, a child with signs of adrenarche may still experience delayed puberty. Pubarche is usually a result of adrenarche (maturation of the ZR of the adrenal gland), associated with skin changes and development of adult-type body odour.

5.2.2 External Pubertal Development

External pubertal development can be objectively classified using the Tanner staging system. This system has some limitations, most notably that it may not apply to all populations, having been designed on a small population of English children. However, it is still widely used internationally. In boys, the first external change is an increase in testicular volume (gonadarche) to 4 mL [4]. Orchidometers are used to help gauge size (Fig. 5.1) [5]. After this, the penis lengthens, followed by the development of sperm (spermarche) and then by achievement of peak height velocity [6, 7]. Adrenal features of puberty may begin anywhere along this progression but usually begin between initial testicular enlargement and the development of sperm.

5.2.3 Onset of Puberty

Although pubertal development follows a specific sequence, with relatively predictable onset and progression, judgement of which adolescents require further investigation can be challenging [8]. The onset of puberty can vary greatly, influenced by both intrinsic and extrinsic factors. Sex, race, ethnicity, nutrition, environmental exposure and genetic factors all contribute to this variability. Generally, it is advised to consider investigation when abnormalities fall 2–2.5 standard

Fig. 5.1 A photo of an orchidometer



deviations (SDs) outside the population mean. Normal puberty in boys is expected to start from age 9 years for the ‘early developers’ and up to age 14 years for the ‘late developers’.

5.3 Normal Variants of Puberty

Any deviation from normal puberty is likely to induce stress and anxiety in both the patient and his family. However, normal variants of early or delayed puberty must be differentiated from true pathological disorders.

Early puberty discussions are beyond the scope of this chapter and will be covered in another part of this book.

5.3.1 Delayed Puberty

If there are no signs of puberty in boys by age 14 years, then this is regarded as delayed puberty. Delayed puberty is seven times more frequent in boys than girls. Girls are more likely than boys to have a pathological cause. Since pubertal onset is not perfectly normally distributed, population studies suggest that up to 5% of children may be affected by delayed puberty.

The most common normal variant of delayed puberty is constitutional delay of growth and puberty (CDGP), accounting for up to 60% of cases of delayed puberty in boys. This is a diagnosis of exclusion. In CDGP the onset of puberty occurs more than 2 standard deviations (SDs) later than the population mean age of onset. Eventually, normal sequential puberty does occur. In CDGP the HPG axis is intact but remains dormant beyond the expected age for puberty. It may be more accurate to describe CDGP as ‘a delay in puberty and growth’ as it is the delay in puberty which causes the delay in growth. CDGP can produce significant anxiety in boys, particularly because of short stature in comparison with their peers and the apparent lack of pubertal development. Typically, reassurance is often all that is needed, but in some children, medical intervention may be indicated, discussed later.

5.4 Disorders of Puberty

We must now consider the disorders that can affect pubertal development.

5.4.1 Incomplete/Absent Puberty

Puberty is deemed absent when there is lack of development of secondary sexual characteristics by age of 14 years. This syndrome of impaired gonadal function is termed ‘hypogonadism’. Features of adrenarche do not indicate pubertal development. Hypogonadism can be classified as hypergonadotropic (primary) or hypogonadotropic (secondary).

Aspects relating to hypergonadotropic hypogonadism are covered elsewhere in this book.

Hypogonadotropic (secondary) hypogonadism involves failure of the HPG axis, typically, a pituitary or hypothalamic problem (some texts will refer to hypothalamic hypogonadism as ‘tertiary’). It is termed ‘hypogonadotropic hypogonadism’, due to the failure of hypothalamic production of GnRH or failure of pituitary production of LH and FSH.

Hypogonadotropic hypogonadism can be divided into functional, congenital or acquired types.

5.5 Functional Hypogonadotropic Hypogonadism

The term functional hypogonadotropic hypogonadism is particularly used to describe pubertal delay or arrest that is induced by chronic disease or stress. Psychosocial deprivation, intense exercise, anorexia and malnutrition are all linked to hypogonadotropic hypogonadism. This is thought to be an adaptive mechanism to prevent reproduction in suboptimal circumstances.

5.5.1 Nutritional Hypogonadotropic Hypogonadism

Puberty is an energy-demanding period of development, requiring sufficient calorie intake. During puberty, there is significant weight gain. Approximately 50% of adult body weight is gained during adolescence (average 9 kg/year), with peak weight velocity in males occurring at about the same time as peak height velocity. Under the influence of testosterone and growth hormone there are associated changes in the body composition and relative proportions of water, fat and bone [9].

The metabolic control of puberty is determined by the action of different central neurotransmitters and peripheral hormones. These sense the metabolic state of the individual and interact with the hypothalamic GnRH neurons. Studies have

confirmed the importance of leptin (an adipose hormone) in a permissive regulatory role in puberty. Leptin is secreted from adipocytes proportionally to the body fat content. Leptin levels fall dramatically in conditions of starvation. There are also interactions with kisspeptin (from the Kiss 1 Gene). Kisspeptin is an upstream regulator of GnRH [10]. Increases in kisspeptin have been shown to increase GnRH, which subsequently leads to increased LH pulsatility, thus triggering puberty [11, 12]. Figure 5.2 illustrates some of the hormonal interplay between puberty and nutrition [13]. There is compelling evidence from animal models that there are changes in kisspeptin expression in response to a negative energy balance (calorie restriction). In most studies, there was a reduction in KISS1 expression in response to calorie restriction/starvation [14]. This translates clinically to delayed or arrested puberty, as seen in malnutrition (undernutrition), anorexia nervosa, chronic illness with malabsorption or excessive exercise without matched calorie intake.

Calorie deficit due to poverty-related malnutrition is relatively uncommon in the developed world. The United Kingdom (UK) government does not routinely collect data on food poverty, and this has been largely left to the charitable sectors. According to recent international data, more children in the United Kingdom (10%) live in severe food insecurity compared with other countries in Europe, where the

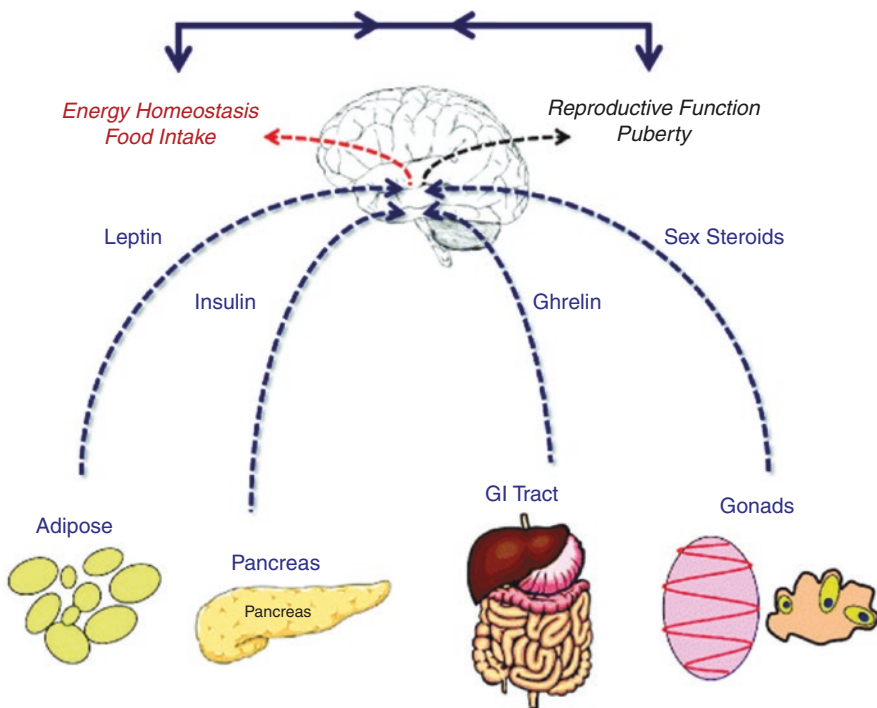


Fig. 5.2 Hormonal interplay between puberty and nutrition (Kisspeptin Signaling in Reproductive Biology (2013) Springer publications)

average is 4% [15]. It is unlikely that many endocrinologists will routinely manage children with hypogonadotropic hypogonadism due to malnutrition secondary to poverty.

Many chronic illnesses are associated with malnutrition, through reduced food absorption or an increased catabolic state. Examples include Crohn's disease, cystic fibrosis, cardiac failure, and coeliac disease - which is often under diagnosed and under-treated. The negative energy balance will result in a delayed pathophysiology similar to malnutrition.

Eating disorders (EDs) are historically considered to predominantly affect females; however, epidemiological studies indicate that males are also at risk of developing EDs. A recent report from 2018 quoted ED rates of 1.2% and 2.2% in Canadian and Australian adolescent males, respectively, and 1.2% in young adult Dutch men [16]. These values are likely to be underestimates as most boys and men will under-report symptoms of EDs. EDs which result in calorie deficit, e.g. anorexia nervosa and bulimia nervosa, typically cause functional hypogonadotropic hypogonadism. Puberty has frequently been identified as a time of risk for developing EDs. Sex steroids, in particular, appear to have a role in unmasking genetic risks for developing EDs, although this phenomenon is more apparent in girls than boys [17, 18].

Excessive exercise can have a role in both the development and maintenance of a number of EDs and is most frequently seen in people with anorexia nervosa as a way of purging calories. It is also often used as a way to manage mood or affect in people with EDs, either to help produce a positive mood state or to help avoid a negative mood state related to not exercising. Reports show that excessive exercise is frequently one of the most persistent symptoms of EDs, often interfering with recovery [19]. It is important to note that excessive exercise can also occur in a non-pathological state, e.g. long-distance or marathon runners, scholastic wrestling, dancers and gymnasts. These sports emphasise strict weight control and high-energy output and predispose to functional hypogonadotropic hypogonadism [9].

Contrastingly, it is interesting to note that energy excess such as that seen in obesity or the metabolic syndrome is also associated with functional hypogonadotropic hypogonadism [20, 21]. In obese adolescent boys, serum testosterone concentrations were reported to be up to 40–50% lower than matched normal BMI peers [22].

5.5.2 Psychosocial Factors

Stress and/or depression are known to cause functional hypogonadotropic hypogonadism, and this is likely to be hypothalamic in origin. Research has shown that high levels of corticotrophin-releasing hormone (CRH) have a direct inhibitory action on the kisspeptin system. Other studies have shown that at the time of puberty there is a reduction in CRH activity and blockade of CRH actions in the brain; with anti-CRF drugs stimulating earlier puberty. This would account for why puberty is delayed in people who are chronically stressed. More recent research is focusing on

the role of the amygdala -which is already known to regulate emotion, enhance the stress response, and control anxiety [23].

5.5.3 Clinical Impact of Functional Hypogonadotropic Hypogonadism

As described above, functional hypogonadotropic hypogonadism can cause an overall delay in growth and puberty. In addition, the underlying cause of the calorie deficit, e.g. malnutrition or malabsorption, may also result in other disorders, for example, anaemia, osteopenia and/or deficiencies of minerals, vitamins, essential fatty acids and amino acids and trace elements.

Delayed puberty/growth can lead to emotional and psychological dysfunction and reduced educational attainments. Bullying and victimisation can result in increased depression and anxiety [24]. Reports also show that boys with a history of delayed puberty have a greater risk for metabolic and cardiovascular disorders [25].

5.5.4 Assessment of Suspected Functional Hypogonadotropic Hypogonadism

Investigation will be guided by the history and examination findings, but a basic structure to follow is outlined in Table 5.1.

5.5.5 Management of Functional Hypogonadotropic Hypogonadism

Efforts should be made to address the underlying cause of the functional hypogonadotropic hypogonadism. In most cases, these causes are reversible, and puberty should commence/continue once the underlying issue is resolved.

It is also important to ensure that clear explanations of the conditions and risks are given to both the patient and the family. Clinicians should ensure the child has adequate support to meet their psychological needs. These may extend to concerns

Table 5.1 Assessment and investigation of suspected functional hypogonadotropic hypogonadism

History	Examination	Investigations
Presenting complaint	Height	Bone age assessment
Diet	Weight	LH
Exercise	BMI	FSH
Social circumstances	General system examination	Testosterone
Past medical history	Appropriate endocrine	<u>Second line as needed:</u>
Medication history	assessment, e.g. thyroid	Renal, liver, bone profile
Family history of illnesses/puberty	Pubertal assessment and staging	Thyroid function, prolactin, Full blood count, ESR, CRP, coeliac screen

Table 5.2 Causes of congenital and acquired hypogonadotropic hypogonadism

Congenital
<u>Isolated GnRH deficiency</u>
Kallmann syndrome (with anosmia)
Without anosmia
<u>GnRH deficiency associated with obesity and/or mental retardation</u>
Prader-Willi syndrome
Laurence-Moon-Biedl syndrome
<u>Idiopathic hypogonadotropic hypogonadism</u>
Acquired
<u>Tumours</u>
Craniopharyngiomas
Pituitary adenomas and cysts
Germinomas, gliomas, meningiomas, astrocytomas
Pituitary apoplexy
<u>Infiltrative disease</u>
Granulomatous disease
Histiocytosis
Haemochromatosis
<u>Drugs</u>
Anabolic steroids
Opiates
Marijuana
<u>Iatrogenic</u>
Post-surgery
Post-radiotherapy

relating to personal identity, psychosexual development and future fertility. In some cases, testosterone therapy may be required, as discussed in the management section. Quite often this group of patients may need to have an ongoing input beyond the paediatric age cut-off (usually 16 years in most institutions). These young and emerging adults should be seen in an endocrine transition clinic, ideally with input from both paediatric and adult endocrine teams [24].

We will now consider causes of congenital and acquired hypogonadotropic hypogonadism. These have been summarised in Table 5.2.

5.6 Congenital Hypogonadotropic Hypogonadism

Congenital pituitary abnormalities, causing gland hypoplasia or aplasia, often affect multiple hormones, which may have presented earlier in life. There are also ‘migration disorders’ resulting from abnormal migration of GnRH neurons during embryonic development. In normal development, GnRH neurons are derived from the olfactory placode. Several genes may be implicated in disrupting this migration and subsequent adhesion. Therefore, congenital hypogonadotropic hypogonadism may be linked to anosmia (lack of sense of smell). In this case, it is defined as Kallmann syndrome [26]. Associated features of Kallmann syndrome include cleft lip/palate, sensorineural deafness and cerebellar ataxia. As there are several implicated genes,

there are several modes of inheritance: X-linked recessive, autosomal dominant and autosomal recessive.

Other congenital syndromes may also affect the HPG axis, resulting in hypogonadotropic hypogonadism. Prader-Willi syndrome is a complex genetic condition affecting hypothalamic function, muscle tone and cognitive development. Bardet Biedl syndrome is another multifaceted genetic condition linked to HPG axis dysfunction, as well as retinal, renal, limb and cognitive abnormalities. Rarely, there are specific hypothalamic receptor abnormalities that lead to failure of GnRH secretion. Other genetic causes of isolated GnRH deficiency occur with a wide spectrum of clinical presentation ranging from microphallus and cryptorchidism in the neonatal period to delayed or arrested puberty in adolescence [27]. The diagnosis is confirmed biochemically followed by imaging to confirm normal appearance of the hypothalamus and pituitary on MRI. The main differential diagnosis is with CDGP and can be very challenging to differentiate. Unless there are clear associated features such as anosmia or prior genetic testing, the diagnosis can be difficult to determine until the individual is at least 18 years.

5.7 Acquired Hypogonadotropic Hypogonadism

Acquired hypogonadotropic hypogonadism is often secondary to structural central nervous system lesions such as pituitary adenoma, craniopharyngioma or autoimmune hypophysitis. Radiotherapy to the head is an iatrogenic cause of secondary hypogonadism.

5.7.1 Pituitary Tumours

Pituitary tumours can be classified as intrasellar and suprasellar, with the former being largely made up of (>90%) pituitary adenomas. The latter is mostly represented by disorders in embryogenesis such as craniopharyngioma, germinoma and dermoid and epidermoid cysts. Neoplastic and infiltrative processes can also occur including gliomas, meningiomas, germ cell tumours arising from the pituitary stalk, granulomatous disease including sarcoidosis and histiocytosis (see Table 5.1) and the iron deposition disorder, haemochromatosis. Craniopharyngiomas are the most common cause of hypopituitarism in childhood. Adenomas are the most common cause of the pituitary lesions to present in childhood and adolescence.

Craniopharyngiomas arise from squamous rest cells in the remnant of Rathke's pouch between the adenohypophysis and neurohypophysis. They are rare with an annual incidence of 0.5–2 per million; however 30–50% of cases are present in childhood and adolescence and account for 1–4% childhood intracranial tumours [28, 29]. Although they are histologically benign, their papillae or cysts may invade and compress local structures.

Craniopharyngiomas commonly present with the neurological symptoms of headache and visual field defects coupled with manifestations of endocrine

deficiency such as stunted growth and delayed puberty. At diagnosis GH is the most common axis deficiency (75%), followed by FSH and LH (40%) and then ACTH and TSH deficiency (25%). Posterior pituitary deficit in the form of diabetes insipidus is less common (17%) [30]. In a child presenting with delayed puberty and gonadotrophin deficiency combined with short stature, headache and visual disturbance, craniopharyngioma would be high on the list of differentials. Diagnosis is made with gadolinium-enhanced MRI, although CT may also be used and is specifically useful for identifying calcification in association with craniopharyngiomas. Surgery is the mainstay of treatment and is increasingly a balanced approach between aiming for total resection and also achieving optimal functional outcome. Radiotherapy is also used where significant residual remains post-operatively and risk of recurrence deemed high. Recent identification of the BRAFV600E mutation in papillary craniopharyngiomas has led to trials of combination therapy with BRAF and MEK inhibitors and subsequent therapeutic response reported [31, 32], giving potential for other adjuvant therapy options in the future.

Pituitary adenomas are a relatively rare cause of hypogonadotropic hypogonadism in childhood, with an estimated average annual incidence of 0.1/million children [33]. Prolactinoma is the most frequent adenoma cell type in children, followed by corticotrophs and somatotrophs [34]. Non-functioning adenomas, TSH- and gonadotrophin-secreting adenomas are very rare, accounting for only 3–6% of all pituitary tumours in children. Diagnosis of functioning (hormone-secreting) pituitary adenomas is usually clinical with confirmation of the lesion on contrast MRI and identification of co-existing pituitary dysfunction with biochemistry. Prolactinomas tend to present in the peripubertal age group with deficiency of the pituitary-gonadal axis. This manifests as menstrual irregularities in girls and gynaecomastia and delayed puberty in boys. Large adenomas show a predominance of neurological symptoms.

Prolactinomas may cause hypogonadotropic hypogonadism due to compression of the pituitary gonadotrophs; however they also lead to secondary hypogonadism due to the suppressive effect of hyperprolactinaemia. Both normalisation of prolactin levels and reduction in size of the prolactinoma usually occur on treatment with dopamine agonist therapy. Other pituitary adenomas are likely to be large, causing structural sequelae in the form of headache and visual field disturbance as well as the hypopituitarism. First-line treatment for other functioning pituitary adenomas and non-functioning adenomas is trans-sphenoidal adenomectomy. Adjuvant somatostatin analogue therapy and radiotherapy are options when surgery is non-curative.

5.7.2 Pubertal Effects of Treatment for Childhood Malignancies

The 5-year survival in childhood and adolescent cancers is now in excess of 80%. It is estimated that 1 in 1000 young adults in the United Kingdom is a childhood cancer survivor [35]. This impressive statistic has brought with it the long-term endocrine effects of the treatment for childhood cancer.

Cranial radiotherapy involving the pituitary and hypothalamus commonly results in long-term dysfunction in gonadotrophin secretion—hypogonadotropic hypogonadism. The effect of radiotherapy on any organ is dictated by the dose of radiotherapy, fraction size, number of fractions, modality of the radiotherapy and the time since exposure [36]. As a result, the radiotherapy dose is generally divided into small pulses given successively over time to reduce the damage to healthy tissues adjacent to the abnormal lesion. The endocrine consequences of radiotherapy take time to develop and increase with time from exposure.

Proton beam radiotherapy has been used increasingly frequently over the past decade. This modality focuses the radiotherapy onto a smaller area with less scatter to neighbouring tissues, aiming to reduce damage to healthy tissues. The long-term outcomes of proton beam versus conventional radiotherapy will become clearer with time. These factors, along with the age of the individual, may lead to absent pubertal development, pubertal arrest or later disruption in gonadal and sexual function. The smaller the radiation dose, the later these effects of cranial radiotherapy are generally seen. Conversely, radiotherapy to the hypothalamus may initially be associated with precocious pubertal development as the hypothalamic ‘break’ is removed, allowing inappropriate activation of the hypothalamic-pituitary pathway and initiating puberty at a younger age than normal [37].

Testicular radiotherapy and chemotherapy treatments can result in hypergonadotropic hypogonadism, due to generalised gonadal damage. This area is discussed elsewhere in this book.

5.8 Management of Hypogonadotropic Hypogonadism

In constitutional delay, treatment is not generally necessary, and often reassurance, understanding and regular review are sufficient. However, due to the distress, treatment may be initiated to induce puberty [38]. Careful consideration is required, as if started at too young an age, treatment may affect final height achieved. Treatment may be initiated after 14 years of age.

For those with permanent hypogonadotropic hypogonadism, treatment needs to continue into adult life. The main aim is start at a low dose with slow increments over a 2–3 year period to mimic testosterone levels during natural pubertal development [39]. This is slowly increased over 2–3 years to an adult dose.

In pubertal arrest, an appropriate dose of intramuscular testosterone can be initiated depending on the stage of puberty completed prior to the pubertal arrest.

5.9 Pubertal Induction

5.9.1 Testosterone Esters

In general, puberty is induced with testosterone esters which are given by deep IM (intramuscular) injection.

1. For constitutional delay of puberty:
 - (a) Start testosterone 50 mg every 4 weeks by IM injection for 6 months.
 - (b) At the end of this period, if testicular volume has increased, this suggests that spontaneous puberty has begun and treatment can be stopped.
 - (c) If testicular volume is <8 mL, then growth may slow on stopping testosterone. If height velocity rather than pubertal progression is the major issue, then consider a further 6-month treatment of 50 mg testosterone every 4 weeks.
 - (d) If no progression in testicular volume, consider continuing 50 mg of the testosterone every 4 weeks for further 6 months. Cases should be discussed individually in the post-clinic meeting.
2. For induction of puberty (not constitutional delay):
 - (a) Testosterone should be commenced at a low dose of 50 mg every 4 weeks. (Consider starting earlier at 12 years and using lower doses/slower progression in boys with bilateral anorchia.)
 - (b) The dose is then gradually increased over 2–3 years to maintain a normal pace of pubertal development until the full adult dose is reached. After 6 months, consider increasing to 100 mg testosterone every 4 weeks, for further 6 months, then increase to 150 mg for 6 months and then 200 mg for further 6 months and then increase to the adult dose of 250 mg given every 4 weeks. A lower dose may be needed in smaller individuals.

5.9.2 Other Options

Intramuscular testosterone remains the most popular method of pubertal induction in the United Kingdom, but recent studies have indicated a role for other preparations of testosterone such as transdermal gels or oral preparations [40].

1. Oral testosterone undecanoate has been used to initiate puberty and is licensed but not commonly used due to variable absorption and hepatic first pass metabolism leading to variable drug levels. The fluctuating levels between doses lead to symptomatic variations and prevent true physiological simulation, making it less reliable for pubertal induction. The usual starting dose is 40 mg on alternate days, increasing to 40 mg a day after 6–8 months (or according to response), then to 80 mg once daily for further 6–8 months and finally up to a maximum of 120 mg daily. Oral testosterone has a short half-life and must be taken with food for satisfactory absorption and has a tendency to be 5 α -reduced to dihydrotestosterone (DHT) in the gut.
2. Transdermal testosterone can also be considered. Transdermal gels are currently unlicensed in the United Kingdom for pubertal induction, and dosing regimens have been extrapolated from adult data. Topical gel can be applied to the skin and is available in a metered-dose pump. A usual starting dose is one press of the canister piston which delivers 0.5 g of gel containing 10 mg testosterone. This

can be increased by one press every 6 months. The dose can be applied to the abdomen (entire dose over an area of at least 10 by 30 cm) or to *both* inner thighs (one half of the dose over an area of at least 10 by 15 cm for each inner thigh). The gel should be applied to clean, dry, intact skin. It should be rubbed in gently with one finger until dry, and then the application site should be covered, preferably with loose clothing. Hands should then be washed with soap and water. Daily rotation between the abdomen and inner thighs is recommended to minimise application site reactions. Transfer of the gel to the skin of children and women should be avoided.

3. Implanted testosterone is available for adult androgen deficiency but is not used for induction of puberty.
4. Lifelong testosterone substitution can be via the IM route or transdermal. Once patients have been stabilised on the adult dose of testosterone for a while then, consider changing to 3 weekly, and then they can be converted to long-acting intramuscular testosterone undecanoate, 1 g IM given every 12 weeks. Prior to the second dose, pre-dose bloods can be requested to include FBC (full blood count) with haematocrit, testosterone and prostatic-specific antigen (PSA). If the transdermal route is preferred, change to testosterone sachets 5 mL sachet daily (=50 mg) or testosterone gel 6 metered doses daily (=60 mg).
5. HCG/FSH. Although physiologically potent, HCG and FSH are not routinely used in induction of puberty because they are time-consuming and expensive and require multiple injections. They will likely be ineffective in the case of gonadal damage. Where used, they are initiated after commencing testosterone treatment. FSH is initiated first at 150 i.u. 3 times a week by subcutaneous injection. Two to three months later, HCG is started at 1500 I.U. twice a week by subcutaneous injection, and the testosterone supplementation then stopped. The dose of HCG is then titrated against physiological testosterone production to maintain normal testosterone levels. Generally these are limited to use in clinical research protocols and in adult fertility clinics for stimulating spermatogenesis in males with hypogonadotropic hypogonadism.

5.9.3 Side Effects

Occasionally boys commencing on testosterone may become moody and slightly aggressive. Injected testosterone may result in fluctuating mood, energy level and libido caused by testosterone levels that rise rapidly upon injection and then fall too low before the next dose. Too rapid an increase in dose may result in premature fusion of the epiphyses.

In adult life, testosterone replacement is sufficient to maintain normal sexual function, but if fertility is desired, gonadotrophins or pulsatile GnRH is used. Further description of fertility induction is outside the scope of this chapter.

5.10 Conclusion

Puberty is an important transitional period in a young person's life. We have summarised the normal physiology of puberty and when puberty is delayed this can be constitutional, functional or pathological. We have discussed the investigations and management strategies above, and therapeutic protocols will depend on the specific cause.

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