Male Puberty

14

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Learning Objectives

- Age at onset of puberty
- Physiology
- Nutritional factors
- Physical and hormonal changes
- Delayed puberty
- Precocious puberty
- Endocrine disruptors and puberty

14.1 Introduction

The term "puberty" is derived from the Latin word *pubescere*, which means "to reach physical maturity, growth of body hair, and attain manhood." Puberty represents the stage of transition from the sexually immature child to the potentially fertile adolescent. Over the last few decades, advances in biochemistry, physiology, and hormone assay techniques have helped in elucidating the complex processes involved in the initiation and progression of pubertal development.

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A. Kumar, M. Sharma (eds.), *Basics of Human Andrology*,
DOI 10.1007/978-981-10-3695-8_14

14.2 Age at Onset of Puberty in Males and Secular Trend

Timing of puberty is affected by genetic as well as environmental factors. Fetal nutrition, childhood dietary habits, obesity, and physical activity have a bearing on age of onset of puberty. Though age of attainment of menarche in girls has declined over the past decades, such secular trend has not been well documented for boys. In the USA, the median age at puberty in boys as per the National Health and Nutrition Examination Survey (NHANES III), from 1988 to 1994, is reported to be 10.1 years in Caucasian Americans and 9.3 years in African Americans, which is lower than that reported previously as 11.9 years (Reynolds and Wines 1951; Tanner and Davies 1985; Herman-Giddens et al. 2001; Karpati et al. 2002; Sun et al. 2002). Boys in more recent surveys are taller at younger ages and attain mature height earlier than in the past, indirectly suggesting advancement in the age of puberty (Herman-Giddens et al. 2001; Karpati et al. 2002).

14.3 The Hypothalamic–Pituitary–Gonadal Axis

The hypothalamus secretes gonadotropin-releasing hormone (GnRH) which stimulates the release of the gonadotropins – luteinizing hormone (LH) and follicle-stimulating hormone (FSH) – from the anterior pituitary, resulting in release of testosterone from testes (see Fig. 14.1).

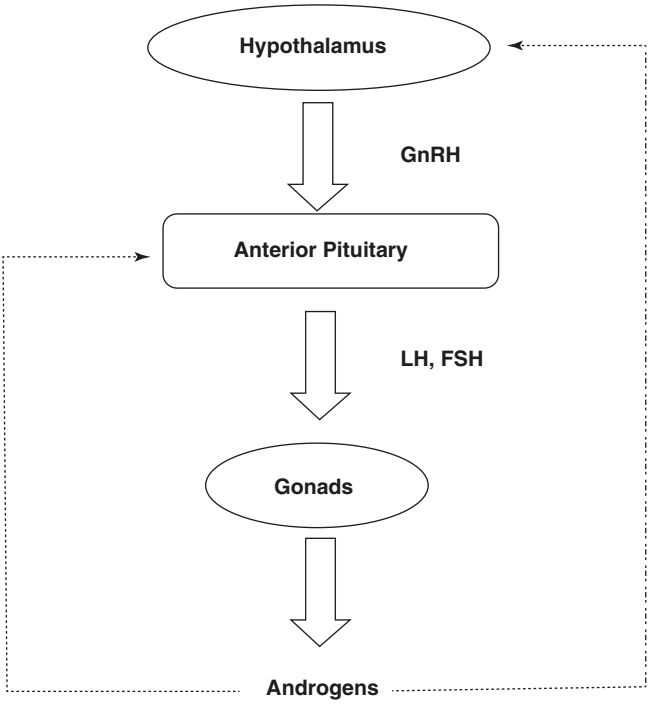


Fig. 14.1 The hypothalamic–pituitary–gonadal axis. *GnRH* gonadotropin-releasing hormone, *LH* luteinizing hormone, *FSH* follicle-stimulating hormone

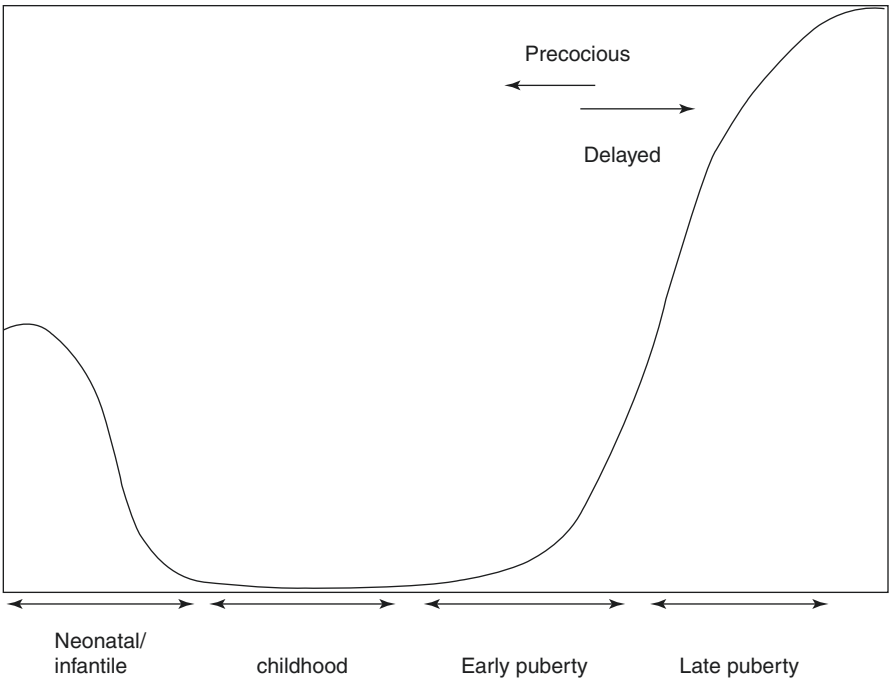


Fig. 14.2 The activity of gonadotropin-releasing hormone (GnRH) pulse generator during different phases of life

The pulsatile secretion of GnRH stimulates the production of LH and FSH, which stimulate the testes resulting in maturation of spermatogonia and increased secretion of testosterone. There is, in turn, a negative feedback loop as well, i.e., the gonadotropins inhibit the secretion of GnRH, and testosterone inhibits the release of gonadotropins as well as GnRH. The hypothalamic-pituitary-gonadal (HPG) axis is active in the fetal period, becomes quiescent by 7–9 months after birth, and remains so till the onset of puberty, when the GnRH pulse generator is reactivated – first during sleep and then during the day as well (see Fig. 14.2).

14.4 Physiology of Initiation of Puberty

The activation of the HPG axis at puberty is regulated by complex interactions among multiple neuronal pathways. The increased pulsatility of the GnRH secretion is central to initiation of puberty. GnRH release in the hypothalamus is controlled by excitatory/inhibitory amino acids, gamma aminobutyric acid (GABA)-ergic, and glutamatergic neurons, neurons responsive to leptin, kisspeptin, neuropeptide Y (NPY)-producing neurons, and prostaglandins (Mitsushima et al. 1994; Terasawa et al. 1999; Gottsch et al. 2004; Irwig et al. 2004). GABAergic neurons have inhibitory influence, restraining GnRH secretion during prepubertal period. However, the exact roles of glutamate and GABA in the initiation of puberty have not been elucidated. For example, no association of functional mutations or polymorphisms in GABA receptor gene with

idiopathic precocious puberty (PP) is observed (Brito et al. 2006). Similarly, association between age at onset of puberty and sequence variation or polymorphisms in GnRH and GnRH receptor (GnRHR) genes has not been established too (Sedlmeyer et al. 2005). The role of kisspeptin, protein encoded by the KISS1 gene (1q32-q41), has been demonstrated as a potent activator of GnRH neurons in animals and humans (Shahab et al. 2005; Plant et al. 2006). After identification of mutation in KISS1R gene encoding GPR54 and in families with isolated hypogonadotropic hypogonadism (HH) and constitutional delay of growth and puberty (CDGP), the role of kisspeptin and its receptor GPR54 in

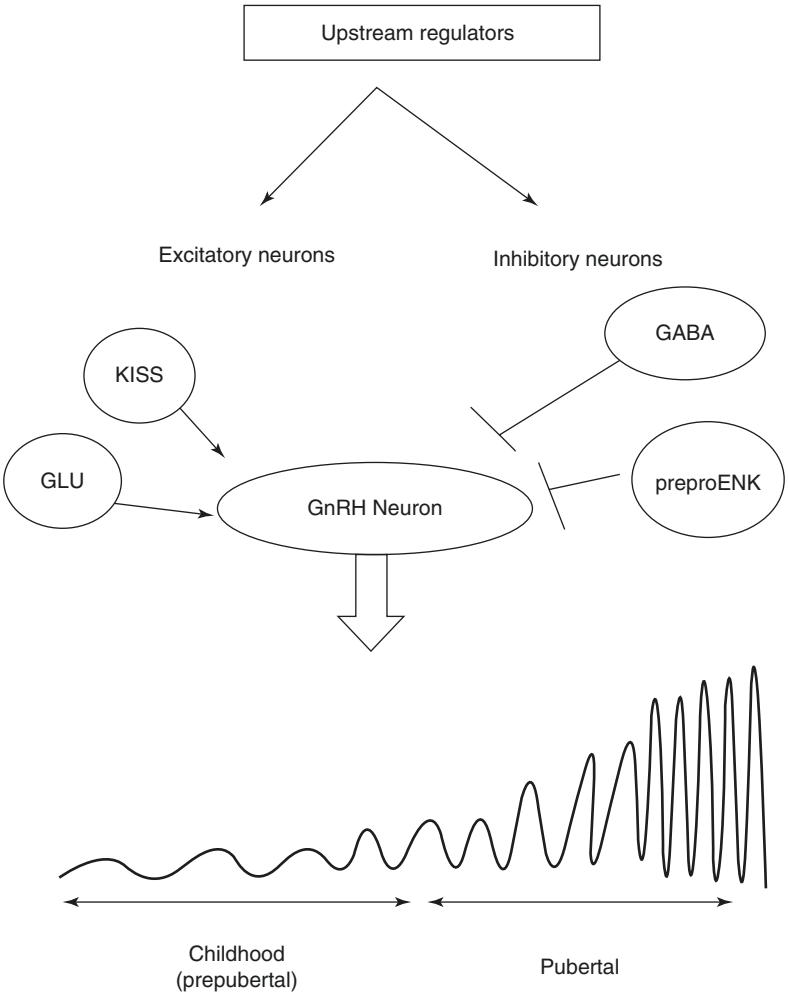


Fig. 14.3 Regulation of onset of puberty by the hypothalamic neurons. *GLU* glutamate, *GABA* gamma aminobutyric acid, *preproENK* preproenkephalin, *GnRH* gonadotropin-releasing hormone

regulation of onset of puberty has been studied in detail. Subsequently, identification of activating mutation in KISS1R gene in a patient with idiopathic precocious puberty (IPP) further confirms its role in puberty too. Though leptin does not affect GnRH secretion but is a permissive factor in onset and progression of mammalian puberty (Garcia et al. 2002; Quennell et al. 2009). A schematic representation of the regulation of onset of puberty by the hypothalamic neurons is shown in Fig. 14.3.

14.5 Role of Nutritional Factors in Timing of Puberty

Environmental factors play a major role in maturation of the HPG axis responsible for initiation of puberty. Pathological conditions, such as chronic illness, psychological distress, and intense physical training, delay pubertal maturation, whereas intracranial hamartoma, glioma, hydrocephalus, and low-dose cranial irradiation for malignancy are commonly associated with early or precocious puberty (Tahirovic 1998; Georgopoulos et al. 1999; Pozo and Argente 2002; Toogood 2004). Differences in timing of puberty in rural versus urban children and earlier maturation in improved health and nutrition condition favor a role for environmental factors (deMuinck et al. 2001).

In chronic childhood undernutrition, pubertal maturation and growth is delayed, in conjunction with lower levels of gonadotropins in blood (Satyanarayana and Naidu 1979; Kulim et al. 1984; Leensatra et al. 2005). Obesity has been shown to be associated with advanced pubertal development in many studies (Guo et al. 1997; Kindblom et al. 2006; Silventoinen et al. 2008). Gain in basal metabolic index (BMI) has been associated with early puberty. Although childhood growth rate is higher, but adult final height remains reduced because of poor height gain during growth spurt (He and Karlberg 2001).

Onset of puberty is often noted to occur at a younger age in children born small for gestational age due to intrauterine growth retardation (IUGR); however, those children with the absence of catch-up growth after birth mature late (Cooper et al. 1996). Rapid catch-up growth in infancy in IUGR children predisposes them to develop greater adiposity during later childhood (Lienhardt et al. 2002). The adiposity-related increase in leptin levels triggers earlier onset of puberty. Increased risk for advanced maturation has been documented in internationally adopted children with early malnutrition and subsequent catch-up growth after reaching new country with better nutrition (Proos et al. 1991; Ong et al. 2000).

In obesity, not only the levels of testosterone and estrogen are elevated, but the aromatization of androgens and bioavailability of sex steroids, secondary to low levels of sex hormone-binding globulin, increase as well. Adrenal gland function is also enhanced (Teilmann et al. 2006). The changes in hormonal milieu may contribute to earlier onset and/or accelerated tempo of maturation (deRidder et al. 1992). Early puberty in African American in comparison to Caucasian Americans may be explained partly by obesity as the mean body fat, as well as higher leptin levels in former population (Herman-Giddens et al. 1997; Biro et al. 2006). The secular

trends of early puberty in children with obesity are more marked in girls as compared to boys probably because of lack of definitive pubertal event such as menarche in girls (Kaplowitz et al. 2001).

14.6 Physical Changes of Puberty

The physical changes of puberty can be broadly divided into development of secondary sexual characteristics and changes in anthropometric measures (bone age, height, weight, and body fat).

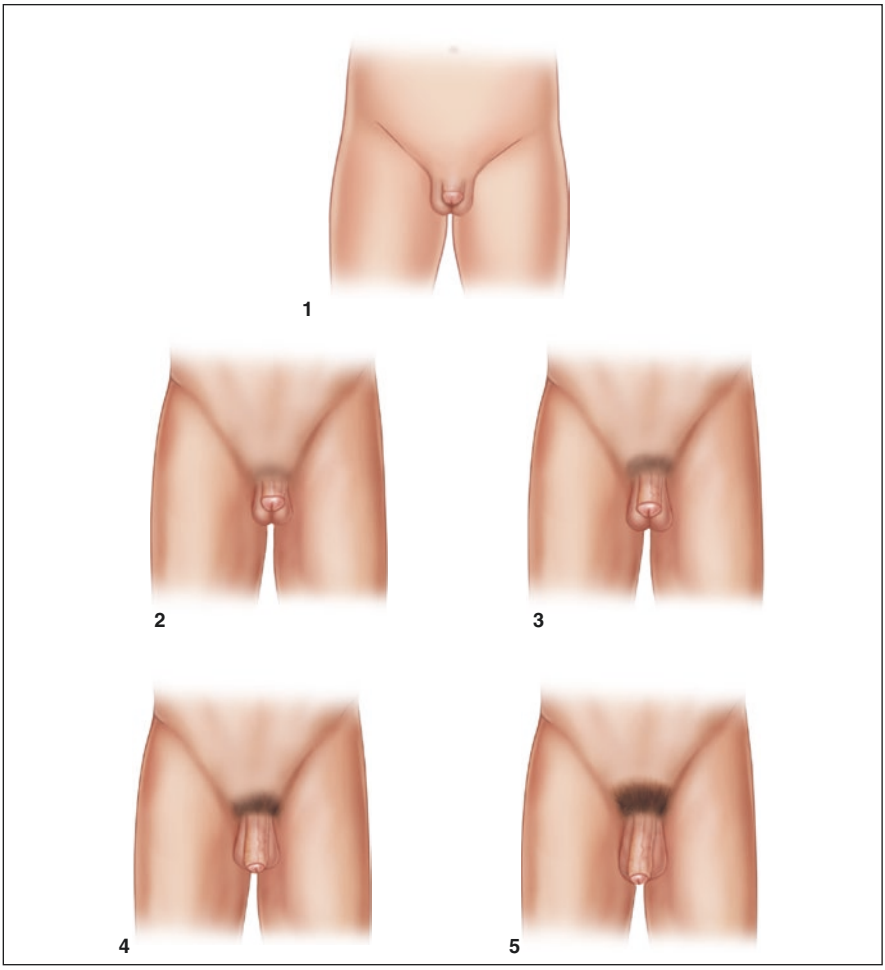
Secondary sexual characteristics are described using the five stages of development (Tanner et al. 1976). "Tanner stages" range from stage 1 (prepubertal) to stage 5 (postpubertal) and delineate the growth of pubic hair and genital development in boys. The Tanner staging or sexual maturity rating for boys is presented in Table 14.1 and illustrated in Fig. 14.4.

Increased testicular size is the first physical evidence of puberty. Pubertal testicular enlargement is considered to have begun when the longitudinal measurement of the testis is greater than 2.5 cm or volume $\geq$ 4 ml as assessed by orchidometer (see Fig. 14.5). This enlargement is predominantly due to increase in Sertoli cells and seminiferous tubules. The mean age of achieving a testicular volume of 4 ml has been reported to be 11.5–12 years in various studies (Tanner et al. 1976). Completion of genital development takes average time of 3 years (range 2–4.7 years) although testes reach adult volume over 5–7 years (Karlberg and Taranger 1976).

The phallus is more accurately measured in the stretched, flaccid state. The stretched penile length averages 6.2 cm in the prepubertal stage. During puberty it increases to 12.4 ± 2.7 cm (mean ± SE) in white adults, in black men the mean length is 14.6 cm, and in Asians it is 10.6 cm (Sutherland et al. 1996). There is gradual increase in male larynx and cricothyroid cartilage too resulting in change in quality of voice (Abbassi 1998).

Table 14.1 Tanner staging or sexual maturity rating in boys (Marshall and Tanner 1970)

Tanner staging: genitalia
G1: Penis and testis are of the same size during childhood; no scrotal thinning or reddening
G2: Enlargement of the testis to >4 ml; thinning and reddening of the scrotum
G3: Increase in penile length; further growth of testis and scrotum
G4: Further increase in penile length and width and darkening of the scrotal skin
G5: Adult size and configuration of genitalia
Tanner staging: pubic hair development
PH1: No pubic hair
PH2: Sparse long, slightly pigmented, downy hair, chiefly near the base of the penis
PH3: Darker, coarser, curly pubic hair joining sparsely in the midline over the symphysis pubis
PH4: Adult-type hair, but in a smaller area than in adults; no spread to the medial thighs
PH5: Adult-type hair in the classic inverse triangle distribution; might spread to the medial thighs



Stage 1: prepubertal with no pubic hair
Stage 2: Sparse light coloured hair at the base of penis, scrotal skin textured
Stage 3: pubic hair spread across public symphysis with increase in size of testis and scrotum, increase in penile length
Stagr 4: abundant pubic hair with curling, further, enlargemant of scrotum and testis, darkening of skin, increase in penile length and diameter as that of adult type
Stage 5: pubic hair extending up to medial aspect of thigh and umbilicus, scrotum and testis become adult size

Fig. 14.4 Tanner staging (Adapted and modified from Marshall and Tanner 1970)

Boys reach peak height velocity (PHV) approximately 2 years later than girls, at a mean age of 13.5 years (Delemarre-Van De Waal et al. 1991). PHV occurs at Tanner pubic hair stages 3 or 4 of puberty in most boys. The total height gain in boys during puberty averages 31 cm with mean difference between adult height in men and women being 12.5 cm (Boyar et al. 1974).

Fig. 14.5 Orchidometer

14.7 Hormonal Changes at Puberty

14.7.1 Gonadotropins

LH and FSH levels are low at birth but there occurs a surge in gonadotropins in early neonatal period termed as "mini puberty" before returning to the low level at which they stay till puberty. The onset of pubertal hormonal changes is marked by increase in pulsatile secretion of GnRH resulting in increased release of LH and increased frequency of LH pulses during sleep. As puberty progresses, GnRH pulse becomes more persistent throughout the day (August et al. 1972). LH causes increased sex hormone production by the testes, whereas spermatogonia maturation is stimulated by FSH**.**

14.7.2 Testosterone

Prepubertal boys have low plasma testosterone level (<0.3 nmol/l or 0.1 ng/ml), except during the first 3–5 months of life. Serum testosterone level is elevated only

during night time at onset of puberty. Sustained elevation of testosterone is detected in daytime when testicular volume becomes 4 ml and continues to increase thereafter during puberty (Knorr et al. 1974) with peak at stages 2 and 3 of puberty.

14.7.3 Estrogens

Estradiol levels are low in prepubertal stage and rise during puberty but decrease thereafter. Aromatization of testosterone and androstenedione is the predominant source of estradiol in males. This aromatized estradiol not only helps in skeletal maturation but also helps in acquisition of bone mass (Weinstein et al. 1974).

14.7.4 Adrenal Androgens

The plasma levels of dehydroepiandrosterone (DHEA) and its sulfated form (DHEAS) begin to increase by the age of 7–8 years and remain elevated till early adulthood. Though there is no sex difference in secretion of adrenal androgen in early stage puberty, but later on it is higher in males. In some children, pubic hair and axillary hair may develop without appearance of the other sexual maturation signs and symptoms. They may be associated with advanced bone age too. Dissociation of adrenarche and gonadarche is noticed in premature adrenarche and central/true precocious puberty (CPP; Sklar et al. 1980).

14.7.5 Growth Hormone

Serum growth hormone (GH) and insulin-like growth factor-1 (IGF-1) levels rise during puberty in both boys and girls (Veldhuis et al. 2000).

14.8 Delayed Puberty

Delayed puberty is defined as the absence of secondary sexual characters by the age of 14 years in boys. It is more common in boys as compared to girls with overall prevalence of 2.5% in adolescent children. The causes are classified into temporary delay, which is common, and permanent sexual infantilism, which can be hypogonadotropic–hypothalamic–pituitary in origin or hypergonadotropic testicular failure.

14.8.1 Temporary Delay

14.8.1.1 Constitutional Delay of Growth and Puberty

Constitutional delay of growth and puberty (CDGP) is the commonest cause of delayed puberty in boys. The patients have a delayed tempo of growth and development. Endocrine function is appropriate for the stage of physiological development, but not for chronological age. The typical boy with constitutional delay of puberty

presents at 14–15 years of age with complaints of being shorter compared to peers and lacking secondary sexual characters. Boys with CDGP present more commonly than girls probably because of higher psychosocial concern. They may have history of delayed puberty in siblings and other family members. Bone age, though delayed, usually correlates well with the stage of sexual maturation. Prognosis is good and final adult height remains unaffected.

14.8.1.2 Chronic Illness

Chronic illness may delay puberty by disturbing normal physiology or due to prolonged undernutrition. Long-term use of glucocorticoids, anticancer chemotherapy, or radiation therapy delays growth or sexual maturation. Adolescents with chronic conditions should be monitored for pubertal development. In milder conditions, reassurance is sufficient. However, pathologic causes of delayed puberty must be detected early and should be treated timely to attain catch-up growth. Hormone replacement with exogenous sex steroids may be considered. Nutritional rehabilitation is essential in children with malabsorption (e.g., inflammatory bowel disease, cystic fibrosis, celiac disease) causing delayed puberty. Children with chronic illness should be evaluated for other causes also if the primary disease fails to fully explain the delayed puberty.

14.8.1.3 Hypothyroidism

Thyroid hormone is essential for normal puberty. Thyroid hormone deficiency delays the onset and retards the progress of pubertal maturation by interfering with gonadotropin secretion.

14.8.1.4 Hyperprolactinemia

Hyperprolactinemia with or without a pituitary microadenoma or galactorrhea can delay the onset or progression of puberty.

14.8.2 Permanent Sexual Infantilism

14.8.2.1 Hypogonadotropic Hypogonadism

Delayed onset of puberty with low serum gonadotropin levels is defined as hypogonadotropic hypogonadism. It may be secondary to hypothalamus or pituitary dysfunction. The defect in gonadotropin secretion may be absolute or partial. It may be isolated deficiency or present in combination with deficiency of other pituitary hormones. Undescended testes and gynecomastia are commonly seen in these children. A list of some of the causes is given in the Table 14.2.

14.8.2.2 Isolated Gonadotropin Deficiency

Stature is normal till adolescence in patients with isolated gonadotropin deficiency. After reaching pubertal age, the deficiency of sex steroids leads to slowing of growth. However, growth continues beyond the usual age because of delayed epiphyseal fusion, so that the final height is normal or above normal. Body proportion is eunuchoid, i.e., limbs are longer, and the upper to lower body segment decreases (below 0.9).

Table 14.2 Causes of hypogonadotropic hypogonadism in males

Genetic: Kallmann syndrome, multiple pituitary hormone deficiency, isolated luteinizing hormone deficiency, X-linked adrenal hypoplasia congenital, Prader–Willi syndrome, Laurence–Moon–Bardet–Biedl syndrome
CNS tumors: germinoma, hypothalamic glioma, craniopharyngioma, etc.
Infiltrative diseases: Langerhans cell histiocytosis, sarcoidosis, hemochromatosis
Trauma: pituitary stalk transaction, skull fracture
Infection: tuberculosis, human immunodeficiency virus (HIV), fungus
Miscellaneous: chronic systemic illness, hypothyroidism, Cushing's disease, hyperprolactinemia, eating disorders, psychogenic disease

The commonest form of isolated gonadotropin deficiency is Kallmann syndrome. The clinical features consist of hyposmia or anosmia (from aplasia or hypoplasia of the olfactory lobes) associated with gonadotropin deficiency. Microphallus is present at birth in about 50% of the affected boys. Though most cases are sporadic but familial cases are also reported. It may have X-linked, autosomal dominant, or recessive inheritance with variable penetrance. There is heterogeneity of presentation. It is caused by mutations in the KAL gene, which is normally responsible for the typical pattern of migration of GnRH and olfactory neurons (Schwanzel-Fukuda and Pfaff 1989). Unilateral or bilateral absence of olfactory bulbs and sulci is noted on magnetic resonance imaging (MRI) in a majority of patients. Recently, mutations in other genes have also been implicated in Kallmann syndrome. These are FGFR1, prokineticin 2 (PROK2), and its receptor (PROKR2) genes (Dode et al. 2003, 2006).

Mutations in the GNRH gene (8p11.2-p21) have not been identified in humans, but a number of autosomal recessive mutations in the GNRHR are known to cause isolated hypogonadotropic hypogonadism (Layman et al. 1998).

14.8.2.3 Congenital or Acquired Hypopituitarism

Hypopituitarism is associated with deficiency of gonadotropin along with other pituitary hormones and can be congenital or secondary to other systemic illness. Isolated untreated GH deficiency also presents with delayed puberty, and till the achievement of pubertal bone age, it is difficult to determine whether gonadotropin deficiency is also present. Mutations in HESX-1 and PROP-1 genes, which lead to abnormal development of the pituitary, are associated with congenital hypopituitarism. Acquired causes of hypopituitarism include CNS tumors, commonest being craniopharyngioma, tuberculosis, trauma, and histiocytosis X. Hydrocephalus and cranial irradiation are conditions that may lead to either precocious or delayed puberty.

Syndromes such as Prader–Willi syndrome and Bardet–Biedl syndrome are also associated with hypogonadotropic hypogonadism.

14.8.2.4 Hypergonadotropic Hypogonadism

Bilateral testicular failure results in markedly elevated concentrations of serum gonadotropins, due to loss of feedback inhibition. The commonest cause of primary testicular failure is Klinefelter syndrome.

14.8.2.5 Klinefelter Syndrome

Males with Klinefelter syndrome usually have fibrotic testes and poorly developed external genitalia with gynecomastia. Because of the tall stature, children usually present late despite of delay in puberty onset. Borderline intellectual disability and behavioral difficulties are often present. Although genotype is typically 46 XXY, genetic variability and mosaicism also occur. Testes remain small with adult size of less than 6 ml. Though FSH, LH, and testosterone remain to be normal at beginning of puberty but as it progresses, testosterone tends to decline and FSH and LH levels increase.

14.8.2.6 Other Causes of Congenital Gonadal Failure

Noonan syndrome is caused by delayed sexual maturation, cryptorchidism, testicular atrophy, or anorchia. "Vanishing testes syndrome" is characterized by 46 XY karyotype and presents as delayed puberty with the absence of the testis. They can present as male with unilateral nonpalpable testis or as isolated micropenis depending on the time of assault during sexual maturation in utero. Other rare causes of congenital gonadal failure include defects in steroid hormone synthesis such as cholesterol desmolase complex and 3-beta-hydroxysteroid dehydrogenase that usually present with ambiguous genitalia.

14.8.2.7 Acquired Causes of Gonadal Failure

Acquired forms of primary hypogonadism may have postinfectious, autoimmune, traumatic, or metabolic etiology. Mumps orchitis occurring during adolescence or adulthood can cause gonadal failure. It can also occur after long-term use of chemotherapy like cyclophosphamide, radiation therapy or surgery.

14.8.3 Principles of Diagnostic Evaluation

Evaluation of delayed puberty is undertaken if puberty has not begun, i.e., testicular size is <4 ml or 2.5 cm in longitudinal axis, after 14 years of age or there is pubertal arrest after initiation. Detailed history, including history of any chronic illness, medication, and pubertal timing of siblings should be asked. Detailed anthropometric evaluation should be done including height, weight, arm span and upper to lower segment ratio, in addition to BMI. The presence of any dysmorphic features should be carefully noticed for syndromic association. Sexual maturation rating as given by Tanner should be done after detailed examination. Phallic length should be measured accurately. Other secondary sexual characteristics including facial and body hair, acne, and voice quality should be noted. The presence of gynecomastia should be noted as it may be indicative of prolactinoma or Klinefelter syndrome.

Diagnostic investigations are guided by the clues from history and examination. X-ray for bone age is useful as it correlates best with pubertal staging. Measurement of serum gonadotropins – LH, FSH, and testosterone – should be done, to differentiate between hyper- and hypogonadotropic hypogonadism. Complete blood count, renal function, liver function, and thyroid function test should be done to rule out associated systemic illness on the basis of clinical clues from history. If there is

short stature or poor growth velocity, screening IGF-1, followed by dynamic testing for GH levels, may also be suggested to rule out GH deficiency. Karyotype is suggested if clinical features are suggestive of Klinefelter syndrome. If CNS causes are suspected, MRI of the brain is indicated.

Since it is difficult to distinguish CDGP from permanent hypogonadotropic hypogonadism (HH) as both present with low levels of LH, FSH, and testosterone, longitudinal observation till 17–18 years of age is needed to resolve the issue. An early morning testosterone levels of >0.7 nmol/L (20 ng/dL) in a sensitive assay have been stated to indicate secondary sexual development over the next 12–15 months. The GnRH stimulation test using GnRH or GnRH agonist has very low diagnostic value in distinguishing CDGP from hypogonadotropic hypogonadism due to significant variability in response. A more robust response to GnRH is observed in CDGP, whereas very low, flat responses are seen in HH. GnRH stimulation test using buserelin has shown a positive predictive value of 89% in distinguishing HH from CDGP (Wilson et al. 2006). The increment in testosterone after human chorionic gonadotropin (hCG) stimulation test has been reported to be >9 nmol/L in CDGP, compared to <3 nmol/L in permanent hypogonadotropic hypogonadism (Degros et al. 2003). An algorithmic approach to evaluation of delayed puberty is shown in Fig. 14.6.

14.8.4 Management

The treatment depends on the diagnosis and whether the pubertal delay is temporary or permanent. In patients with CDGP, reassurance of attainment of puberty at a later age than usual is generally sufficient. However, if there is considerable psychological distress and parental anxiety for delayed puberty, low-dose testosterone may be administered for a short period. Usually, 100 mg of testosterone enanthate is given intramuscularly every 4 weeks for 3 months. This not only helps in growth spurt and development of secondary sexual characters but also primes for spontaneous puberty. Repeat course of monthly injection of testosterone can be tried if there is no spontaneous progression to puberty after initial treatment (Soliman and De Sanctis 2012).

Permanent hypogonadotropic hypogonadism is managed with intramuscular injections of testosterone every 4 weeks. The starting dose is 100 mg, initiated at the normal age of pubertal onset. The dose is increased to 200–300 mg, which is continued indefinitely. Dermal patches or androgen gel preparations can also be used in place of injectable testosterone. In boys with concomitant GH deficiency, testosterone is started at a later age in lower doses to maximize height gain before epiphyseal fusion.

14.9 Precocious Puberty

Puberty in boys is considered as precocious if secondary sexual characters appear before 9 years of age. Precocious puberty (PP) is much less common in boys than girls. PP may be gonadotropin dependent which can be central/true precocious puberty (CPP) or gonadotropin independent that can be pseudo- or peripheral

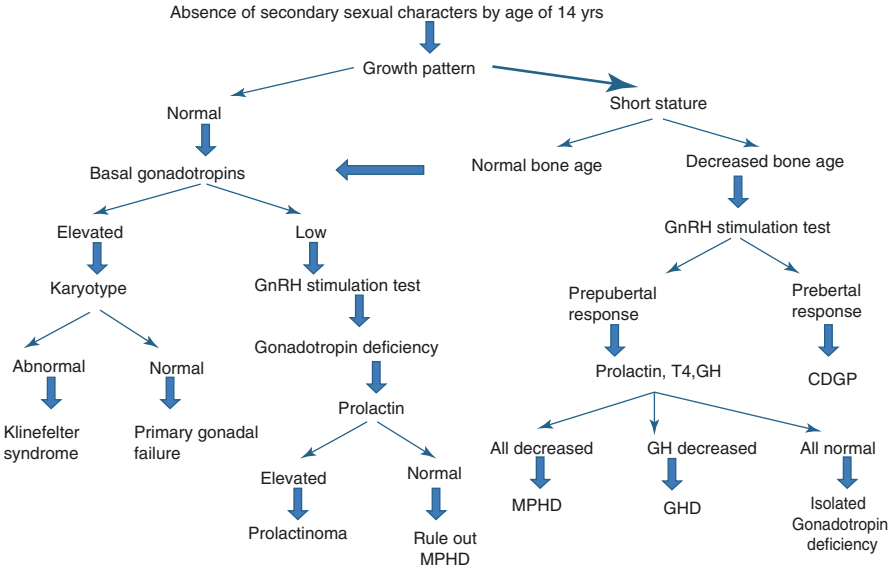


Fig. 14.6 Flowchart showing an approach to evaluate a boy with delayed puberty. *GnRH* gonadotropin-releasing hormone, *GHD* growth hormone deficiency, *CDGP* constitutional delay of growth and puberty, *MPHD* multiple pituitary hormone deficiency, *GH* growth hormone, *T4* thyroxine

precocious puberty (PPP). The HPG axis is active in central PP whereas there is no such activation of HPG axis in pseudo- or peripheral precocious puberty (Lee and Kerrigan 2004). The etiological classification of PP is given in Table 14.3.

14.9.1 Central/True Precocious Puberty (CPP)

Precocious activation of the HPG axis is defined as CPP. This condition is more common in girls as compared to boys. Boys with CPP have basal and GnRH-stimulated LH and testosterone levels as that in puberty but at an early age. Patients have features of puberty, such as development of sexual hair and other secondary sex characteristics, bilaterally symmetrical enlarged testes along with accelerated linear growth, and advanced bone age with early closure of epiphysis. Though the affected children are tall in childhood, but have a short final height as the epiphyseal fusion occurs early. Organic causes of CPP are more common in boys in comparison to girls. Hypothalamic hamartoma is the most common pathology seen in boys with CPP.

Hypothalamic hamartomas are nonneoplastic, tumor like lesions, composed of ectopic hypothalamic tissue, attached to the hypothalamus. These usually contain GnRH neurons, but in some tumors, transforming growth factor-alpha (TGF-α) may be found (Feuillan et al. 1999). Hamartomas are typically diagnosed by MRI. Some

Table 14.3 Causes of precocious puberty

1. Central/true precocious puberty (gonadotropin dependent)
(a) Idiopathic
(b) CNS abnormalities:
(i) Tumors: hypothalamic hamartoma, astrocytoma, craniopharyngioma
(ii) Infection: tuberculosis, abscess, encephalitis, trauma
(iii) Congenital malformation: hydrocephalus, arachnoid cyst
(iv) Others: cranial irradiation, chemotherapy
2. Pseudo- or peripheral precocious puberty (gonadotropin independent)
(a) Genetic: McCune–Albright syndrome
Familial testotoxicosis (activating mutation of LH receptor)
Congenital virilizing adrenal hyperplasia
(b) Tumors: Leydig cell tumor
Adrenal functional adenoma/carcinoma
CNS: chorioepithelioma
Hepatoma
(c) Others: primary hypothyroidism, iatrogenic
3. Combined (secondary) precocious puberty
(a) McCune–Albright syndrome
(b) Congenital adrenal hyperplasia

may present with gelastic – laughing/giggling – seizures that are resistant to anticonvulsant treatment. CPP due to hamartoma is usually diagnosed at an earlier age as compared to idiopathic and other organic etiologies. Medical management with GnRH agonists is the mainstay, although gamma knife surgery may be required in children with refractory seizures (Barajas et al. 2005). Figure 14.7 shows the MRI finding of hypothalamic hamartoma.

Other causes of CPP in boys include other CNS tumors such as glioma, pineal tumors, neurofibroma, astrocytoma, and rarely craniopharyngioma. History of cranial irradiation in children with malignancy, history of CNS infections such as tuberculosis, and other CNS conditions such as hydrocephalus are also associated with CPP. There may be associated GH deficiency in neurogenic CPP resulting in delayed rather than advanced bone age, as expected in precocious puberty.

Clinical photograph of a child with CPP due to neurofibromatosis type 1 is shown in Fig. 14.8.

Idiopathic CPP is a diagnosis of exclusion. With advances in the understanding of genetic determinants of pubertal onset, especially GPR54 receptor gene, its ligand kisspeptin, and GnRH receptor gene, the etiopathogenesis of more and more "idiopathic" cases is likely to be unraveled in the future.

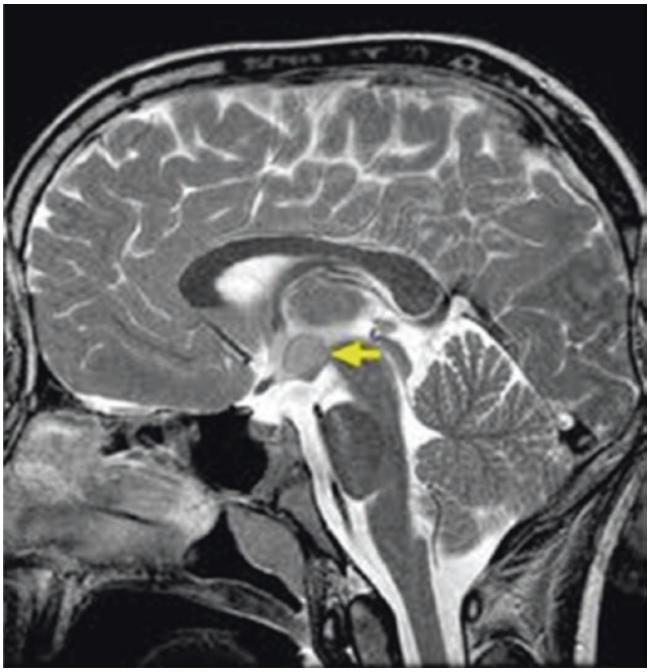


Fig. 14.7 Magnetic resonance imaging of brain, sagittal view showing hypothalamic hamartoma (*arrow*)

14.9.2 Pseudo- or Peripheral Precocious Puberty (PPP) or Gonadotropin-Independent Precocious Puberty

PPP accounts for up to 25% of all cases of precocious puberty in boys, whereas in girls PPP is very uncommon. The testosterone levels are usually in pubertal range, while gonadotropin levels are low and do not show a rise after stimulation with GnRH agonists.

Adrenal causes: Boys with simple virilizing type of congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency often present with precocious puberty. Usually, CAH is diagnosed late due to the absence of salt-wasting features in early infancy. Patients typically present with enlargement of the penis, and pubic hair development, without any enlargement of testes. Patients have tall stature for age with advanced bone age. Boys with inadequately treated CAH also present similarly. Some of these boys may develop secondary CPP as well with activation of HPG axis once the bone age is advanced to greater than 11–12 years.

CAH due to 11-β-hydroxylase deficiency may present with precocious puberty with hypertension. Children with adrenal tumors also present with pubic hair development and enlargement of the penis, in association with other features of adrenal excess, such as hirsutism, hypertension, and cushingoid facies.

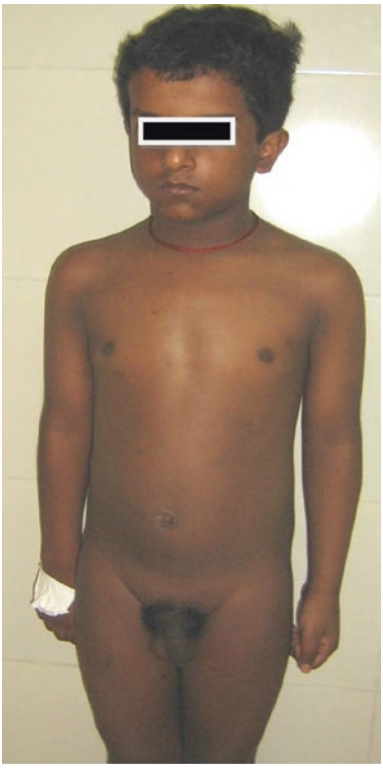


Fig. 14.8 Central/true precocious puberty in a 7-year-old boy with neurofibromatosis 1 (Note the muscular appearance and enlarged testis)

Familial testotoxicosis or male-limited gonadotropin-independent precocious puberty is an autosomal dominant inherited rare condition caused by activating mutations in the LH receptor. LH levels are low but testosterone levels are high, and there is symmetrical testicular enlargement with increased spermatogenesis, even though the HPG axis is not activated (Gondos et al. 1985).

Another cause of PPP in boys is hCG-secreting tumor and may be localized to organs other than gonads such as the liver, brain, or mediastinum. The α-subunit of hCG is identical to that of LH. Because of this similarity, hCG stimulates production of testosterone by Leydig cells resulting in testicular enlargement. Though the basal LH levels may be high due to cross-reactivity with hCG, but the response to GnRH is prepubertal. Serum alpha-fetoprotein (AFP) levels are usually elevated in patients with these tumors.

Conditions such as Leydig cell tumors and McCune–Albright syndrome are other rare causes of sexual precocity in boys.

14.9.3 Premature Adrenarche/Pubarche

Onset of sexual hair before the age of 9 years in boys, in the absence of development of other secondary sexual characters, is labeled as premature adrenarche/pubarche.

Premature adrenarche/pubarche is due to the increase of adrenal androgens as a result of increase in the activity of 17, 20 lyase, and 17 alpha hydroxylase enzymes. It may manifest only as a small increase in growth velocity in some children or as pubarche, i.e., development of genital and axillary hair. It requires close follow-up at regular intervals of 4–6 months as in some cases children with early adrenarche have early gonadarche as well.

14.9.4 Principles of Diagnostic Evaluation

Management of precocious puberty depends on identifying the underlying etiology. Detailed history and clinical examination is essential to establish an etiology. History includes information about the onset and progression of puberty and the presence of other secondary sexual characteristics. Family history of PP provides a clue in the diagnosis of familial testotoxicosis.

The presence of pubic hair and increase in penile size, in the absence of testicular enlargement, point toward adrenal etiology. Asymmetrical enlargement of the testis is more commonly seen in McCune–Albright syndrome and Leydig cell tumor cases, whereas symmetrical enlargement is observed in CPP, hCG-secreting tumors, and testotoxicosis. Children having only pubarche with normal bone age are considered normal variants and need to be followed-up. They have increased risk of having PP later on.

Baseline estimation of LH, FSH, testosterone, and DHEAS is essential in evaluation of precocious puberty, followed by GnRH or GnRH agonist stimulation test. On basal measurements, LH and FSH are suppressed in PPP cases, while pubertal level of LH is observed in CPP patients. Basal plasma testosterone is high in CPP as well as PPP, but the level is much higher in PPP. In GnRH stimulation test, single bolus of GnRH of 2.5 mcg/kg (maximum of 100 mcg) is administered followed by measurement of LH and FSH at 0, 30, and 60 min. For GnRH agonist stimulation test, leuprolide acetate 20 mcg/kg, to a maximum of 500 mcg, is administered intravenously, and LH and FSH are measured at 0, 60, 120, and 180 min. Only two measurements at 0 and 180 min may also be taken subsequently. The cutoffs for diagnosis of CPP vary according to the test protocol used. For the GnRH agonist test, a peak LH of >7 IU/L is generally considered as diagnostic of CPP (Partsch et al. 2002). The other endocrinological evaluations may include thyroid profile, basal and ACTH stimulated serum 17-hydroxyprogesterone level, serum hCG and α-fetoprotein measurement depending on the clinical signs.

Bone age analysis should be done in all cases of PP for advanced bone age. MRI for evaluating hypothalamus and pituitary should be performed in all boys with CPP. Other imaging investigations can be performed as guided by clinical and hormonal assays.

Approach to evaluation of precocious puberty in boys is given in Fig. 14.9.

14.9.5 Management

Boys with isolated adrenarche do not require any treatment, but regular follow-up is warranted. Hypothyroidism is treated with adequate dose of thyroxine. PP due to CAH

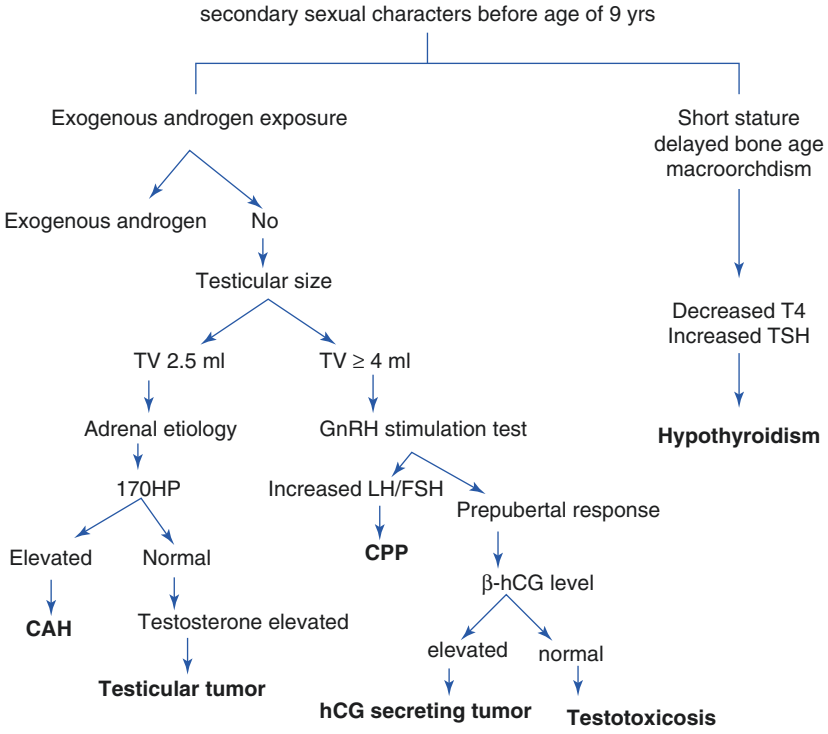


Fig. 14.9 Flowchart showing an approach to evaluate a boy with precocious puberty. *TV* testicular volume, *17OHP* 17-hydroxyprogesterone, *CAH* congenital adrenal hyperplasia. *β-hCG* beta human chorionic gonadotropin, *CPP* central/true precocious puberty, *GnRH* gonadotropin-releasing hormone, *T4* thyroxine, *LH* luteinizing hormone, *FSH* follicle-stimulating hormone, *TSH* thyroid-stimulating hormone

is managed with hydrocortisone and fludrocortisone. Though, there is no definite consensus regarding treatment for boys with CPP, but the decision is mostly based on the presence of psychological/behavioral concerns and prognosis regarding final height.

14.9.5.1 Central/True Precocious Puberty (CPP)

The treatment of choice for CPP is GnRH agonists. These are basically D-amino acid synthetic analogs with enhanced receptor occupancy. This results in receptor downregulation and suppression of the HPG axis in contrast to the physiological pulsatile exposure (Kaplan and Grumbach 1989). Depot preparations of GnRH agonists are given intramascularly on a once monthly or quarterly basis. The most commonly used preparations in our country are depot leuprolide acetate and depot triptorelin (Neely et al. 1992; Carel et al. 1995). Clinical response is assessed by monitoring pubertal stage, height velocity, and skeletal maturation. Plasma LH level < 2 IU/L, when measured 1 h after the dose of GnRH agonist depot, is also indication of adequate suppression. GnRH agonists are safe and well-tolerated drugs, but may have adverse effect of bone mineral accrual.

14.9.5.2 Pseudo- or Peripheral Precocious Puberty (PPP)

Treatment of PPP is difficult. Testolactone, spironolactone, ketoconazole, flutamide, cyproterone, and medroxyprogesterone are the available options used in various circumstances.

Treatment of PP with GnRH agonist should be discontinued when child has reached the usual age of puberty. The gonadotropin secretion is expected to resume within 4 months of stopping medication (Manasco et al. 1988).

14.10 Endocrine Disruptors and Puberty

Exogenous environmental chemicals that mimic or block the actions of endogenous hormones are known as endocrine disruptors (EnD; Rasier et al. 2008). EnD can be estrogenic, antiestrogenic, androgenic, antiandrogenic, or direct stimulant of GnRH production. They can alter hormonal signaling by targeting the hypothalamic–pituitary axis. EnDs with androgenic potential cause virilization phenotypes. EnDs with estrogenic activity can accelerate pubertal onset through kisspeptins, whereas those with antiandrogenic effects via suppression of testicular steroidogenesis and androgen receptor blockade cause delayed puberty. Dichlorodiphenyltrichloroethane (DDT), a commonly used pesticide, is an example of EnDs causing early puberty due to its estrogenic effect.

Key Questions

- Describe the environmental and nutritional factors influencing onset of puberty.
- At what age will you consider evaluation of a boy for delayed puberty?
- What are the causes of hyper- and hypogonadotropic hypogonadism?
- Write approach to a boy with precocious puberty.
- What are the treatment options for central/true precocious puberty in boys?

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