Disorders of puberty

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Abstract

Puberty is the process of development of adult secondary sexual characteristics. Disorders of puberty can be classified into early (precocious) and late (delayed) puberty. Early (precocious) puberty can be secondary to either activation of the hypothalamic-pituitary-gonadal axis (gonadotrophin-dependent, or central) or altered regulation of sex hormone production in the gonads, adrenals or other tissues (gonadotrophin-independent or peripheral). Delayed puberty is most often constitutional, but hypogonadotrophic (central) and hypergonadotrophic (peripheral) hypogonadism should be considered. In this article, we discuss the clinical and biochemical features of normal and abnormal puberty.

Keywords Constitutional delay of growth and puberty; gonadotrophins; hypogonadism; precocious puberty; premature adrenarche; puberty

Key points

- Normal timing of pubertal development is between 8 and 13.4 years of age in girls and 9 and 14 years in boys
- The first sign of pubertal development in girls is breast budding and a marked increase in height velocity. The first sign in boys is testicular enlargement to 3 ml or greater, with peak height velocity occurring only in the later stages of puberty
- Early (precocious) or delayed puberty can be caused by problems at the hypothalamic–pituitary level (central) or at the gonadal and adrenal level (peripheral)

Normal puberty

When approaching the abnormal, it is important to first appreciate what is normal. Puberty is the biological process of sexual maturation, which culminates in the ability to reproduce. In humans, age of onset is considered to be normal in girls after the age of 8 years, and in boys after the age of 9 years. In addition to the development of secondary sexual characteristics, growth velocity increases during puberty, and there are marked changes in body composition, with boys doubling their lean body mass. On average, from beginning to end, puberty lasts approximately 3–4 years, although there can be considerable interindividual variation in both the timing and tempo of puberty.

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The clinical features of puberty

In girls, the first sign of puberty is a marked increase in height velocity, in conjunction with breast budding. Menarche occurs, on average, 2 years after the onset of puberty (mean age 13 years). Pubic and axillary hair development is more variable, but occurs after breast budding in most girls.

In contrast, boys enter puberty later and do not reach their peak height velocity until the end of puberty. The first sign of puberty is an increase in testicular volume to 3 ml or greater (prepubertal testes are by definition <3 ml in volume), with subsequent development of pubic and axillary hair, associated genital enlargement and then voice breaking. In both girls and boys, acne and the adult body odour are common, with changes in mood and behaviour, but there is a large amount of variation between individuals.

The biochemistry of puberty

Sex hormone production is under the regulation of the hypothalamic-pituitary axis, with gonadotrophin-releasing hormone (GnRH) stimulating gonadotrophin secretion from the pituitary gland: luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Concentrations of these are high at birth, but then rapidly reduce and remain very low during childhood.

Around 2 years before the onset of puberty, pulsatile secretion of gonadotrophins recommences, followed by production of sex hormones from the gonads: oestradiol in girls, testosterone in boys (known as gonadarche). The regulation of this initiation is unknown, but it is clear there are permissive factors acting on the hypothalamic-pituitary axis, such as leptin. Human genetics studies have recently identified three new pathways that regulate GnRH release:

- kisspeptin, an important GnRH activating factor; mutations in its gene (*KISS1*) or its receptor gene (KISS1R) result in hypogonadotrophic hypogonadism

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- neurokinin B, which has similar characteristics and is thought to control kisspeptin release
- makorin ring finger protein 3, the first inhibitory factor of GnRH release. Mutations in its gene (*MKRN3*) have been found in families with central precocious puberty.[1]

In addition to gonadarche, approximately 18 months before the onset of central puberty, the zona reticulosa of the adrenal gland in both sexes enlarges (having been largely quiescent during childhood) and begins to release adrenal androgens. The biological significance of this is uncertain, but it is unique to higher primates and, in most children, is not associated with clinical manifestations.

Clinical assessment of puberty

This includes assessment, by Tanner staging, of breast, pubic and axillary hair development in girls, and assessment of testicular volumes (most accurately determined using an orchidometer) in boys, in addition to clinical assessment of penile enlargement and development of pubic and axillary hair (Figure 1).

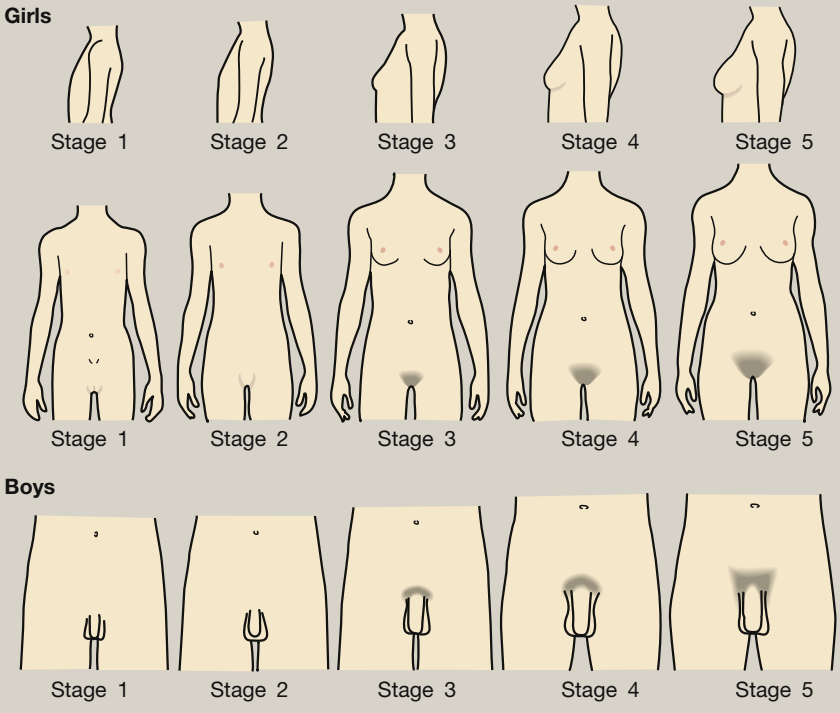
For biochemical assessment of puberty, as with other pituitary hormones, single measurements of gonadotrophins can be hard to interpret. Therefore a stimulation test, using a synthetic form of the hypothalamic hormone GnRH, is performed, particularly when early (precocious) puberty is suspected. Serial determination of both FSH and LH is performed over an hour following administration of GnRH.

Abnormal puberty

Precocious puberty

All children who develop secondary sexual characteristics before 8 years in girls, or 9 years in boys, should be referred to a paediatric endocrinologist for clinical evaluation and investigation.[2] A detailed history should be taken, exploring the chronology and sequence of changes and other associated symptoms. Direct questions should be asked regarding the coexistence of headaches or visual disturbance, or history of brain injury (e.g. cranial irradiation), to explore potential triggers. Particularly in girls, adoption can result in a triggering of gonadotrophin-dependent puberty.

Gonadotrophin-dependent precocious puberty: also known as central or consonant precocious puberty, activation of the hypothalamus leads to the onset of puberty secondary to pulsatile release of gonadotrophins, with a normal pattern of puberty as described above, but at an early age. Investigation should include an LH-releasing hormone (LHRH) stimulation test to confirm activation of the axis. Bone age is advanced and, in girls, ultrasound of the ovaries may demonstrate follicles. In most girls, central precocious puberty is idiopathic, but in boys there is more likely to be an intracranial cause such as hypothalamic hamartoma or glioma. Therefore cranial magnetic resonance imaging should be performed urgently in boys with central precocious puberty and is commonly also performed in girls. Treatment is



The stages of puberty in girls and boys. (After Carel JC, Leger J. Clinical practice. Precocious puberty. *N Engl J Med* 2008; **358** (22): 2366-77. Copyright (2008) of the Massachusetts Medical Society, reproduced with permission.

Figure 1

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