

Late Sexual Development

If a delay or lack of pubertal development is defined as above the 97th centile for population references, a recent Dutch study showed that the 97th centile for B2 is 12.7 years and for G2 13.4 years. For practical purposes, however, delayed puberty can be diagnosed if breast stage 2 in girls has not started at 13 years of age, and if genital stage 2 (testicular volume ≥ 4 mL) has not started in boys at age 14 years. In practice, many children present because of concern about their appearance several years before these limits. Because of the lack of a pubertal growth spurt, many of these patients will present primarily with short stature (see Ch. 2).

CLASSIFICATION OF LATE PUBERTY

Delayed puberty is classified according to the serum gonadotropin levels: high concentrations indicate primary gonadal failure and low concentrations indicate disorders at the hypothalamic–pituitary level.

HYPERGONADOTROPIC HYPOGONADISM

Congenital primary gonadal failure

- Gonadal dysgenesis associated with sex chromosome abnormalities (e.g. Ullrich–Turner and Klinefelter syndromes).
- Idiopathic syndromic abnormalities. There are more than 20 named syndromes that are associated with hypergonadotrophic hypogonadism.
- Genetic disorders of enzyme production causing sex steroid deficiency.
- Pure gonadal dysgenesis (defective germ cell migration).
- Complete androgen insensitivity caused by receptor/post-receptor abnormalities. Here the gonads are functional but the tissues unresponsive (see Ch. 8). Complete forms that do not present as female infants with bilateral inguinal hernias usually present as primary amenorrhea.

Acquired primary gonadal failure

- Autoimmune disorders.
- Galactosemia.

- Infections.
- Irradiation to the gonad and some chemotherapy regimens (see Ch. 11).
- Trauma *in utero* or later torsion, ‘vanishing testes’, etc.

HYPOGONADOTROPIC HYPOGONADISM

Temporary deficiency, associated with delayed maturation

- Constitutional delay of growth and adolescence (physiologic).
- Chronic illnesses and systemic diseases.
- Hypothyroidism (also associated with sexual precocity).
- Anorexia nervosa.
- Excessive physical training.
- Excessive emotional and/or physical stress.
- Malnutrition.

Permanent pathological deficiency

- Isolated (with anosmia = Kallmann syndrome).
- As part of a syndromic malformation (Again there are a number of eponymous conditions associated with central gonadotropin lack.)
- In the context of multiple pituitary deficiencies, idiopathic or due to anatomic malformations and acquired lesions.

DIAGNOSTIC WORK-UP

MEDICAL HISTORY AND EXAMINATION

Features of importance in the history:

- Family history of delayed sexual development.
- Family history of autoimmune or endocrine disease.
- Family history of infertility.
- Parental size.
- Birth and pregnancy details.
- Any learning problems.
- Previous medical treatments and surgery, including ‘minor’ procedures such as orchidopexy or neonatal hernia repair.



Fig. 7.1
Eunuchoid body habitus (47XXY).



Fig. 7.2 Excess lanugo hair as may be seen in anorexia nervosa.



Fig. 7.3 Cryptorchidism, here with functioning intra-abdominal testes.

- Disordered eating behavior.
- Absent sense of smell. (A patient with anosmia may be able to detect the presence of an odor, especially of volatile substances, but be unable to differentiate between smells.)
- Social pressures – the sexual development of the close peer group.
- Levels of exercise.

The physical examination should concentrate on:

- Height, weight, adiposity (see **Fig. 2.10**).
- Body proportions. Because much of the growth of the back at puberty is mediated by sex hormone secretion, patients with delayed puberty, but no other endocrinopathy, will tend to have long legs compared with their backs – so-called eunuchoid body proportions (**Fig. 7.1**)
- Hirsutism (see Ch. 6).
- Lanugo hair (may be a sign of eating disorders) (**Fig. 7.2**).
- Hernia repairs or other operative scars.

- External genital appearance (measure gently stretched penis length; see Ch. 8). Anatomic abnormalities of the genital tract such as imperforate hymen or absent uterus, presenting as primary amenorrhea without delay of other sexual characteristics, may require ultrasonographic investigation, examination under anesthesia or laparoscopy.
- The presence of cryptorchidism (**Fig. 7.3**).
- Dysmorphic features.
- Signs of thyroid disease.
- Neurologic signs.
- Gynecomastia (see **Fig. 6.29**).
- Lactorrhea (see **Fig. 6.49**).
- Sense of smell.

Interpretation of the clues

- Typical dysmorphic features and short stature = Ullrich–Turner syndrome (see Ch. 2). Remember that up to 40% of girls with the Ullrich–Turner syndrome will have no external phenotypic abnormality (**Fig. 7.4**).

Fig. 7.4

Ullrich–Turner syndrome with few dysmorphic features except infantilism and a wide carrying angle.

**Fig. 7.5**

Prader–Labhart–Willi syndrome.



- Dysmorphic features, short stature and obesity = Prader–Labhart–Willi syndrome (Figs 7.5 & 7.6).
- Dysmorphic features, other abnormalities such as retinitis pigmentosa (see Fig. 1.117) = syndromic malformation such as the Bardet–Biedl or Laurence–Moon syndromes (see Fig. 5.18).
- Other specific dysmorphic syndromes and hypogonadism.
- Tall stature, disproportion and cryptorchidism or small firm testes = Klinefelter syndrome.
- Under-virilized male with gynecomastia and hypertension = late presenting 17 α -hydroxylase deficiency.
- Under-virilized male or phenotypic 46XY female with late virilization = late presenting partial 17-ketosteroid reductase deficiency (or 17 β -hydroxysteroid dehydrogenase deficiency); partial androgen insensitivity syndrome (see Ch. 8).
- Failure of breast development, often with some evidence of adrenal androgen activity = gonadal dysgenesis (Fig. 7.7).
- Hypogonadism with alopecia, vitiligo, candidiasis = autoimmune polyendocrinopathy IIIc (Fig. 7.8).
- Family history of delay (often in same-sex parent or sib) = constitutional delay of growth and adolescence.

Fig. 7.6 Close up of genitalia in Prader–Labhart–Willi syndrome.

- Extreme thinness or falling weight, disordered eating and behavior in relation to food = anorexia nervosa (Fig. 7.9). Past anorexia can cause severe delay of puberty for many years after



Fig. 7.7 Gonadal dysgenesis with adrenal source of pubic hair.

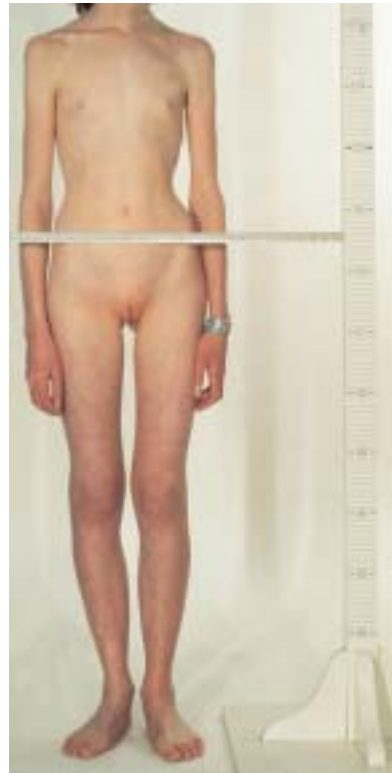


Fig. 7.9 Anorexia nervosa.



Fig. 7.8 Vitiligo.

successful restoration of adequate weight (**Fig. 7.10**). In addition to this psychiatric spectrum, simple fear of obesity with dieting is very common and can produce delay.

- Anosmia, small penis and testes or cryptorchidism = Kallmann syndrome.

- Hypogonadism and lactorrhoea = prolactinoma (see **Figs 6.48 & 6.49**).
- Hypogonadism with hypothyroidism and short stature = panhypopituitarism (**Fig. 7.11**).

FURTHER INVESTIGATIONS

On the basis of a proper history and physical examination, a tentative diagnosis can often be made. Thereafter, basal serum testosterone or estradiol and gonadotropin levels should be measured in specialized units, along with a bone age. Inhibin levels can be a useful marker of gonadal function. In permanent hyper- or hypogonadotropic hypogonadism, bone age can be higher than 11 (girls) or 13 (boys) years in the absence of pubertal signs, while this is unusual in temporary deficiency. Thereafter tests will depend on whether there is hyper- or hypogonadotropism.

Hypergonadotropic hypogonadism

By definition, the levels of gonadotropins are raised – often the follicle stimulating hormone (FSH) level to a greater extent than that of luteinizing hormone (LH).

Even in the absence of abnormal genitalia or dysmorphic features, karyotyping should be performed. It may be necessary to take both blood and fibroblast specimens to exclude tissue mosaicism.

Fig. 7.10 Past anorexia causing later extreme delay of puberty (menses at 20 years).



Fig. 7.11 Panhypopituitarism with infantilism, age 13.5 years.



If there is hypertension, a urinary adrenal steroid profile will help diagnose variants of steroid synthesis disorders.

Pelvic ultrasonography will reveal the absence of even small prepubertal ovaries if streak gonads are present. When the testes in a male are impalpable, they may be localized with ultrasonography either in the inguinal canal or intra-abdominally (**Fig. 7.12**). To determine whether there is functioning gonadal tissue a short human chorionic gonadotropin (hCG) test can be performed (see Appendix). Administration of this LH-like compound will cause production of estrogen or testosterone, which can be measured as a rise from the basal values. Occasionally a prolonged test is required for absolute proof of lack of gonadal tissue.

In a male with impalpable gonads and a rise in testosterone concentration in response to hCG, but in whom ultrasonography fails to locate the tissue, laparoscopy is needed to assess the possibility of orchidopexy or the need for gonadectomy to prevent undetected malignant change.

Autoantibodies to the thyroid, adrenal and ovary

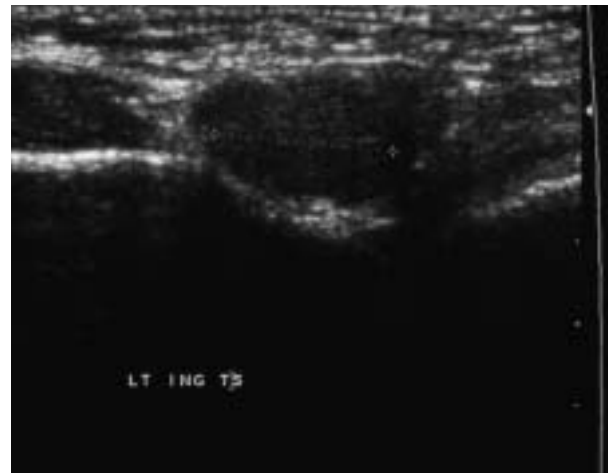


Fig. 7.12 Ultrasonographic localization of left inguinal testis.

can be estimated in the presence of a family history or suggestive physical signs.

Inhibin A (in the female) and inhibin B levels in both sexes can serve as useful markers of gonadal function. Inhibin A levels (produced from the corpus) fall

before FSH levels rise in ovarian damage. Inhibin B (produced by granulosa cells in the female and Sertoli cells in the male) fall early in ovarian or testicular damage – for instance after radiotherapy – and levels rise if testicular function returns.

Hypogonadotropic hypogonadism

To differentiate between permanent and temporary gonadotropin deficiency, a luteinizing hormone releasing hormone (LHRH) test can be performed (see Appendix). The results may be equivocal because, although complete failure of a rise of gonadotropin concentration is suggestive of central hypogonadism, a blunted response can occur just before the onset of delayed puberty. Differentiation from partial central deficiency may thus be difficult without serial retesting before or after a period of treatment (see below).

If there is short stature or signs of hypothyroidism, a combined anterior pituitary function test with basal thyroid function (FT_4) is indicated (see Appendix), along with imaging of the central nervous system if multiple deficiencies are proven.

Occasionally the short stature and long legs in comparison to the back that is seen in delayed puberty can be mimicked by the milder forms of spondyloepiphyseal dysplasia, and a limited skeletal survey may be needed.

THERAPY

HYPERGONADOTROPIC HYPOGONADISM

Males

In males, counseling is indicated regarding the need for treatment (long-term testosterone), infertility and the option of testicular prostheses. Testosterone treatment is started at about 12.5 years (50–100 mg once a month by depot i.m. injection, or oral testosterone undecanoate 40 mg on alternate days increasing to a daily dose after 6 months) to ensure normal physical and psychosocial development, normal sexual function and to protect the cardiovascular system and bone mineral density. Prostheses are usually placed at the end of pubertal development and the dose of testosterone is increased (250 mg by depot i.m. injection once every 3 weeks, or oral testosterone undecanoate 80–240 mg per day) to achieve a normal level of sexual activity.

Females

In females treatment is needed with estrogens to induce breast development, to prevent osteoporosis and to ensure a normal psychosocial development.

Ethinylestradiol is commonly used. The starting dosage is 0.05 μg per kg body weight given orally (usually about 2 μg per day or on alternate days). Alternatively matrix-based patches of 25 μg can be cut up into halves and quarters to provide similar low doses transdermally. An initial low dosage appears to improve final height by preventing early bony fusion and there is an improved cosmetic appearance of the breasts. The dosage is gradually increased over a period of 2–3 years to reach a substitution dosage of 20–30 μg with progestagens at a dosage of 5–10 mg medroxyprogesterone per day for 10–14 days per month. When growth is completed, transcutaneous patches or a triphasic contraceptive pill can be conveniently used. Counseling regarding infertility is required, although the use of egg donation and gametocyte transfer allows the possible artificial induction of pregnancy in some individuals.

HYPOGONADOTROPIC HYPOGONADISM

Males

In males initially it may be difficult to separate constitutional delay from central hypogonadism. For psychologic reasons a pragmatic approach is to offer testosterone treatment. This may be given either in a depot dosage of 50–100 mg testosterone esters every 3–4 weeks intramuscularly or as oral testosterone undecanoate 20–40 mg per day. Testosterone is also available as a buccal pellet, a gel and as various designs of patch, but experience of these preparations in pediatric practice is limited. An alternative approach is to use the anabolic steroid oxandrolone in a dose of 1.25–2.5 mg per day orally.

Usually these treatments are discontinued after 3–4 months, and the development of testicular size is checked along with serum testosterone measurements. If puberty starts (testicular volume >4 mL), testosterone or oxandrolone treatment can be stopped to allow natural puberty to progress. If there is failure of subsequent development, a further 3-month course and re-evaluation of the possibility of permanent central hypogonadism may be necessary. In cases of a permanent gonadotropin deficiency, testosterone treatment is continued for life. Intermittent biosynthetic gonadotropin administration, human menopausal gonadotropin (hMG), hCG and pulsatile LHRH infusion have all been used to induce spermatogenesis; a rise in inhibin B levels can be used as a marker of successful treatment.

Females

In females pubertal delay requiring treatment is rare but may be treated with low dosages of ethinylestradiol as

described above. In case of permanent central hypogonadism, estrogen substitution is indicated. The dosage is gradually increased over 2–3 years, for example from 4 to 10 to 20 and later 30 µg ethinylestradiol per day (either as tablets or a divided matrix patch), while medroxyprogesterone (for 10–14 days per month) is added to ensure regular menses. Patches or triphasic contraceptive preparations may again be used con-

veniently until menopausal age or hormone replacement therapy continued life-long.

Hypopituitary females often have sparse pubic hair growth (secondary to lack of adrenal maturation and androgen production). This cosmetic problem can be treated with topical, or low-dose oral or injected, testosterone, or with oral dehydroepiandrosterone sulfate (DHEAS), if required.

