Puberty (Delayed)

Definition / Supporting Information

Normal puberty is a series of complex hormonal changes that begins at 8–13 years of age in girls and 9–14 years of age in boys.

Delayed puberty in girls: no breast development by age 13 years and delay of more than 4–5 years from onset of puberty to menarche.

Delayed puberty in boys: no testicular enlargement by age 14 years.

Essential History

Ask about:

- Faltering growth
- Developmental delay
- Long-term conditions, such as:
  - Asthma
  - Diabetes
  - Chronic Kidney Disease
- Exposure to medications that can affect puberty such as cytotoxic chemotherapy (eg, cyclophosphamide, busulfan) and long term treatment with corticosteroids
- Exposure to radiotherapy
- Family history of delayed puberty
- Impact of delayed puberty on child / family

‘Red Flag’ Symptoms and Signs

Ask about:

- Signs and symptoms related to the endocrine and central nervous systems:
  - Fatigue
  - Behaviour change
  - Deterioration in academic performance
  - Loss of interest in usual activities
  - Alteration in appetite
  - Headache
  - Loss of balance
  - Sensory change
    - Visual disturbance
    - Absent sense of smell
    - Hearing loss

        - Numbness
    - Galactorrhoea

Look for:

- Changes in growth parameters / growth velocity / body mass index (BMI)
- Delay in Tanner staging (see Puberty and the Tanner Stages (pdf))
- Dysmorphic features (see Congenital Malformations)
    - Turner's syndrome
    - Klinefelter's syndrome
- Evidence of chronic or systemic disease
    - Rash
    - Hepatomegaly
    - Abnormal findings on auscultation of lung fields
    - Evidence of fluid overload
- Abnormalities of tone / power / co-ordination / visual fields / fundoscopy
    - Intracranial pathology
- Thyroid goitre

Differential Diagnosis / Conditions

Hypogonadotrophic hypogonadism (low levels of luteinising hormone (LH) and follicle stimulating hormone (FSH))

- Functional causes
    - Constitutional delay
    - Malnutrition
        - Including due to anorexia nervosa
    - Excessive exercise
- Long-term conditions
    - Congenital heart disease
    - Chronic pulmonary disease
        - Asthma
        - Cystic fibrosis
    - Inflammatory bowel disease / coeliac disease
    - Chronic kidney disease / renal tubular acidosis
    - Hypothyroidism
        - If undiagnosed or poorly controlled
    - Poorly controlled diabetes mellitus
    - Sickle cell anaemia / thalassaemia
    - Collagen–vascular disease
    - Anorexia nervosa

  - HIV infection
  - Treated cancers
- Genetic and developmental causes
  - Isolated gonadotrophin deficiency
  - Isolated LH deficiency (normal FSH secretion)
  - Kallmann's syndrome (with anosmia)
  - Leptin or leptin-receptor deficiency (impaired gonadotrophin-releasing hormone (GnRH) release and action)
  - Multiple pituitary hormone deficiencies (including transcription factor mutations in PROP1, HESX1, and LHX3)
  - Congenital glycosylation disorders
  - Midline defects (septo-optic dysplasia)
  - Syndromic associations:
    - Laurence–Moon–Bardet–Biedl syndrome
    - Präder–Willi syndrome
- Acquired causes
  - Neoplasm
    - Craniophayngioma
    - Germinoma
    - Hypothalamic glioma
    - Pituitary tumour (including prolactinoma)
  - Infection
  - Infiltrative disease
    - Langerhans cell histiocytosis
    - Granulomatous disease
    - Sarcoidosis
    - Lymphocytic hypophysitis
  - Trauma
  - Cranial irradiation

Gonadal disorders (hypergonadotrophic hypogonadism; elevated levels of LH and FSH)

- Girls
  - Genetic and molecular
    - Turner's syndrome (45,X or structural X abnormalities, or mosaicism)
    - Mixed gonadal dysgenesis (46,XY / 45,X)
  - Disorders of steroid synthesis and action
    - Receptor mutations (LH / FSH resistance)
    - SF1, StAR, CYP11A, HSD3B2, CYP17, aromatase (46,XX karyotype)

        - HSD17B2, 5α-reductase, syndrome of complete androgen insensitivity (no sexual hair) (46,XY karyotype)
    - Other causes of primary ovarian failure
        - Autoimmune
        - Metabolic (galactosaemia, storage disorders)
        - Pelvic / spinal irradiation
        - Chemotherapy
- Boys
    - Genetic and molecular
        - Klinefelter's syndrome (47,XXY)
        - Myotonic dystrophy
        - Mixed gonadal dysgenesis (46,XY / 45,X)
        - Noonan's syndrome
    - Disorders of steroid synthesis and action
        - SF1, StAR, CYP11A, HSD3B2, HSD17B2
        - Partial androgen insensitivity
    - Acquired
        - Gonorrhoea
        - Virus (mumps, coxsackie)
        - Tuberculosis
        - After radiation or chemotherapy
        - Torsion
        - Cryptorchidism
        - Congenital anorchia (vanishing testes syndrome)
        - Autoimmune
        - Sertoli cell only syndrome

Investigations

To be undertaken by non-specialist practitioners (eg, General Practitioner (GP) Team, where indicated, following advice from specialist practitioners) or specialist practitioners (eg, General Paediatric / Paediatric Endocrinology Team(s)) according to the clinical condition or age:

- LH, FSH
- Testosterone or oestrogen, depending on sex
- Thyroid-stimulating hormone, thyroid hormone
- If systemic disease is thought to exist
    - Full blood count
    - Erythrocyte sedimentation rate, C-reactive protein
    - Urea and electrolytes
    - Serum bicarbonate

  - Serum glucose
  - Bone biochemistry
  - Liver function tests
  - Insulin-like growth factor 1, insulin-like growth factor binding protein 3
  - Urinalysis
  - Coeliac disease panel
    - Anti-endomysial IgA antibody or tissue transglutaminase IgA and total IgA level
  - Prolactin

To be undertaken by specialist practitioners (eg, General Paediatric / Paediatric Endocrinology Team(s)):

- Above tests, if not already done
- Karyotype
- GnRH or GnRH analogue stimulation test
- HCG stimulation test
- Urinary steroid profile
- Magnetic resonance imaging of hypothalamus and pituitary

Treatment Approach

To be undertaken by non-specialist practitioners (eg, GP Team):

- Constitutional delay
  - Waiting may be the best course.
  - Treatment with low-dose injectable testosterone in boys or oral or transdermal oestrogen in girls if required, should be initiated by a paediatric specialist (see below)

To be undertaken by specialist practitioners (eg, General Paediatric / Paediatric Endocrinology Team(s)):

- Constitutional delay
  - Waiting may be the best course.
  - Boys
    - A short course of low-dose injectable testosterone (eg, testosterone enantate 25–50 mg/m^2 monthly for 4–6 doses) if delayed development affects psychological wellbeing
  - Girls
    - Low-dose oral or transdermal oestrogen (ethinylestradiol) if delayed development affects psychological wellbeing
    - Treatment needs to be gradual to avoid premature closure of the epiphyses and prevent overdevelopment of the areolae of the breast.

        - Initial treatment needs to be followed by a combined oestrogen/progestogen preparation.
- Gonadal failure or gonadotrophin deficiency
    - Treatment focuses on replacing the appropriate sex steroid.
- GnRH or gonadotrophin deficiency
    - Fertility may be induced with GnRH (Gonadorelin) or gonadotrophin therapy.

When to Refer

Refer to paediatric specialists (eg, General Paediatric / Paediatric Endocrinology Team(s)) if:

- No breast development in girls by 13 years of age
- No menarche 4–5 years after onset of breast development in girls (see Amenorrhoea)
- No testicular enlargement in boys by 14 years of age
- Maturational arrest
- Hormonal abnormalities identified by initial screening tests
- Parental or physician discomfort

‘Safety Netting’ Advice

- Patients with delayed puberty require regular monitoring for the emergence of red flag signs and symptoms.
- Psychological support may be required for adolescents.

Patient / Carer Information

Please note: whilst these resources have been developed to a high standard they may not be specific to children.

- Puberty (Web page), the NHS website
- Puberty – symptoms (Web page), the NHS website
- Puberty – complications (Web page), the NHS website
- Stages of puberty: what happens to boys and girls (Web page), the NHS website

Resources

National Clinical Guidance

Coeliac disease: recognition and assessment of coeliac disease (Web page), NICE guideline NG20, National Institute for Health and Care Excellence

Endocrine conditions overview (Web page), NICE pathway, National Institute for Health and Care Excellence

Suggested Resources

Please note: these resources include links to external websites. These resources may not have national accreditation and therefore PCO UK cannot guarantee the accuracy of the content.Gravholt CH, Anderson NH, Conway GS *et al.*

Clinical practice guidelines for the care of girls and women with Turner syndrome. Eur J Endocrinol. 2017;177(3):G1-G70 [PubMed]

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Tanner JM. Growth and endocrinology of the adolescent. In: Gardner LI, ed. Endocrine and Genetic Diseases of Childhood and Adolescence. Philadelphia, PA: WB Saunders; 1975.

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