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| Title:  **Guideline for Investigation of Early (precocious) and Late (Delayed) Puberty in Girls and Boys** | | | |
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| **Executive Lead:** |  | | |
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# Precocious and Delayed Puberty

# Quick Reference Guide

**Who to refer to secondary care: Precocious (early) Puberty**

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| --- | --- |
| Boys <9 years | Girls < 8 years |
| Increased testicular volume (≥4ml) and/or  virilisation of genitalia (penile growth) | Breast development  Virilisation of external genitalia (clitoromegaly) |
| Accelerated height growth | Accelerated height growth |
|  | Excessive tall stature |
|  | Menarche (Before age 10 years) |

**\***Note development of: pubic/axillary hair, body odour, skin oiliness and acne without signs of central puberty (those described in the table above) is called **Adrenarche**. This can be a normal variant. Please see the separate Adrenarche guideline for further information and referral criteria (<https://www.speg.scot.nhs.uk/wp-content/uploads/2019/03/2019-SPEG-Adrenarche-Guideline-v1.1.pdf>).

**Who to refer to secondary care: Delayed Puberty**

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| --- | --- |
| Boys ≥14 years | Girls ≥13 years |
| No increase in testicular volume (< 4mls) | No breast development |
| No accelerated height growth (may not occur until potentially 16yrs when testicular volume 10 mls+ but if psychologically distressed can see pre age 14/16 yrs) | No accelerated height growth  Short stature for family |
| Short stature for family | No menarche within 3 years of onset of puberty (by age 15 years latest) |

**Key information to include in the referral:**

* Growth history with the height at the time of referral and previous height measurements if available
* Parental heights
* Family history of early or delayed puberty
* Assessment of any androgen-dependent characteristics e.g. axillary/pubic hair, clitoromegaly, penile growth
* Any other medical problems. Many chronic health conditions can lead to pubertal delay
* Any concerns about pathological cause e.g., space occupying lesion

**Investigations:**Baseline investigations can be arranged by the referring clinician. These should be interpreted in the clinical context and therefore if a patient has clinical signs of precocious puberty but normal tests (low LH/FSH/oestradiol) referral is still appropriate as further investigation may be required. Referrals should be routine unless there are concerns about pathological cause, for example space occupying lesion.

* Blood tests: FSH, LH, testosterone/oestradiol, TSH, fT4
* Coeliac screen if symptoms suggestive of this
* Full blood count, CRP/ESR if delayed puberty (IBD may present with delayed puberty)
* Bone age x-ray
* Pelvic USS (girls): request ovarian and uterine volume

# Introduction

Puberty is the stage of development in boys and girls which involves:

1. Maturation of the gonads
2. Increase in the secretion of sex hormones
3. Accelerated linear growth
4. Development of secondary sexual characteristics

Puberty is controlled centrally by the pituitary gland via the **hypothalamic-pituitary-gonadal axis**. In girls LH and FSH stimulate maturation of the ovaries and secretion of oestradiol, whilst in boys they stimulate testicular maturation and testosterone production.

**Hypothalamus**

nRh

**Anterior Pituitary**

LH

FSH

**Girls**

Regulates oestrogen secretion

**Girls**

Stimulates follicular cells to support ovulation

**Boys**

Regulates testosterone secretion

**Boys**

Stimulates Sertoli cells to support sperm production

Oestrogen and testosterone are the key players in the pubertal growth spurt. They work directly on the growth plate to stimulate growth. Oestrogen (from the ovary or aromatised testosterone from the testes) contributes to an increase in response to growth hormone during puberty.

The pituitary also stimulates the adrenal glands to produce androgens. This process occurs independently of the pituitary-gonadal axis. If this process occurs in isolation, it is called **Adrenarche** and results in the development of: pubic/axillary hair, body odour, skin oiliness and acne without signs of central puberty. This can be a normal variant. Please see the separate Adrenarche guideline on RefHelp for further information.

**Normal Patterns of Puberty**

In girls the first sign of puberty is breast development (breast buds). This is usually followed by accelerated linear growth in early to mid-puberty (growth spurt). Menarche usually signals the end of pubertal development. Androgen dependent characteristics (axillary hair, pubic hair, acne, oily skin etc) usually develop in mid-puberty.

In boys the first sign of puberty is an increase in testicular volume. As in girls, androgen dependent characteristics usually develop in mid-puberty. Accelerated linear growth occurs in mid to late puberty in boys.

Girls and boys have different ages at which pubertal development is considered to be normal. Early (precocious) or delayed puberty is defined as the presence or absence of pubertal signs before or after the following ages.

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| --- | --- | --- |
|  | Boy | Girl |
| Early Puberty | <9 years | <8 years |
| Delayed Puberty | ≥14 years | ≥13 years |

Puberty is normally completed in 2-5 years.

# Precocious (early) Puberty

Signs of puberty in girls <8 years of age and boys <9 years of age are indicative of precocious puberty.

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| --- | --- |
| Boys < 9 years | Girls < 8 years |
| Increased testicular volume (≥4ml) | Breast development |
| Accelerated linear growth | Accelerated linear growth |
| Tall stature | Tall stature |
|  | Menarche |

There are two types of Precocious Puberty:

* **Gonadotrophin- Dependent (Central) Precocious Puberty**

This is the most common type and results from premature activation of the hypothalamo-pituitary-gonadal axis. The pattern of pubertal development follows that of normal puberty.

* **Gonadotrophin-Independent Precocious Puberty**

This results from excess peripheral production of sex steroids. Pubertal development does not follow the normal pattern of puberty.

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| History | Examination- Girls | Examination- Boys |
| * Onset of secondary sexual characteristics (and is pattern of development the same as normal puberty) * Rate of development * Recent growth * Parental heights * Parental pubertal history * History of adoption * Medication history | * Height- plot on growth chart * Height velocity * Breast development * Androgen-dependent characteristics * Neurological examination (including fundoscopy to exclude raised ICP) * Dysmorphic features (including skin examination for: café-au-lait spots/ freckles/neurofibromas)\* | * Height- plot on growth chart * Height velocity * Testicular volume * Androgen-dependent characteristics * Neurological examination (including fundoscopy to exclude raised ICP) * Dysmorphic features (including skin examination for: café-au-lait spots/ freckles/ neurofibromas)\* |

**Key Fact**

Central Precocious Puberty is more common in girls:

* Girls are more likely to have the idiopathic form (90% of cases)
* Boys are more likely to have an underlying pathological cause (90% of cases)

\*May reveal multisystem syndrome- midline defects, McCune-Albright Syndrome, Neurofibromatosis

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| --- | --- | --- | --- | --- | --- | --- |
| Differential | Growth/pubertal Signs | Signs of Adrenarche | Biochemistry | Bone Age | Presenting age | Refer? |
| Central precocious Puberty | **Girls**- Breast development, increased HV  **Boys**- TV ≥4ml  Accelerated linear growth, only if TV > 10ml | Yes | LH + FSH  Sex steroids  (although can be normal at baseline) | Advanced | **Girls**: <8 years  **Boys**:< 9 years | **Yes** |
| Premature Adrenarche | No (minimal increase in HV) | Yes | Gonadotrophins- prepubertal  Mildly increased androgens |  | Typically girls | Not always (see separate guideline) |
| Premature Thelarche (girls only) | Isolated breast development  Often fluctuates | No | Prepubertal LH (<0.5)  FSH sometimes slightly raised | Not advanced | 6 months- 3 years | Yes |
| Premature Thelarche Variant (girls only) | Breast development- persistent | Not initially- may progress to central precocious puberty | FSH  ?LH may be raised | Not advanced unless progresses to central precocious puberty | Older age of onset >2 years | Yes |
| Gonadal Tumours:  Can secrete oestrogen or testosterone | Disconsonant\* | Yes | Sex steroids  LH +/-FSH | Advanced | Variable | Yes |
| Congenital Adrenal Hyperplasia | Disconsonant\* |  | Raised adrenal hormone precursors | Advanced | Variable | Yes |
| Adrenal Tumours:  Can secrete oestrogen or testosterone | No breast budding (will be present if tumour oestrogen-secreting)/ testicular enlargement  Accelerated linear growth | Virilisation | Urine steroid profile- abnormal pattern  Raised androgens and/or sex steroids | Advanced | Variable | Yes |
| Primary Hypothyroidism | Breast budding  Testicular enlargement  No increase in height velocity | No | TSH | Delayed | Variable | Yes |

\*increased height velocity, advanced bone age and advanced genital maturation in the absence of bilateral testicular enlargement in boys and enlargement of ovaries in girls (breast development if tumours are oestradiol/testosterone producing). **Unilateral gonadal enlargement should always be considered as a pathological sign**.

HV = height velocity, TV = testicular volume

Initial Investigations (could be performed at time of referral to endocrinology team or in secondary/tertiary care **but do not delay referral for results if signs in keeping with precocious puberty**):

1. Bone age x-ray
2. Gonadotrophins (LH/FSH)
3. Oestradiol / testosterone
4. Thyroid function tests (TSH/fT4)

Further investigations in central precocious puberty, guided by initial investigations and examination findings:

1. Pelvic ultrasound scan (girls)
2. MRI Brain- in all boys age <9 years and in girls presenting at <6 years of age or with features suggestive of pathological cause (e.g. symptoms of raised intracranial pressure)
3. Adrenal androgen profile (17OHP, androstenedione, DHEAS, testosterone)
4. GnRH Test (if clear signs of puberty in girls e.g. accelerated growth velocity)
5. Other pituitary hormones (cortisol, prolactin, IGF-1)

# Delayed Puberty

No signs of central puberty in girls ≥13 years of age and boys ≥14 years of age is indicative of delayed pubertal development.

**Key Facts**

Delayed puberty is more common in boys.

The majority of patients seek medical advice due to concern about growth rather than pubertal development.

**Mechanisms of delay in puberty:**

* Functional:
  + Constitutional delay (most common cause, particularly in boys)
  + Underlying chronic disease
  + Malnutrition
  + Excessive exercise
* Hypothalamic-pituitary disorders
  + Hypogonadotrophic hypogonadism
* Gonadal Disorders
  + Hypergonadotrophic hypogonadism

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| History | Examination |
| * Chronic medical conditions (e.g. coeliac, inflammatory bowel disease, thyroid disease, inflammatory disorders such as JIA) * Eating pattern/diet/weight loss * Parental pubertal history/height * Previous surgery/radiotherapy to the brain * Boys- testicular pain/swelling/inflammation * Other hormone deficits (hypothyroid etc) * Sense of smell (Kallmann Syndrome\*) | * Height and weight and plot on growth chart (+ previous measurements if available) * Signs of chronic medical conditions * Pubertal stage (girls- breast development, boys- testicular volume, both- androgen characteristics) * Neurological examination, including visual field assessment * Body disproportion (tall stature with greater lower limb length in Klinefelter Syndrome**\***) * Dysmorphic features- Turner Syndrome, midline defects, Prader-Willi, CHARGE) |

**\***Associated with normal or tall stature as opposed to other causes of delayed puberty

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| --- | --- | --- | --- | --- | --- |
| Differential | Presenting Sign | Signs of Adrenarche | Investigations | Bone Age | Refer? |
| Constitutional Delay  (most common) | Short stature  No secondary sexual characteristics  Family history of delayed puberty | Yes/No | Pre-pubertal: LH/FSH +  Sex steroids  Observation | Delayed | Yes |
| Hypogonadotropic hypogonadism | Short stature  No pubertal development/delay in pubertal development/arrest of pubertal development  Anosmia (in Kallmann Syndrome) | No | LH +/-FSH  Sex steroids  MRI head  DSD Gene panel  Pituitary function | Delayed | Yes |
| Premature Ovarian Failure | Primary amenorrhoea | Yes | LH +/-FSH  Sex steroids  AMH  Ovarian antibodies  Karyotype (for Turner Syndrome)  Genes for fragile X (FMR1) | Delayed | Yes |
| Premature Testicular Failure | May have had normal pubertal development and then pubertal arrest | Yes | LH/FSH  Sex steroids  Karyotype (for XXY or variants) | Delayed | Yes |
| Hypothyroidism | Lethargy, cold intolerance, constipation, weight gain, menstrual irregularities | Yes | Normal LH  Thyroid function (TSH/fT4) | Delayed | Yes |
| PCOS | Obesity, hirsutism, acne, weight gain, oily skin.  Anovulation- irregular/ absent menarche | Yes | DHEAS  SHBG  Testosterone  Androstenedione | Normal | Yes |
| Complete Androgen Insensitivity | Phenotypic female- normal breast development  No menarche | No | Karyotype: 46XY  Pelvic USS- testes, no ovaries/uterus | Normal | Yes |
| 5-alpha Reductase Deficiency | Boys- ambiguous genitalia at birth  Development of male secondary sexual characteristics at puberty | No | hCG Test (Testosterone:DHT ratio)  Genetics | Normal | Yes |
| Anatomical (imperforate hymen, absent uterus) | Primary amenorrhoea  Other secondary sexual characteristics present | Yes | Pubertal LH, FSH + oestrogen  Pelvic USS | Normal | Yes |

Initial Investigations (could be performed at time of referral to endocrinology team or in secondary/tertiary care):

1. Bone age x-ray
2. Gonadotrophins (LH/FSH)
3. Oestradiol / testosterone
4. SHBG
5. Thyroid function tests (TSH/fT4)
6. Cortisol
7. Prolactin
8. Pelvic ultrasound scan (females)

Additional investigations if concerned about underlying chronic illness

1. Coeliac screen
2. Faecal calprotectin