Hirsutism, Hypertrichosis, and Precocious Sexual Hair Development

Definitions / Supporting Information

Hirsutism: Excessive body hair growth in the sex hormone-dependent areas.

Hypertrichosis: Generalised increase in fine body hair with no preferential sites.

Virilisation, or masculinisation: Androgen overproduction in females, manifest as phallic or clitoral enlargement, masculine body habitus, temporal hair loss, voice changes, breast atrophy, menstrual disorders.

Gonadotropin-dependent (central) precocious puberty: Early* maturation of the hypothalamic–pituitary–gonadal axis.

Gonadotropin-independent (peripheral) precocious puberty: Early* production of sex steroids independent of an activated hypothalamic–pituitary–gonadal axis (in boys, from either the testes or the adrenals; in girls, from the ovaries, the adrenals, or both).

*Girls before 8 years, boys before 9 years

Essential History

Ask about:

- Timing and speed of progression of symptoms
- Family history of cardiovascular disease, atherosclerosis, obesity, or diabetes
  - Reported in families of patients with premature adrenarche and polycystic ovarian syndrome (PCOS)
- Family history of early spontaneous abortion
  - May indicate congenital adrenal hyperplasia.
- Obesity / hirsutism / acne / hyperpigmentation in areas where skin rubs together such as axilla (acanthosis nigricans), male pattern baldness in girls
  - Consider PCOS

‘Red Flag’ Symptoms and Signs

Ask about:

- Rapid growth
  - Increase in growth velocity with crossing percentiles may suggest precocious puberty.

- Early development of pubic / axillary hair, odour, acne, and breast development in girls, or testicular growth and full physical pubertal development in boys
  - Gonadotropin-dependent (central) or gonadotropin-independent (peripheral) precocious puberty
- Rapid development of sexual hair associated with signs of virilisation (eg, severe acne, voice changes, change in body habitus, clitoral or phallic enlargement, rapid growth)
  - Consider congenital adrenal hyperplasia / adrenal or ovarian tumour
- Abdominal symptoms (cramps, pain, mass, distension)
  - Consider ovarian androgen-producing tumours
- Vaginal discharge or irregular uterine bleeding

Look for:

- Fusion of labia majora with rugosity and pigmentation of skin
  - May indicate hyperandrogenism during foetal life, which occurs in the congenital adrenal hyperplasia syndromes
- Hypertension
  - 11-hydroxylase deficiency
  - Adrenal tumour
  - Obesity
- Virilisation
  - Indicates severe hyperandrogenism

Differential Diagnosis / Conditions

Gonadotropin-dependent (central) precocious puberty

- In girls, most cases (90%) are not caused by a specific identifiable lesion
- May be associated with:
  - Tumours (astrocytoma, craniopharyngioma, ependymoma, germinoma, glioma, hypothalamic hamartoma)
    - Consider hypothalamic or pituitary lesion in a child < 6 years
  - Central nervous system (CNS) insult
    - Trauma
    - Surgery
    - Radiation
    - Inflammation
    - Cerebral palsy
  - Prolonged exposure to sex steroids
  - Different genetic origin from that of adoptive parents

Gonadotropin-independent (peripheral) precocious puberty (GIPP)

- Male-limited (autosomal dominant) GIPP due to abnormal LH receptor function
- McCune–Albright syndrome
  - Associated with large, irregular areas of skin pigmentation and fibrous dysplasia of bone
  - Cortisol, thyroid and growth hormone excess may also occur
- Ovarian androgen-producing tumours
  - Symptoms can mimic true precocious puberty in the young child
  - A markedly elevated oestradiol, androstenedione, or testosterone level is consistent with an ovarian lesion.
- Androgen-producing cells
  - Can occur in association with:
    - Embryonal carcinoma
    - Dysgerminoma
    - Choriocarcinoma
    - Gonadoblastoma
    - Granulosa–theca cell tumour
    - Sertoli–Leydig cell tumour
    - Arrhenoblastoma
  - These tumours can occur in phenotypic girls who have an abnormal karyotype containing components of the Y chromosome.

Polycystic ovarian syndrome (PCOS)

- The precise cause of PCOS is not known.
- Several factors have been implicated
  - Altered gonadotropin secretion
  - Hyperinsulinism
  - Insulin-like growth factor-1 and alterations of insulin-like growth factor-1 binding proteins
  - Hyperprolactinaemia
  - Adrenal hyperandrogenism
- Girls with precocious puberty who had low birth weight are at high risk of one of the following variants of PCOS, even if they are not obese.
  - Hyperinsulinaemic hyperandrogenism
  - Dyslipidaemia
  - Dysadipocytokinaemia
  - Central fat excess
  - Deficit of lean body mass

Testicular androgen production

- Gonadotropin-dependent (central) precocious puberty
  - CNS disease in boys

Testicular tumours

- Leydig cell tumours and seminomas can produce testosterone.
- Boys with cryptorchidism and delayed orchidopexy after the age of 6 years are at increased risk.
- Dysgenetic gonads associated with androgen insensitivity, persistent müllerian syndrome, ovotesticular disorder of sexual development (true hermaphroditism), and Klinefelter's syndrome have a higher incidence of germ cell tumours as well.

Chorionic gonadotropin-secreting tumours

- Teratomas, embryonal tumours, hepatoblastomas, and CNS germinomas can produce human chorionic gonadotropin (HCG).
  - HCG has been implicated in gonadotropin-independent (peripheral) precocious puberty among male patients.

Adrenal hyperandrogenism

- Premature adrenarche (before 8 years of age in girls and 9 years of age in boys)

Drug-related hirsutism and hypertrichosis

- Hirsutism may result from use of:
  - Anabolic steroids
  - Danazol
  - Progestogens
  - Corticosteroids
  - Carbamazepine
  - Phenytoin
  - Sodium valproate
  - Tacrolimus
  - Testosterone
- Hypertrichosis may be caused by:
  - Ciclosporin
  - Diazoxide
  - Minoxidil
  - Latanoprost (local changes to eye lashes)

**If prescribing sodium valproate to a young person, be aware of the risks and ensure contraception is being used to protect against becoming pregnant. More information can be found on the Medicines for Children website.*

Idiopathic hirsutism or acne

- Girls with these signs have no other signs of androgen excess and normal circulating androgen concentrations.
- Menses and reproductive function are normal.
- Hirsutism and acne in these women have been attributed to 'increased peripheral metabolism' of androgens

Investigations

To be undertaken by non-specialist practitioners (eg, General Practitioner (GP) Team) or by specialist practitioners (eg, Emergency Department / General Paediatric / Paediatric Endocrinology Team(s)):

- Basal gonadotropins and sex steroids (testosterone or oestrogen)
  - The presence of virilisation or very high levels of testosterone or of dehydroepiandrosterone sulphate may suggest an ovarian or adrenal tumour.
- Pelvic ultrasonography
  - Suspicion of cystic or solid ovarian lesions

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

- Glucose tolerance test in girls with PCOS
- GnRH stimulation test
  - To distinguish gonadotropin-dependent (central) from gonadotropin-independent (peripheral) precocious puberty
    - Pubertal gonadotropin response to a GnRH stimulation test confirms central precocious puberty
    - Gonadotropin response is suppressed in peripheral precocious puberty.
  - Pubertal pattern of gonadotropin release in testicular androgen production
  - Low GnRH-stimulated gonadotropin levels in familial gonadotropin-independent puberty, McCune–Albright syndrome
- ACTH stimulation test
  - If ACTH testing is consistent with an enzymatic defect in the virilised patient, the non-malignant nature of the condition should be confirmed by suppression of hyperandrogenism with dexamethasone.
- Karyotype
  - If an ovarian tumour is suspected
- Luteinising hormone/follicle-stimulating hormone
  - Ratio > 2 in PCOS

- Δ-4-androstenedione
  - Increased in PCOS
- Total and free testosterone
  - Increased in PCOS
  - Increased in testicular androgen production
- 17-hydroxyprogesterone level
  - Increased in 21-hydroxylase deficiency
- 11-deoxycortisol
  - Increased in 11-β-hydroxylase deficiency
- Urinary steroid profile
  - Useful in identifying disorders of adrenal steroid biosynthesis and adrenal tumours
- Bone-age radiograph
- Magnetic resonance imaging with gadolinium contrast of the hypothalamic–pituitary area
  - If evidence of pubertal gonadotropin response to a GnRH stimulation test

Treatment Approach

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

- For mild hirsutism, local measures, such as shaving, bleaching, depilatories, and electrolysis can be used for localised hair growth.
- Obese patients should be encouraged to lose weight.
- PCOS
  - Oral contraceptives
  - Metformin hydrochloride
    - Adolescents with PCOS are severely insulin resistant compared with a control group matched for body composition and abdominal obesity.
    - Metformin has been reported to prevent development of PCOS symptoms in prepubertal and adolescent girls with premature pubarche and a history of low birth weight.

To be undertaken by specialist practitioners (eg, Emergency Department / General Paediatric / Paediatric Endocrinology Team(s)) if not already done:

- Gonadotropin dependent (central) precocious puberty
  - Long-acting preparations of GnRH (Leuprorelin acetate or Triptorelin)
- Peripheral precocious puberty
  - Ovarian androgen-producing tumours
    - Prophylactic gonadectomy is recommended in these girls.
- Enzymatic effects of steroidogenesis
  - 21-hydroxylase deficiency

    - Treatment includes glucocorticoid replacement therapy as hydrocortisone at a dose of 9–15 mg/m^2 daily to maintain normal growth and development and normal rate of bone-age advancement.
    - Treated with the salt-retaining mineralocorticoid fludrocortisone acetate (sometimes useful when elevated plasma renin activity) at an initial dose of 50-100 micrograms once daily.
- 11-β-hydroxylase and 3-β-hydroxysteroid dehydrogenase deficiency
    - Treatment is similar to that for 21-hydroxylase deficiency, with glucocorticoid replacement.

When to Refer

Refer to a specialist practitioner (eg, General Paediatrician / Paediatric Endocrinologist) if:

- Pubic hair, axillary hair, or axillary odour before 8 years of age in girls and 9 years of age in boys
- Breast development, vaginal discharge, or menses in girls before 8 years of age
- Increased facial or body hair (chest, abdomen, back) in girls with or without menstrual irregularities
- Signs of virilisation in girls (clitoromegaly, masculine body habitus, voice changes) or in boys before the age of 9 years (phallic enlargement, change in body habitus, voice change)
- Rapid virilisation (< 1 year) in a pubertal boy

Escalate care to Oncologist and / or Paediatric Surgeon if:

- Concern about possible tumour

Consider admission if:

- Severe hypertension with precocious sexual development
- Severe anaemia secondary to vaginal bleeding
- Severe headaches, visual loss, change in mental status
    - Increased intracranial pressure associated with CNS lesion
- Hypotension or shock
    - Addison’s disease secondary to ACTH deficiency
    - Pituitary apoplexy secondary to a bleed into a pituitary lesion
- Marked hyperglycaemia requiring insulin
    - Type 2 diabetes mellitus
    - PCOS
- Severe abdominal pain (torsion of ovarian cyst)

‘Safety Netting’ Advice

- In children and young people with hirsutism or precocious sexual hair development monitor the response to the therapy or progression of pubertal changes, because this may lead to short stature.

Patient / Carer Information

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

- Hirsutism (Web page), the NHS website
- Early or delayed puberty (Web page), the NHS website

Resources

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.

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