Delayed puberty and its management

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Abnormalities of puberty

IMAGE 2016: Insights into MAnaging Growth for Endocrine Nurses

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Hypothalamo-pituitary-gonadal axis

Hypothalamus

Gonadotrophin releasing hormone

Pituitary gland

Luteinising hormone and Follicle Stimulating Hormone

Ovary and Testis

Testosterone → 17β-estradiol
Inhibin A and B, Anti-Müllerian Hormone

Target cell
Pubertal (Tanner) staging

Boys

Testes < 2.0 cm max. length
Testes > 2.0 cm max. length
Penis lengthening, testes increasing in size
Penis broadening, glans develops, testes increasing in size
Adult male genitals, testes average 5–6 cm max. length

Girls

Genitals Tanner stage

Testes < 2.0 cm max. length
Testes > 2.0 cm max. length
Penis lengthening, testes increasing in size
Penis broadening, glans develops, testes increasing in size
Adult male genitals, testes average 5–6 cm max. length

Pubic hair Tanner stage

Boys and girls

No mammary tissue
Small nubbin mammary tissue behind areola
Distinct breast contour
Double contour of breast
Single adult breast contour

P1
P2
P3
P4
P5

No pubic hair
Sparse growth, slightly pigmented downy hair at base of penis or along labia
Sparse growth, darker, curled pubic hair at base of penis or along labia
Small adult configuration
Adult configuration
Height velocity graph showing different growth patterns in boys (solid line) and girls (dotted line)
Distance chart showing different growth patterns in boys (solid line) and girls (dotted line)
Puberty – pattern of growth

Girls
- grow fast at start of puberty
- peak height velocity at 12 yr (B2-3)
- slow down in later stages of puberty when breast development is mature (B4-5)
- when menarche occurs (13-13.5 yr) the girl is near final height
Puberty – pattern of growth

Boys

- grow slowly at start of puberty (G2) - still in childhood growth phase

- accelerate in mid-puberty (coincides with growth of penis, G3)

- peak height velocity at 14 yr (G4)

- further growth after pubertal development is complete (G5)
Normal puberty – which statement is true?

1. Girls enter puberty 2 years earlier than boys
2. Girls grow at their fastest in late puberty (B4)
3. The first sign of puberty in boys is penile enlargement
4. Boys grow at their fastest in late puberty (G4)
Normal puberty – which statement is true?

1. Girls enter puberty 2 years earlier than boys
2. Girls grow at their fastest in late puberty (B4)
3. The first sign of puberty in boys is penile enlargement
4. Boys grow at their fastest in late puberty (G4)
Definitions of delayed and abnormal puberty

• Delayed puberty: absence of secondary sexual development aged >13 years in girls and >14 years in boys

• Pubertal failure: failure of puberty to begin or, having begun, to complete

• Hypogonadism: impairment of the gonadal axis at hypothalamic (3°), pituitary (2°), or gonadal (1°) levels
Classification of delayed & abnormal puberty (including delayed/absent menarche)

- Central delay with an intact gonadal axis
- Central delay with impairment of the gonadal axis
- Primary gonadal impairment/disorder of sexual development (DSD)
Gonadotrophin levels in central and primary delayed/incomplete puberty

- Central delay with an intact gonadal axis
  Luteinising hormone (LH) and Follicle stimulating hormone (FSH) levels will be low
- Central delay with impairment of the gonadal axis
  LH & FSH levels will be low
- Primary gonadal impairment
  LH & FSH levels will be high (FSH>LH)
Central delay with intact H-P axis

• Constitutional delay in growth & adolescence (CDGA)

• Chronic systemic disease (e.g. inflammatory bowel disease)

• Poor nutrition (e.g. anorexia nervosa)

• Psychosocial deprivation

• Steroid therapy
Short stature and delayed puberty in a boy with coeliac disease (note abdominal distension)
Centrally delayed/abnormal puberty with impaired H-P axis

Prenatal/genetic

• Congenital hypopituitarism
• GnRH/gonadotrophin deficiency (e.g. Kallmann’s syndrome, Prader-Willi syndrome)

Postnatal

• Tumours adjacent to H-P axis e.g. craniopharyngioma, optic glioma
• Irradiation e.g. for tumour in hypothalamo-pituitary region e.g. germinoma
• Surgery e.g. for craniopharyngioma
Craniopharyngioma

L.J. Abernethy
Incomplete/absent puberty due to primary gonadal failure or to DSD

**Prenatal**
- Gonadal dysgenesis e.g. Turner syndrome, pure gonadal dysgenesis (46,XX or 46,XY)
- Complete androgen insensitivity syndrome

**Postnatal**
- Irradiation e.g. TBI +/- chemotherapy, cranio-spinal
- Galactosaemia
- Karyotype 46,XY
- Note full breast development but scanty pubic and axillary hair
- No Mullerian structures on pelvic US other than blind vagina
- Diagnosis?
Delayed puberty – which statement is true?

1. Central delay in puberty is always abnormal
2. Primary gonadal failure is associated with high levels of follicle stimulating hormone
3. Craniopharyngioma will cause central delay with an intact axis
4. The gonadotrophins LH and FSH are often high in anorexia nervosa
Delayed puberty – which statement is true?

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Clinical assessment of delayed puberty – history of presenting complaint

- Growth pattern
  longstanding (borderline) short stature followed by pubertal delay suggests constitutional delay

- General health

- Systematic review if history suggests lack of energy, tiredness

- History of asthma (associated with constitutional delay)

- Sense of smell (Kallmann’s syndrome)
Clinical assessment of delayed puberty – past medical history

• Enquiry for past events making hypogonadism likely/certain e.g.
  - bilateral cryptorchidism/orchidopexy
  - gonadal irradiation or TBI
  - craniopharyngioma post surgery

• Features suggestive of Turner syndrome e.g.
  short stature, middle ear disease, coarctation of aorta/aortic stenosis, horseshoe kidney

• Previous treatment with steroids, e.g. for asthma, nephrotic syndrome
Clinical assessment of delayed puberty – family history

• Family patterns of puberty:
  - delayed menarche (>15 years) in mother and sisters
  - delayed adolescent growth spurt in father, brothers, and uncles

• History of relatives with history of genital surgery; infertility; amenorrhoea
Clinical assessment of delayed puberty – social and educational aspects

- School - attendance, performance, peer relationships, relationships with authority figures
- Sport - ability to participate in activities such as PE and football
- Leisure activities - music, drama, computer, partying
- Family situation
Crohn’s disease causing short stature and delayed puberty

The principal feature in was fatigue and poor school attendance. Gastrointestinal symptoms were vague
Clinical assessment of delayed puberty – examination

• General assessment
  - affect, mood, well being

• Auxology
  - height and weight
  - measured parental heights
  - pubertal staging

• Nutritional assessment

• Search for dysmorphic features
Clinical assessment of delayed puberty – examination (contd.)

• Systemic examination
  - Clubbing
  - Cardiovascular assessment including femoral pulses, blood pressure
  - Examination of fundi for optic nerve atrophy
  - Urinalysis
Diagnosis of incomplete/delayed puberty

- A clinical diagnosis can usually be made on the basis of the history and examination.

- The need for investigation is determined by the clinical assessment.

- Most boys and girls with delayed puberty have constitutional delay and do not require investigation.
Investigation of delayed puberty

• No investigations required in constitutional delay other than bone age and final height prediction
• Screening investigations are indicated when the cause of delay is unclear
• Detailed investigation of gonadal axis is indicated in selected cases
Screening investigations for delayed puberty

- Chromosomes (e.g. for Turner’s syndrome)
- Basal FSH (N<10 U/l), LH, serum Testosterone and Estradiol
- IGF-1
- T4 & TSH, cortisol
- Full blood count and film, ferritin, red cell folate, LFTs, IgA anti-endomysial a’bodies
- Creatinine and electrolytes, urinalysis and culture
Investigations of gonadal axis

- **Biochemistry**
  - LHRH test (100ug I.V.) Limited value – cannot distinguish between intact and impaired central axis!
  - Prolactin
  - Additional pituitary stimulation testing including growth hormone if hypopituitarism suspected. But beware low GH levels in constitutional delay!
  - hCG test (100u/kg [max 1500u]I.M. on day 1 measuring serum testosterone on day 4)

- **Smelling test** for Kallmann’s syndrome

- **Imaging**
  - MRI scan of hypothalamo-pituitary area
  - Pelvic ultrasound examination in girls
Diagnosis and investigation of delayed puberty. Which statement is true?

1. In a 14-year-old boy with short stature and delayed puberty it is usually advisable to check growth hormone levels.

2. Delayed puberty in an adolescent with tiredness and poor school attendance rarely requires investigation.

3. Chromosome analysis may be helpful in a girl with short stature despite tall parents, and pubertal delay.

4. In a girl with delayed puberty, a history of menarche around 13 years in the mother and sisters is suggestive of constitutional delay.
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Management of delayed puberty – three scenarios

• A 14-year-old boy with short stature and delayed puberty
• A boy of 15.5 years with pubertal delay but normal stature
• A girl of 15.6 years with no breast development or menses
14-year-old boy with short stature and delayed puberty

- Always small for age, more obvious since secondary school entry
- Mild asthma, not on treatment now
- Normal birthweight and gestation.
- General health excellent (plays football three times a week)
- Looks healthy, but more like a boy of 11 or 12 years of age
- Pubertal staging shows testes 6 ml but prepubertal penis, fine pubic hair, no axillary hair
- Bone age 11 years
- Diagnosis? Other information?
Diagnosis: constitutional delay in growth and adolescence (CDGA). N.B. mother had menarche at 16 years!

- Correct management is dependant on correct diagnosis!

- Reassurance and counselling

- Prediction of final adult height

- Therapy to promote growth and pubertal development if desired
X-ray of Left Wrist and Hand for Bone Age Assessment and Height Prediction
Options for growth promoting therapy in boys with CDGA

- Oxandrolone 2.5 mg daily, for 3-6 months
- Low-dose testosterone (e.g. 50 mg IM 4-6 weekly; 40 mg orally daily for 3-6 months)
- Moderate-dose testosterone (e.g. 100-125 mg IM 4-6 weekly, for 3 months)*
- Higher dose testosterone (e.g. 200 mg three-weekly x 4)

A boy of 15.5 years with pubertal delay

- Normal birthweight and gestation
- Average in height at 11 years but no growth spurt since, so current height around 25th centile (weight 50th centile)
- No family history of pubertal delay
- Looks healthy, general examination normal
- Pubertal staging shows testes 1 ml in volume, penis pre-pubertal and smallish (2.5 cm length)
- Bone age 13 years
- Diagnosis? What other information would you request?
A boy of 15.5 years with pubertal delay

- Cannot smell burnt toast!
- LH and FSH < 1 U/l, testosterone 0.4 nmol/l (prepubertal)
- MRI scan of brain ordered (looking at olfactory tracts and bulbs)
- Diagnosis?
A boy of 15.5 years with pubertal delay

- Cannot smell burnt toast!
- LH and FSH < 1 U/l, testosterone 0.4 nmol/l (prepubertal)
- MRI scan of brain ordered (looking at olfactory tracts and bulbs)
- Diagnosis is Kallmann’s syndrome
- What counselling and treatment should the boy and family receive?
Counselling and treatment for boy of 15 with Kallmann’s syndrome

- The testes are “factories” which make a) male hormone (testosterone); and b) sperm
- With testosterone treatment the boy can expect full sexual development and normal sexual function
- Testosterone treatment is important for wellbeing (bone, heart, brain) as well as for sexual function
- Once puberty is complete (after 3 or 4 years) it may be possible to induce testicular growth and sperm production with LH & FSH injections or LHRH pump
- Lifelong testosterone therapy is going to be needed, so compliance needs to become a way of life
Options for testosterone therapy in male hypogonadism

- Intramuscular injections every 1-3 months (tried and tested; good for compliance).
- Implants with insertion of cylindrical pellets to abdomen, buttock or thigh every 3-6 months (not commonly used)
- Oral capsules daily (arguably less effective)
- Transdermal patches or gel applied daily (requires good compliance)
- Gum or buccal testosterone
- I.M. testosterone, given by practice nurse, suits most young men well
Example of intramuscular testosterone regime for pubertal induction and maintenance in hypogonadal males

• Sustanon (testosterone blend) 100mg IM once every 6 weeks for a year
• Sustanon 100mg IM once every 4 weeks for a year
• Sustanon 250mg IM once every 4 weeks for a year
• Nebido (testosterone undecanoate) 1g (4ml) IM once every three months thereafter
A girl of 15.6 years with no breast development or menses

• Presentation with absent breast development and no periods
• Slim normal looking girl, tall (height +1.6 SD) in relation to parents (+1.5 SD)
• Tanner stage B1P4A1
• 46,XX karyotype, FSH 119 IU/L, LH 33.7 IU/L, estradiol <5 pmol/L
• Uterus 3.75 cm with cylindrical shape and absent ovaries
• Diagnosis?
A girl of 15.6 years with no breast development or menses

- Presentation with absent breast development and no periods
- Slim normal looking girl, tall (height +1.6 SD) in relation to parents (+1.5 SD)
- Tanner stage B1P4A1
- 46,XX karyotype, FSH 119 IU/L, LH 33.7 IU/L, estradiol <5 pmol/L
- Uterus 3.75 cm with cylindrical shape and absent ovaries
- Diagnosis is pure gonadal dysgenesis
- What counselling and treatment should be given?
Counselling and treatment for girl of 15 years with Pure Gonadal Dysgenesis

- The ovaries are “factories” which make a) female hormone (estrogen); and b) eggs
- With estrogen replacement the girl can expect full sexual development and periods
- Estrogen is very important in both sexes for wellbeing (bone, heart, brain) as well as sexual function
- In the future it should be possible for the girl and her partner to go onto an egg donation programme so that she can carry a child.
- Lifelong hormone replacement therapy is needed. Compliance needs to become a way of life!
Options for hormone replacement therapy in girls and women with hypogonadism

• Oral estrogen therapy to induce and maintain puberty (tried and tested; convenient; but unphysiological!)

• Patch estrogen therapy to induce and maintain puberty (limited evidence suggests better bone, uterine and cardiac health; not as easy as tablets)

• Oral contraceptive pill once puberty established (convenient; only 9 months of treatment per year); or HRT preparation (as for postmenopausal women)

• In the UK oral pubertal induction is still the norm. Studies are needed to compare oral vs transdermal induction and maintenance
Pubertal induction in Turner syndrome – a study proposal

Prepubertal girls with TS randomised to Group 1 or 2 for three years

<table>
<thead>
<tr>
<th>Year 1</th>
<th>Group 1: Oral Ethinylestradiol</th>
<th>Group 2: Transdermal estradiol (Evorel patch applied twice/wk)</th>
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<tr>
<td>2µg daily</td>
<td>2µg daily for 1 year</td>
<td>3.1µg/24hrs (⅛ '25' patch) for 1 year</td>
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<tr>
<td></td>
<td>4µg daily</td>
<td>4.1µg/24hrs (⅛ '25' patch) for 1 year</td>
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<tr>
<td></td>
<td>6µg daily for 4 months</td>
<td>6.25µg/24hrs (¼ '25' patch) for 1 year</td>
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<td></td>
<td>8µg daily for 4 months</td>
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<td></td>
<td>10µg daily for 4 months</td>
<td>12.5µg/24hrs (½ '25' patch) for 1 year</td>
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<tr>
<td>Year 2</td>
<td></td>
<td>18.75µg/24 hrs (¾ '25' patch) for 6 months</td>
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<tr>
<td>4µg daily</td>
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<td></td>
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<td>25µg/24 hrs ('25' patch) for 6 months</td>
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<td>Year 3</td>
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<td>6µg daily</td>
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<td>10µg daily</td>
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<tr>
<td>25µg/24 hrs</td>
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</tr>
</tbody>
</table>

Norethisterone 5mg x 12 days/month at 3 yrs from induction, or at breakthrough bleeding, whichever is earliest
Management of delayed puberty. Which statement is true?

1. 3 months of testosterone therapy in a 14-year-old boy with constitutional delay will speed up growth and development but not alter the final height

2. A 15-year-old boy with central hypogonadism (e.g. due to hypopituitarism) can expect normal fertility with LH and FSH injections

3. Oral testosterone replacement therapy is widely held to be as effective as intramuscular testosterone

4. A girl with primary ovarian failure due to total body irradiation should be counselled to expect normal pubertal development but no menses when given estrogen and norethisterone replacement
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Acknowledgments

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