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Physiology - Topic 9 - Reproductive Physiology

Sex Determination and Sexual Differentiation

Chromosomal, gonadal and phenotypic development

- **Sex determination** establishes the developmental pathway of the gonad.
    - **Sexual differentiation** produces the internal ducts, external genitalia and later secondary sexual characteristics.
    - Chromosomes, gonadal development, hormone production and hormone responsiveness are related but distinct parts of this process.

Stages of Sexual Development

A. Chromosomal Sex

- In the common chromosomal patterns, an ovum contributes an **X chromosome** and a sperm contributes either X or Y.
- The resulting XX or XY pattern is established at fertilisation.
- Variations in chromosomes or developmental genes can alter the usual relationship between chromosomes and reproductive anatomy.

B. Gonadal Differentiation

- Early gonads are initially undifferentiated.
- **SRY** activity in the usual XY pathway promotes SOX9 and testicular development.
- **Ovarian development** involves active gene networks, including WNT4 and FOXL2; development of an ovary is not simply an absence of all developmental signals.

C. Differentiation of Ducts and External Genitalia

- Fetal **Sertoli cells** secrete **anti-Müllerian hormone**, which causes regression of the paramesonephric ducts.
- Fetal **Leydig cells** produce testosterone, initially supported strongly by placental hCG.
- **Testosterone** supports mesonephric ducts, which form the epididymis, ductus deferens and related male internal structures.
- The enzyme **5α-reductase** converts testosterone to dihydrotestosterone in target tissues.
- Dihydrotestosterone is particularly important for differentiation of the penis, scrotum and prostate.
- A normal hormone concentration cannot produce its usual effect if the relevant receptor or enzyme is absent.
- Without fetal **anti-Müllerian hormone**, the paramesonephric ducts persist and form the uterine tubes, uterus and upper vaginal region.

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- Without effective androgen action, external genital development follows the usual female pattern.
- These ductal and external changes must be considered separately from development of the gonad.

Variations in Sexual Development

Hormone Production, Conversion and Receptor Action

Characteristic Developmental Patterns

A. Complete Androgen Insensitivity

- **Complete androgen insensitivity** usually occurs in a person with a 46,XY chromosome pattern and testes, but ineffective androgen receptors.
- External genitalia are typically female.
- Sertoli cell **anti-Müllerian hormone** still acts, so a uterus is absent; pubic and axillary hair may be sparse.

B. 5α-Reductase Deficiency

- In **5α-reductase deficiency**, testosterone can support male internal ducts, but reduced dihydrotestosterone alters external genital differentiation.
- The presentation varies, and increased **testosterone** at puberty can produce further virilisation.
- This is different from resistance to all androgen action.

C. Congenital Adrenal Hyperplasia

- In a 46,XX fetus with androgen excess from **congenital adrenal hyperplasia**, external genitalia may be virilised while a uterus and ovaries are present.
- The common **21-hydroxylase** defect also reduces cortisol production and may reduce aldosterone; salt loss is a separate, potentially serious endocrine consequence.

D. Turner Syndrome

- **Turner syndrome** commonly involves loss of all or part of one X chromosome, with impaired ovarian development and reduced sex steroid production.
- Reduced ovarian function can cause incomplete spontaneous puberty, primary amenorrhoea and infertility, while short stature is a common associated feature.
- Primary ovarian failure reduces oestrogen feedback, so gonadotropins are often elevated at the appropriate developmental age.

E. Klinefelter Syndrome

- **Klinefelter syndrome** commonly has a 47,XXY pattern, impaired testicular function and infertility.

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- Small testes, reduced testosterone, impaired sperm production and variable breast enlargement are common features.
- Reduced testicular hormone and inhibin feedback commonly raises gonadotropins, although severity and reproductive function vary.
- Individual features vary, so a chromosome label does not predict every clinical finding.
- A respectful assessment considers anatomy, hormone function, chromosomes when indicated, and the person's needs.
- Sex development, gender identity and sexual orientation are different concepts.
- Physical variation must not be interpreted as a measure of personal identity or worth.

Effects of Gonad Removal

Effects Before and After Puberty

Loss of Gonadal Hormones and Gametes

A. Removal Before Puberty

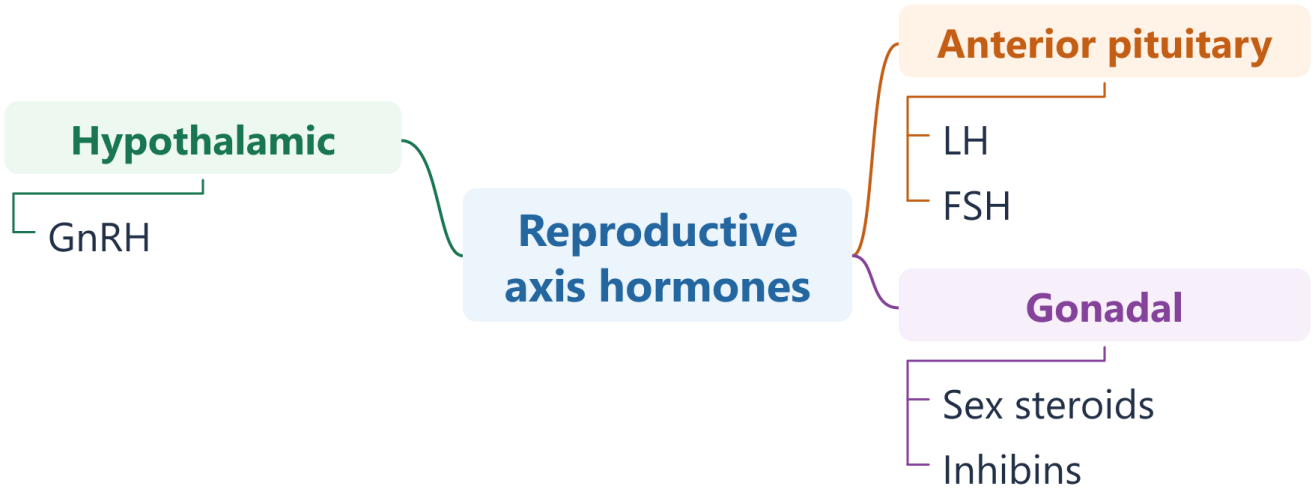
- Removal of both gonads before puberty prevents the usual gonadal rise in sex steroids.
- Secondary sexual development is impaired, growth plates may close late, and normal gamete production is lost.
- The effect depends on the person's previous development and whether hormone replacement is provided.

B. Removal After Puberty

- After puberty, bilateral testicular removal lowers **testosterone** and can reduce libido, muscle mass, bone mass and androgen-dependent hair over time.
- Bilateral ovarian removal before natural menopause causes an abrupt fall in ovarian steroids, with loss of **ovulation**, vasomotor symptoms and increased bone loss.
- Loss of gonadal steroids and inhibin removes **negative feedback**, so LH and FSH usually rise if the hypothalamus and pituitary are intact.
- Adrenal androgen secretion continues.
- Removing only one healthy gonad does not necessarily cause endocrine failure because the remaining gonad may maintain function.

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Puberty



Reactivation of the reproductive axis

Pulsatile Activation and Pubertal Onset

Pulsatile GnRH and Gonadotropins

- The hypothalamus releases **gonadotropin-releasing hormone**, or GnRH, in pulses.
- These pulses stimulate anterior pituitary LH and FSH.
- Childhood suppression of this axis is gradually reduced at puberty, and **kisspeptin**-related neuronal networks help increase pulsatile GnRH activity.
- Early pubertal pulses are particularly evident during sleep.
- Increasing **gonadotropins** stimulate gonadal growth, steroid secretion and gametogenesis.

Metabolic Influences

- Adequate nutrition, general health and genetic timing influence this change; **leptin** signals energy availability but is not a single independent puberty switch.

Gonadarche and Adrenarche

- **Gonadarche** means activation of the gonadal axis.
- **Adrenarche** means increased adrenal androgen secretion, which contributes to pubic hair, axillary hair and body odour.
- Pubic hair alone therefore does not prove complete activation of the gonadal axis.
- Puberty usually starts between **8 and 13 years in girls** and **9 and 14 years in boys**, with population and individual variation.
- **Breast budding** is commonly the first visible sign in girls.
- Testicular enlargement, rather than penile growth or facial hair, is commonly the first sign in boys.

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Sequence and Tanner staging

Tanner Stages of Puberty

- **Tanner staging** describes physical development in five stages.
  - Stage 1 is prepubertal and stage 5 is the mature pattern.
  - Breast development, male genital development and pubic hair are assessed separately because their stages need not match.

A. Stage 2: Onset of Puberty

- **Stage 2** marks breast budding in girls and enlargement of the testes and scrotum in boys, with little penile growth.
- **Stage 2 pubic hair** is sparse and lightly pigmented, appearing along the labia or at the base of the penis.

B. Stage 3: Continuing Growth

- **Stage 3** shows further breast enlargement without a separate areolar mound.
- **Stage 3 in boys** includes penile growth mainly in length while the testes and scrotum enlarge further.
- **Stage 3 pubic hair** becomes darker, coarser and curlier and spreads over the pubic region.

C. Stage 4: Advanced Development

- **Stage 4** shows a secondary areolar mound in girls.
- **Stage 4 in boys** includes further development of penile width and the glans, and darkening of the scrotum.
- **Stage 4 pubic hair** has an adult character but a smaller distribution, without the usual stage-5 spread to the medial thighs.

D. Stage 5: Adult Maturity

- At **Tanner stage 5**, breasts have an adult contour with the areola usually returning to the general breast contour.
- Male genitalia reach adult size and shape, and pubic hair has an adult distribution that may extend to the medial thighs.

Sequence and Growth Changes

A. Sequence in Girls

- In girls, **breast budding** is followed by further breast enlargement and changes in the areola.
- The growth spurt usually occurs relatively early.
- **Menarche** commonly occurs about two to three years after breast development begins, and early cycles may be anovulatory while the axis matures.

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