YU - Medicine Passion Academic Team

The Urogenital System

Sheet# 7 - Physiology

Lec. Title : Sexual Differentiations & Puberty

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Sexual differentiation and puberty

للتأكيد، رقم هاي المحاضرة 7، المفروض ضلت محاضرة عن ال renal physiology ما بعرف إذا الدكتورة رح تبعثها أو لا..

تبدأ المحاضرة في الكتاب – النسخة السادسة- من صفحة 462

دعواتكم، كل الحُبّ...

Sexual differentiation

- Sexual differentiation can be characterized in three ways:

1. genetic sex, whether the sex chromosomes are XY or XX
2. gonadal sex, whether the gonads are testes or ovaries
3. phenotypic or genital sex, whether the person looks like a male or a female

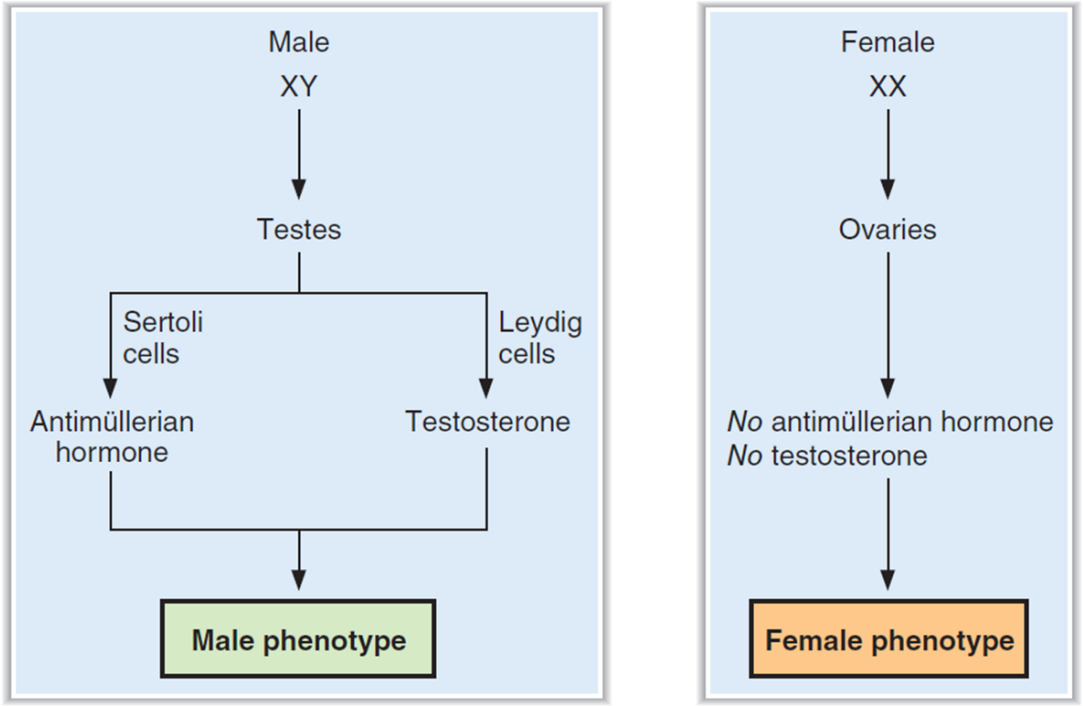

FIGURE 7-15 Sexual differentiation in males and females.

- **First: Genetic sex :**

is defined by the sex chromosomes, **XY in males** and **XX in females.**

- During the **first 5 weeks** of gestational life, the gonads **are indifferent** or **bipotential** - they are neither male nor female.

- At approximately gestational **week 7 in genetic males**, the gene product of the sex-determining region of the Y chromosome **(SRY gene) causes the testes to begin developing**.

- At gestational **week 9 in genetic females** (in the absence of the SRY gene) the **ovaries begin to develop**.

❖ **Genetic sex normally determines gonadal sex**, and the gonads appear in **males slightly before** they appear in females.

- **Second: Gonadal sex**

is defined by the presence of the gonads; testes in males and ovaries in females.

- The **testes**, the male gonads, consist of three cell types:
  1. **Germ cells**: produce **spermatogonia,**
  2. **Sertoli cells**: synthesize a glycoprotein hormone called ***antimüllerian hormone***
  3. **Leydig cells**: synthesize ***testosterone***.
- The **ovaries**, the female gonads, also have three cell types:
  1. **Germ cells:** produce **oogonia**.
     - Meiotic oogonia are **surrounded by granulosa cells** and **stroma**
       - called ***oocytes*** in this configuration.
     - *They remain in the prophase of meiosis until ovulation occurs.*
     - Attrition of oocytes: **apoptosis**
  2. **Granulosa cells**: synthesize **estradiol**.
  3. **Theca cells**: synthesize **progesterone** and **estradiol**
  - We start off oogensis with 7 million oogonias.
- Estradiol is **steroidal** hormone and works intracellularly, its synthesis in ovaries follows the **2-cell theory**. This means that it starts with theca cells (as **precursors**) and continues to granulosa cells until estradiol is formed.

- **Third: Phenotypic sex**

is defined by the physical characteristics of the internal genital tract and the external genitalia.

i. **Male phenotyoe:**

- The testes of gonadal males synthesize and secrete **antimüllerian hormone** and **testosterone**.
- **Antimüllerian** hormone works on the **cell surface** since it is a glycoprotein.
- **Antimüllerian hormone causes atrophy of the *müllerian ducts*** (which would have become the female internal genital tract).
- If the **antimüllerian hormone is not high enough in males**, this leads to **gender ambiguity (with both gonads**).

- **Testosterone** hormone works **inside the cell** since its a steroid.
- **Testosterone** stimulates the **growth** and **differentiation** of **the *wolffian ducts***, which develop into the male **internal genital tract**(epididymis, vas deferens, seminal vesicles, and ejaculatory ducts.)
- Testosterone from each testis acts **ipsilaterally** (same side) on its own wolffian duct. And **does *not* have** to be converted to dihydrotestosterone (in formation of internal genital tract)….will be discussed.
- The **external male genitalia**, the penis and scrotum, **differentiate** at gestational weeks 9–10. Growth and development of **the external male** genitalia **depend on conversion of testosterone to dihydrotestosterone** (Vs internal tract**)** and the **presence of androgen receptors on the target tissues**
- Phenotypic sex is the result of **hormones binding to their receptors.** Some diseases effect the receptors and render them **nonfunctional**. This leads to **ambiguous gender characteristics**. This is because all three aforementioned steps need to be followed to create a male with male characteristics.

Clinical physiology cases

CASE # 1

DESCRIPTION OF CASE. A girl who is apparently normal begins to develop breasts at age 11, and at age 13, she is considered to have larger-than-average breasts among her peers. However, by age 16, she has not begun to menstruate and has scant pubic and axillary hair. Upon pelvic examination, a gynecologist notes the presence of testes and a short vagina, but no cervix, ovaries, or uterus. Chromosomal evaluation reveals that the girl has an XY genotype. Suspecting a form of androgen insensitivity syndrome (a testicular feminization), the physician orders androgen-binding studies in genital skin fibroblasts. The studies show no binding of testosterone or dihydrotestosterone, suggesting that androgen receptors in the tissue are absent or defective. She has mildly elevated levels of plasma testosterone and elevated levels of luteinizing hormone (LH). The young woman's testes are removed, and she is treated with intermittent estrogen replacement therapy. She is advised, however, that she will never have menstrual cycles or be able to bear children.

EXPLANATION OF CASE. This girl has a female phenotype with female external genitalia (lower vagina, clitoris, and labia). At puberty, she develops breasts. However, she has a male genotype (XY) and male gonads (testes).

The basis for her disorder, a form of androgen insensitivity syndrome, is lack of androgen receptors in target tissues, which results in resistance to androgens. Her testes, which are normal, secreted both antimüllerian hormone and testosterone in utero. As in normal males, antimüllerian hormone suppressed development of the müllerian ducts in utero; therefore, the girl has no fallopian tubes, uterus, or upper vagina. The testes also secreted testosterone in utero, which *should have* stimulated growth and differentiation of the wolffian ducts into the male genital tract and development of the male external genitalia. The male genital tract and external genitalia *did not*develop, however, because the target tissues lack androgen receptors. Thus, although the testes secreted normal amounts of testosterone, testosterone could not act on the tissues of the male genital tract. (Lack of androgen receptors also explains the girl's scant body hair at puberty.) The female phenotype (short vagina, labia, and clitoris) is present because, in the absence of testosterone receptors, the fetus became a phenotypic female by "default."

The girl's breasts developed at puberty because her testes are producing estradiol from testosterone, stimulated by the high circulating levels of LH. The estradiol then promotes breast development.

TREATMENT. In androgen insensitivity syndrome, because the testes can develop a neoplasm, they are removed. Following removal of the testes (and, therefore, removal of the testicular source of estradiol), the girl is treated with estrogen therapy to maintain her breasts. She will not be able to bear children, however, because she lacks ovaries and a uterus.

ii. Female phenotype

- The **ovaries** of gonadal females secrete **estrogen**, but **some** antimüllerian hormone & **no** testosterone.
- Without testosterone, the **wolffian ducts do not differentiate**.

- the müllerian ducts are not suppressed and therefore **develop into the female internal genital tract.(**fallopian tubes, uterus, and upper one-third of the vagina)

- The **external female genitalia** (clitoris, labia majora, labia minora, and lower two-thirds of the vagina) **does not require any hormones**

- **BUT,** growth of these structures to **normal size depends on the presence of estrogen.**

- **in girls**, low levels of AMH ***allowing the development of female reproductive structures***.
- The **AMH** level **in young girls remains low until puberty**, when the ovaries begin to produce it and levels increase. AMH will then steadily **decline in women over their reproductive years**, becoming *very low* and eventually *undetectable* **after menopause.**

- **the amount of AMH present is a reflection of follicular growth**.

- So, AMH level may be useful in determining a woman's remaining egg maturation potential (**ovarian reserve**) and her likelihood of conceiving.
- Females have between **1-3 ng/ml of antimüllerian hormone,normally.**
- **Lower than 1 ng/ml** can make a female **non-fertile.**

CASE # 2

DESCRIPTION OF CASE. At birth, a baby is found to have ambiguous external genitalia. There is no penis, and a clitoris is significantly enlarged. Chromosomal evaluation reveals that the baby has an XX genotype. She is found to have ovaries but no testes. Tests confirm that the baby has a form of adrenal hyperplasia in which there is congenital lack of the adrenal cortical enzyme 21β-hydroxylase. Treatment involves surgical reconstruction of the external genitalia to conform to the female phenotype and the administration of glucocorticoids and mineralocorticoids. The child will be raised as a female.

EXPLANATION OF CASE. The baby has a congenital absence of 21β-hydroxylase, the adrenal enzyme that normally converts steroid precursors to mineralocorticoids and cortisol (see Chapter 9, Fig. 9-23). As a result of this defect, steroid precursors accumulate behind the enzyme block and are directed toward the production of the adrenal androgens, dehydroepiandrosterone and androstenedione. The high levels of androgens caused masculinization of the external genitalia (enlargement of the clitoris) in utero. The genotype is XX (female), and the internal organs are female including ovaries, fallopian tubes, uterus, and upper vagina. The fallopian tubes, uterus, and upper vagina developed because, without testes, there was no source of antimüllerian hormone to suppress differentiation of müllerian ducts into the female genital tract. There is hyperplasia of the adrenal cortex because the absence of cortisol increases secretion of adrenocorticotropic hormone (ACTH), which then has a trophic effect on the adrenal cortex.

TREATMENT. Surgical correction of the ambiguous external genitalia involves reconstruction to conform to a phenotypic female. Because the baby has normal ovaries, fallopian tubes, and uterus, she should begin normal menstrual cycles at puberty and have a normal reproductive capacity. Hormone replacement therapy has two goals: (1) to replace the missing adrenal glucocorticoids and mineralocorticoids and (2) to suppress ACTH secretion (by the negative feedback of glucocorticoids on the anterior pituitary) to reduce the adrenal output of androgens and prevent further masculinization.

Puberty

Gonadotropin secretion over the lifetime

- In both males and females, gonadal function is driven by the hypothalamic-pituitary axis, whose activity varies over the life span.
- Secretion of gonadotropin-releasing hormone (GnRH) begins at gestational week 4, but its levels remain low until puberty.
- Secretion of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) begins between gestational weeks 10 and 12. The levels of FSH and LH remain low until puberty.

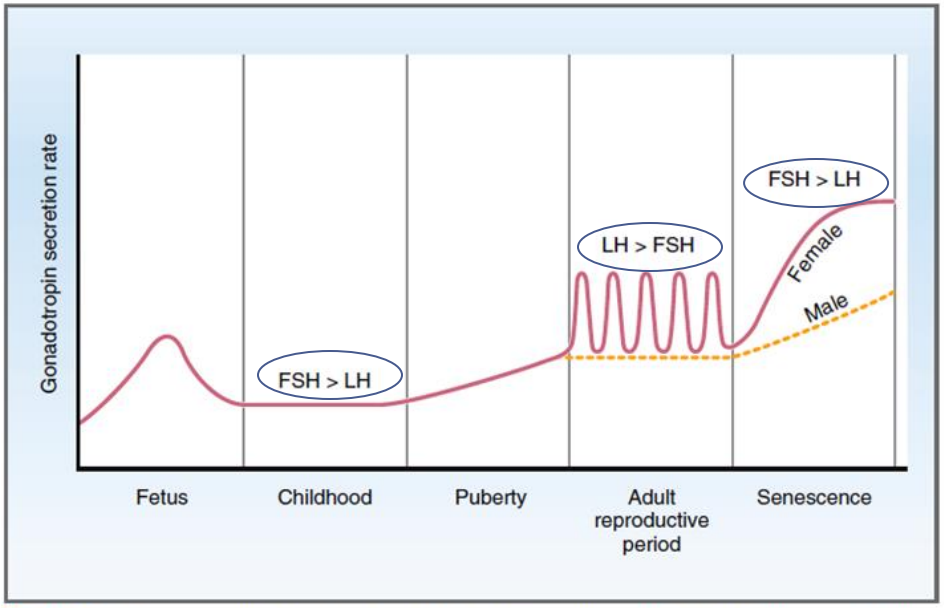

Fig. 10.2 Gonadotropin secretion over the life span in males and females. *FSH*, Follicle-stimulating hormone; *LH*, luteinizing hormone.

Pulsatile Secretion of GnRH, FSH, and LH

- The primary event at puberty is the initiation of **pulsatile secretion of GnRH** → parallel **pulsatile secretion of FSH and LH** by the anterior pituitary gland.
- Early events of puberty include:
  - appearance of **large nocturnal pulses of LH** during rapid eye movement (REM) sleep.
  - **Increased sensitivity of the GnRH receptor** in the anterior pituitary.
- at puberty, **GnRH up-regulates its own receptor** in the **anterior pituitary,** and a given concentration of GnRH produces a *greater stimulation of FSH and LH secretion.*
- Pulsatile secretion of FSH and LH *stimulates secretion of the gonadal steroid hormones*, **testosterone and estradiol** (responsible for the appearance of the **secondary sex characteristics**)
- *Secondary sex characteristics include: surging in growth, hoarseness of voice in males, start of menstrual cycle in females, prominent facial hair growth in males etc.*

- The onset of **the maturational process** at puberty is **genetically programmed**, and **familial patterns** are evident.

- The mechanisms underlying the onset of pulsatile GnRH secretion → not well known.
  - May be **gradual maturation of the hypothalamic neurons** that synthesize and secrete GnRH.
  - The **central nervous system** and **nutritional status** may alter the process. (extreme stress, caloric deprivation or low weight in girls delays the onset of puberty)
  - **Melatonin may be a natural inhibitor of GnRH**
    - Removal of the **pineal gland precipitates early puberty**.
    - Melatonin levels are **highest during childhood** and **decline in adulthood.**
    - If **its too high** it will **delay puberty** but its high level **does not** effect adults.
  - Another hormone that **inhibits GrNH, FSH and LH** is **prolactin**.

Characteristics of puberty

- **Pulsatility** of the hypothalamic-pituitary axis is ***required*** **for normal reproductive function.**
- In the treatment of persons with delayed puberty **caused by GnRH deficiency:**
  - If a GnRH analogue is administered in intermittent pulses to replicate the normal pulsatile secretory pattern, **puberty is initiated** and **reproductive function is established.**
  - However, if a long-acting GnRH analogue is administered, **puberty is not initiated.** The events of puberty and their timing are illustrated in

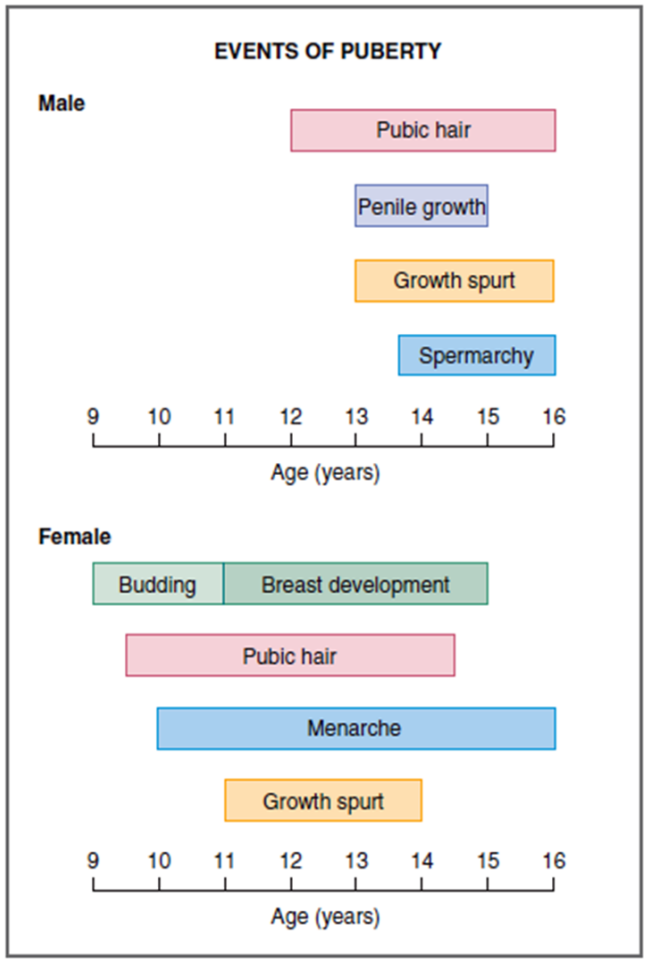

Fig. 10.3 Major events of puberty in males and females.

Puberty in boys

- it's associated with : **Activation of the hypothalamic-pituitary axis**, **Leydig cell proliferation** in the testes and **Increased synthesis** and **secretion** of **testosterone** by the Leydig cells.
- There's Growth of the testes, largely because of an increased number of seminiferous tubules.
- There's Growth of the sex accessory organs such as the **prostate**.
- There's Pronounced **linear growth spurt** and **closing** of the **epiphyses** when adult height is attained.
- As plasma levels of testosterone increase,
  - **at age 12**, facial, pubic, and axillary hair appears
  - **At age 13**, there is growth of the penis
  - Their growth spur starts **at 13 and lasts till 16.**
  - lowering of the voice due to increased size of the larynx and vocal cords
  - **initiation of spermatogenesis**.

Puberty in girls

- Associated with the **activation of the hypothalamic-pituitary axis**, which drives the synthesis of **estradiol by the ovaries.**
- ***(From 9-10 years)*** The first observable sign is **budding of the breasts**.
- Two years later → **menarche** (onset of the menstrual cycle). sometimes start from age 10
- (**from 11-14 years**)The growth spurt and closure of the epiphyses typically **begin and end earlier in girls than in boys.**
- The appearance of pubic and axillary hair precedes menarche and is **dependent on increased secretion of adrenal androgens.** (called adrenarche)