Physiology Team

REPRODUCTIVE BLOCK

Revision - Midterm

Lectures:

1. Hypothalamic & pituitary gonadal axis
2. Physiology of Androgens & control of male sexual act
3. Physiology of ovarian cycle
4. Physiology of uterine cycle
5. Puberty in males & females

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LECTURE 1: HPA AXIS

Control of male sexual functions by hormones from the hypothalamus and anterior pituitary gland :

- GnRH (Gonadotropin releasing hormone) and its effect in **increasing the secretion of LH and FSH**:.
- **GnRH** peptide **secreted by the arcuate nuclei in the mediobasal hypothalamus of the hypothalamus.**
- **The secretion of LH** by the anterior pituitary is **also cyclical flowing the pulsatile release of GnRH .**

Testosterone regulation of its production by LH:

- **Testosterone is secreted by leydig cells**, in the interstitium of the testis, **by LH stimulation** from the AP and **its release is directly proportional to the amount of LH**.
- Mature leydig cells are found in **infants testis , few weeks after birth & then disappear (in childhood) until puberty when it appear again.**

Inhibition of anterior pituitary secretion of LH and FSH by testosterone – negative feedback control of testosterone secretion:

- Testosterone secreted by the testis in response to LH stimulation, but when it exceeds certain limit the testosterone will cause **negative feedback** on both AP and hypothalamus but **mostly on the hypothalamus**.

Regulation of spermatogenesis by FSH and testosterone:

- **FSH** binds with specific FSH receptors attached to **the sertoli cell**.
- causes these cells **to grow & secrete spermatogenic substances**.
- **testosterone & dihydrotestosterone** diffuses into the seminiferous tubules from the leydig cells affect the spermatogenesis, **so both FSH & testosterone are necessary to initiate spermatogenesis.**

Negative feedback control of seminiferous tubule activity – role of the hormone inhibin:

- When the seminiferous tubules fail to produce sperm secretion of FSH from the AP increases.
- Conversely, when spermatogenesis proceeds **rapidly** pituitary secretion of FSH diminishes.
- This is due to the secretion of **inhibin hormone from the sertoli cells** which **strongly** inhibit the AP- FSH

So, we have 2 pathways for the negative feedback:

1. through **testosterone** from leydig cells which inhibit the secretion of GnRH & **LH** (mainly acts on the hypothalamus).
2. through **inhibin** hormone from sertoli cells which inhibit the secretion of the **FSH** and GnRH (mainly acts on the AP)

Lecture 2: Androgens & control of Male Sexual Act

Spermatogenesis

- Begin at age of 13 (puberty) and continue throughout life
- It occur in the seminiferous tubules
- Stimulated by
  - anterior pituitary gonadotropic hormones (FSH and LH)
  - testosterone
  - estrogen
  - growth hormone

Physiology of Sperms

- Are Maturated in the epididymis
- Majority are stored in the vas deferens
- Become motile and capable of fertilizing after ejaculation
- In female genital tract :
  - Their activity is enhanced in a neutral and slightly alkaline medium
  - Their life expectancy is only 1 to 2 days
- Normal male count vary between 35 million to 200 million sperm
- Sperm count below 20 million leads to infertility.

Leydig cells

- numerous in the newborn male infants for the first few months of life
- non-existent in the testis during childhood
- active at puberty to secrete testosterone

Physiology of seminal vesicles

- secrete mucoid material containing
  - fructose
  - citiric acid
  - fibrinogen
  - large amount of **prostaglandin** (most important)

because **it helps in fertilization** , by reacting with cervical mucus making it more receptive to sperm movement and inducing peristaltic contractions in uterus and fallopian tubes to propel the sperm to the ovaries

Physiology of the prostate gland

- alkaline prostate fluid is important for successful fertilization by :
  - neutralizing the acidic fluid of the vas deferens and other seminal fluids
  - enhances motility and fertility of sperm

Semen:

1) **Composed of**
   - (~10%) Fluid and sperm from vas deferens
   - (~30%) fluid from the prostate gland
   - (~60%) fluid from the seminal vesicles
   - small amounts from the mucous glands the bulbourethral glands.
2) **Average pH is 7.5**

Capacitation of the spermatozoa:

Is a process in which:

- **Inhibitory factors** in the seminal fluid which suppress the sperm activity **are washed free** by uterine and fallopian fluids.
- **cholesterol is withdrawn** from the sperm membrane
- sperm **membrane become more permeable to Calcium ion** which increases their motility and help to release hyaluronidase and proteolytic enzymes from acrosome **(acrosome reaction)** which aid in penetrating the ovum
- It require **1 to 10 hours**

Testosterone and other male sex hormones:

- Testosterone is Secreted by leydig cells
- Testosterone is the most abundant while dihydrotestosterone is the most active
- **During fetal life + 10 weeks after birth** , placenta chorionic gonadotropin stimulate the testis to produce testosterone
- **During childhood** , no testosterone is produced
- **At puberty** , anterior pituitary gondaootropic hormones stimulate testosterone production

Testosterone function:

  - **During fetal life:** responsible for development of penis, scrotum, prostate gland, seminal vesicles and male genital duct. also , it cause descent of the testis
  - **After puberty:** is responsible for the development of adult primary and secondary sexual characteristics
- Testosterone is converted to dihydrotestosterone by 5 α reductase

Stages of Male sexual act

Stage	Action	Nerve supply
1) penile erection	Erection of the penis	parasympathetic impulses
2) lubrication	urethral glands and bulbourethral glands secrete mucous	parasympathetic impulses
3) emission	• Contraction of the vas deferens & ampulla to expel sperm • Contraction of the prostate &seminal vesicles to expel their fluid • All these fluid mix in the internal urethra with the mucous secreted by the bulbourethral glands to form the semen	sympathetic nerves
4) ejaculation	Fullness of the internal urethra causes rhythmical contractions of the internal genital organs which increases their pressure to ejaculate the semen	Sensory impulses through pudendal nerves to the sacral region of the cord

Adiposogenitial syndrome (Froehlich's syndrome or hypothalamic eunuchism):

hypogonadism due to genetic inability of the hypothalamus to secrete normal amount of GnRH & abnormality of the feeding center of the hypothalamus result in obesity with eunuchism.

LECTURE 3: Physiology of Ovarian Cycle

There are 2 results of the female sexual cycle:

1. Single ovum is released from the ovaries each month
2. Uterine endometrium is prepared for implantation for the fertilized ovum.

The ovarian changes during the sexual cycle depend on FSH & LH. In the absence of these hormones, the ovaries remain inactive (throughout childhood).

In a female child:

1. Each ovum is surrounded by single layer of granulose cells. (Primordial follicle)
2. Granulosa cells maintain the ovum in its primordial state by secreting oocyte maturation inhibiting factor.

After puberty:

LH & FSH stimulate some primordial follicles to grow into primary follicles by:

1. Increasing the size of the ovum.
2. Growth of additional layers of granulosa cells.

- Proliferation of granulosa cells to multiple layers + development of theca cells, up to antral follicle are primarily under the effect of FSH.

Ovulation:

1. Occurs 14 days after the onset of menstruation in a 28 day cycle.
2. LH surge occurs 2 days before it.
3. Estrogen secretion drops 1 day before it while progesterone increases.
4. Final result is rupture of the follicle and releases of the ovum surrounded by a mass of granulose cells (Corona radiate).

- LH surge → conversion of granulose & theca cells to progesterone secreting cells instead of estrogen.

Luteal phase:

1. After expulsion of the ovum, the remaining granulose and theca internal cells change into lutein cells. Collectively known as Corpus luteum. **(Done by LH)**
2. Granulosa lutein cells begin to secrete large amounts of estrogen and progesterone. **(Done by LH)**
3. Theca lutein cells secrete androgens which are converted to female sex hormones in granulosa lutein cells.
4. 7-8 day after ovulation → corpus luteum grows to 1.5 cm in diameter.
5. 12 days after ovulation (without fertilization) → corpus luteum begins to involute and forms corpus albicans. **(Due to low levels of LH & FSH)**

- If pregnancy occurs, HCG from placenta prolongs the life of corpus luteum for 2-4 months.

Involuation of corpus luteum and onset if the next ovarian cycle: important

- High levels of estrogen & progesterone from corpus luteum have a strong negative feedback effect on AP → inhibition of LH & FSH secretion. + Inhibin from **lutien** cells inhibits FSH → low levels of FSH & LH cause involution and degeneration of corpus luteum.
- After involution of corpus luteum → cessation of secretion of estrogen & progesterone (26^{th} day) → removal of feedback inhibition on AP → increased secretion of FSH & LH to initiate the growth of new follicles, beginning a new ovarian cycle.

LECTURE 4: Physiology of Uterine Cycle

Proliferative phase:

- **Estrogen** is the dominant hormone.
- Occurring **before** ovulation.
- **At the beginning** of each cycle the endometrial is **desquamated** by the menstruation.
- **Before ovulation**, the endometrial **thickness is increases** due to the increase number of stromal cells & progressive growth of the glands and new blood vessels.
- **Re-epithelization** of the endometrial surface

Secretory phase:

- **Progesterone** is the dominant hormone.
- Occurring **after** ovulation.
- These secretory changes prepared the endometrium for **implantation.**

Estrogen	**Causes slight proliferation in the endometriam**
progestrone	**Causes swelling & secretory development of the endometrium.**
Glands	**Increase the tortuosity + excess secretory substance accumulate in the gland.**
Stromal cells cytoplasm	**Increase lipid & glycogen deposits in the cell & increase blood supply to the endometrium.**

Menstruation:

- **If the ovum is not fertilized:** corpus luteum **involutes**, **estrogen & progesterone decrease.**
- **24 hrs. before menstruation**: vasospasm, release of PG, decrease nutrients to endometrium & loss of hormonal stimulation.
- The **normal menstrual blood** is **non-clotting** due to the presence of **fibrolysin.**
- **During menstruation** the uterus is highly resistant to infection because of leukocyte release.
- There is **positive feedback effect of estrogen before ovulation** (pre-ovulatory LH surge)
- During the **post-ovulatory** phase (between ovulation & the beginning of menstruation), the corpus luteum secretes large quantities of both progesterone, estrogen & inhibin which all together cause negative feedback effect on AP & hypothalamus to inhibit both FSH & LH.
- **2-3 days before menstruation**: corpus luteum regresses & secretion of estrogen, progesterone & inhibin **decreases** which remove the negative feedback effect on AP hormones >> a day after menstruation FSH secret begin to increase & LH slightly increase.
- **During 11-12** days **of the follicular growth**, the rate of FSH & LH secretion **decreases** slightly because of negative feedback effect of estrogen on AP.

LECTURE 5: Puberty in Males & Females

Puberty:

"A stage of human development when sexual maturation and growth are completed and result in ability to reproduce"

- Accelerated somatic growth
  - Maturation of primary sexual characteristics (gonads and genitals)
  - Appearance of secondary sexual characteristics (pubic and axillary hair, female breast development, male voice changes,...)
  - Menstruation and spermatogenesis begin

Terms and events:

- **Thelarche:** development of breast
- **Puberache:** development of axillary & pubic hair
- **Menarche:** the first menstrual period
- **Adrenarche:** the onset of an increase in the secretion of androgens, responsible for development of pubic and axillary hair, body odour and acne.

Hormonal changes:

- Young children => LH and FSH levels insufficient to initiate gonadal function
- Gradual activation of the GnRH (LHRH)
- Between 9-12 yrs, blood levels of LH, FSH increase
- Increases frequency and amplitude of LH pulses.
- Amplitude of pulses increases, especially during sleep
- Gonadotropins stimulate secretion of sexual steroids (estrogenes and androgenes)
- Extragonadal hormonal changes (elevation of IGF-I, and adrenal steroids)
- Nocturnal GnRH pulsatility precedes phenotypic changes by several years.
- GH secretion from pituitary also increases
- TSH (thyroid stimulating hormone) secretion from pituitary increases in both sexes

Female hormonal changes:

- Surge of LH release initiates 1st ovarian cycle >> not sufficient to cause ovulation
- Estrogen levels in blood increase, due to growing follicles and cause secondary sexual characteristic to develop :
    - growth of pelvis
    - deposit of subcutaneous fat
    - growth of internal reprod. organs, external genitalia
- Androgen release by adrenal glands increases (not as much as in male) growth of pubic hair, lowering of voice, growth of bone, increased secretion from sebaceous glands
- Breast enlargement usually first sign >> Thelarche
- Menarche usually 2-3 yrs after breast development

Male hormonal changes :

- LH and FSH release increases ~10 yrs. of age
- adrenals also secrete Androgens which initiate growth of sex accessory structures (e.g. prostate), male secondary sex characteristics (facial hair, growth of larynx)
- First signs often go unnoticed >> Testicular enlargement
- Penile and scrotal enlargement occur approx 1 yr after testicular enlargement
- Begins of spermatogenesis; androgen secretion
- Sertoli cells also secrete some estrogen

Timing of Puberty:

- Genetic : 50-80%
- Nutrition
- Life style

Nutrition :

- Critical body weight must be attained before activation of the reproductive system
- obese girls go through early menarche
- malnutrition is associated with delayed menarche
- primary amenorrhea common in lean female athletes
- Leptin : **Increase** GnRH >> Reproduction

  Increase Sympathetic NS >> Thermogenesis

  Decrease NPY >> Decrease the food intake

A) Precocious Puberty: Girls <8 years old | Boys <9 years old

1. **Gonadotrophin-dependent (true / central) "All hormones are HIGH"**
   - Intra-cranial lesions
2. **Gonadotrophin-independent**
   - Precocious pseudopuberty >> FSH & LH suppressed >> No spermatogenesis or ovarian development
   - Congenital adrenal hyperplasia (CAH)
   - Sex steroid secereting tumours
     - adrenal or ovarian

B) Delayed puberty: Girls 13 years old | Boys 14 years old

- Initial physical changes of puberty are not present
- **Causes :-**
- **Gonadal failure (Hypergonadotrophic hypogonadism)** : Turner's Syndrome
  "All Hormones are HIGH BUT NO RESPONSE"
- **Gonadal deficiency**
  - Congenital hypogonadotrophic hypogonadism (+anosmia)
  - Hypothalamic/pituitary lesions.

GOOD LUCK