Reproductive functions

Development of male gender

- genetic sex is determined at the moment of conception by X and Y chromosomes
- development of gonadal sex requires the presence of male or female gonads
- intrauterine and post-natal development of phenotypic sex depends on hormones produced by the gonads
- these sex hormones also influence the development of the CNS - psychological sex
- the male gonad, the testis consists of curled tubules (seminiferous)
- in the wall of the tubules Sertoli-cells (nurse-cells) are found, their function is the spermatogenesis; between the tubules Leydig cells synthesize the gonadal hormones
Hormone production in the testis

- the major steroid produced by the testis is testosterone, it is transformed into dihydrotestosterone in the target cells - it is the most effective androgen
- the necessary cholesterol is provided by LDL particles and by de novo synthesis (50-50%)
- testosterone is transported in blood by testosterone-binding globulin (50%) and albumin (50%)
- effects of the hormones
  - prenatal life: gonadal and phenotypic sex
  - during puberty: male genitalia, secondary sexual marks
  - after puberty: spermatogenesis and preservation of sexual marks
- steroid synthesis is facilitated by LH (ICSH) through cAMP
- LH acts on functioning and synthesis of enzymes
- androgens (and oestradiol) inhibit GnRH, LH and FSH; inhibin from Sertoli-cells FSH

Androgens and development I.

- after the 13 intrauterine week (second trimester) high LH and FSH level, Leydig-cells produce testosterone (maternal hCG also facilitates), no feedback regulation yet - hormonal concentration approaches adult levels
- testosterone causes differentiation of the same group of cells into male genitalia that form female genitalia in girls
- hormone level is low in the last trimester, but there is a few-month long postnatal peak in the first year - function unknown
- around the age of 6-7 androgen production in the adrenal cortex increases adrenarche - hair growth on limbs and around genitalia, acceleration of growth
- after the age of 12 hormone production in the testis starts to increase reaching its maximum in a few years

3/24

4/24
Androgens and development II.

- androgen effects: testis, epididymis, prostate, seminal vesicles, penis grow in size, axillary and pubic hair becomes thicker and curlier, larynx grows, vocal chords thicken
- anabolic effects: growth rate (8 cm/year), bone density, skeletal muscle mass increases
- psychological effects: libido, ability for copulation, emotional lability
- castration after puberty: atrophy of prostate, epididymis, seminal vesicles, regression of muscular tissue, libido ceases
- male menopause: moderate decrease in androgen hormone secretion - no direct relationship between hormone level and sexual activity

Spermatogenesis I.

- total length of seminiferous tubules is 1 m
- on the basal membrane Sertoli-cells connected by tight junctions are sitting
- the junctions separate the wall of the tubules into basal and adluminal compartments: hormones act only in the basal part - blood-testis-barrier
- in the basal compartment between Sertoli-cells stem cells are also found
- their division produces partly stem cells, partly early spermatogonia connected with each other through thin cytoplasmic bridges
- spermatocytes develop from spermatogonia during the meiotic prophase
- Sertoli-cells form processes below the interconnected spermatocytes transferring them into the adluminal compartment
- this is a precondition for meiosis
**Spermatogenesis II.**

- during meiosis round spermatids (1n) are formed from spermatocytes
- further maturation to spermatozoa occurs while spermatids are attached to Sertoli-cells and move gradually toward the lumen
- total maturation lasts for 70 days
- the process requires FSH and testosterone (depending on LH); these hormones are acting through Sertoli-cells (barrier!)
- vitamin-A is also needed – gene expression
- further maturation in epididymis (total length 3-4 m) in 12-24 days - cytoplasm lost, self-dependent motility and fertilization ability
- sperm production is 2x10^8 /day
- lower than rectal temperature is essential: Japanese contraception, problem of tight jeans, descend of testes from the abdomen during development, and during springtime in rabbits
- cooling is achieved by the location outside of the body and by the countercurrent blood flow providing high hormone levels as well

**Physiology of the sexual act I.**

- several emotional and moral aspects – we deal only with the physiology
- phases of the sexual act (intercourse, coitus): erection, intromission, ejection of semen (emission and ejaculation)
- mechanism of erection:
  - central effect: visual and auditory stimuli, imagination and fantasy, in animals odors as well
  - tactile stimuli: reflex arc through sacral spinal chord
  - in general these factors act together
  - during REM phase it always occurs after puberty
- mechanism of erection:
  - increase of blood content in erectile tissues - volume increases 8-fold
  - two dorsal corpora cavernosa, ventral corpus spongiosum, continuing in glans penis
  - within the erectile structures sinusoids and trabecular structure made up by connective tissue and smooth muscle
  - the corpora cavernosa are surrounded by a strong connective tissue capsule: tunica albuginea
  - skeletal muscles in the lumbosacral region also contribute to erection
Physiology of the sexual act II.

- trabecular smooth muscles bear sympathetic α1-receptors - they are slightly contracted at rest, inconvenient stimuli, cold water cause further contraction - penis size decreases
- erection starts with the relaxation of arterioles and trabecular muscles, influx increases, but outflow keeps pace with it, penis elongates
- further relaxation, influx exceeds outflow, venules are pressed against the tunica albuginea, outflow blocked
- pressure reaches arterial value, contraction of skeletal muscles increase it further; penis closes an angle of 45-90 with abdominal wall
- erection is caused by parasympathetic effects - NO release (axon terminals, endothelium), presynaptic cholinergic inhibition on sympathetic terminals

  • ejection of semen
    - spinal reflex, elicited by the rhythmic stimulation of mechanoreceptors (90% free nerve endings) of the penis (mostly in the glans)
    - contractions in the ductus deferens, seminal vesicles, prostate gland (NA α1), ejaculate is forwarded into the urethra (emission)
    - ejaculation is caused by rhythmic contractions in the ductus deferens and in skeletal muscles accompanied by an emotional climax, the orgasm

  • termination of erection by sympathetic effect

Female reproductive system

- female reproductive system is more complicated than the male

- most important differences:
  - all germ cells are formed in prenatal life in females; stem cells continuously divide in males - female germ cells are exposed to harmful environmental effects
  - gonadal hormones are produced in the follicles, production cease after menopause, Leydig-cells persist in males
  - production of ovarian hormones is cyclic
  - ovarian hormones provide both positive and negative feedback for the gonadotropic hormones, in males simple negative feedback exists
  - female gonadal hormones play important roles in gravidity, delivery, and breast-feeding, biological role of males terminates with fertilization

- in many species, reproduction is restricted to a certain season, but humans eat and drink not only when they are hungry or thirsty...
Development of follicles

- Ovary contains 1 million primary oocytes at birth; by puberty it decreases to 400 thousand. 4-500 will undergo full maturation.
- Primary oocytes are locked in 4n state (diplotene phase) during prenatal life; meiosis goes on after puberty.
- In primary follicles, oocytes are surrounded by granulosa cells and a basal lamina.
- After puberty, several primary follicles are recruited in each cycle for further development; only the dominant follicle develops completely.
- In recruited follicles, granulosa cells divide and form zona granulosa; oocyte starts to grow and secretes glycoproteins forming zona pellucida.
- Then, oocyte grows further (up to 120 μ), granulosa cells are proliferating, outside the basal lamina theca interna and externa are formed; secondary follicle.
- In the tertiary follicle, fluid accumulates between granulosa cells, high level of hormones, fast growth; Graafian follicle (10-20 mm).

End of follicular maturation

- Tertiary oocyte reaches Graafian state in 10-14 days (total development is about 220 days).
- Meiosis continues with the release of the first polar body; oocyte has 2n chromosomes now.
- Granulosa and theca cells undergo luteinization - RNA and protein synthesis increases.
- Graafian follicle ruptures, oocyte is released - ovulation.
- Granulosa and theca cells proliferate, basal membrane becomes permeable.
- Vascularization, then bleeding.
- Granulosa and theca interna cells invade the hemorrhagic spot; corpus luteum is formed - bright yellow color, lutein accumulation.
- If the ovum is not fertilized, corpus luteum undergoes degeneration that is visible by day 8 (size 2 cm), it is replaced by a fibrous scar.
- If the ovum is fertilized, corpus luteum persists increasing to about 5 cm.
Ovarian hormone production I.

- Ovaries produce oestrogens, progesterone and androgens
- Hormone production is regulated by FSH and LH, they in turn are controlled by GnRH
- The hormones act in the ovaries, on the genitalia and on other organs
- Oestrogens are synthesized by cooperation between granulosa and theca cells through androstenedione
- Their effects:
  - Amplify the effect of FSH on granulosa cells
  - Effect genital organs (vagina, uterus) and the mammary glands
  - Provide feedback for gonadotropic cells of the hypothalamus
  - Influence metabolism
- Oestrogens are transported in blood by the testosterone-binding protein (38%) and albumin (60%)

Ovarian hormone production II.

- Progesterone is produced by luteinized granulosa and theca cells and in the corpus luteum
- Its effects:
  - Main function is to prepare the endometrium for gestation and pregnancy
  - Increases the expression of its own receptors in luteinized cells of the corpus luteum - positive feedback
  - Provides feedback for the production of gonadotropic hormones
- Functioning of the ovaries is under the control of gonadotropic hormones; in their absence ovaries undergo atrophy
- FSH acting on granulosa cells stimulates maturation of follicles - in addition, indirect effect through oestradiol
- FSH increases the number of LH receptors on granulosa cells - LH can start progesterone synthesis
- FSH - acts on granulosa, LH - on both granulosa and theca cells
The menstrual cycle I.

- the cycle is regulated by the interaction of the ovaries and the hypothalamo–hypophyseal system
- oestrogen: inhibits FSH secretion, but at a continuously high level facilitates LH secretion, both in the hypothalamus, and in the pituitary
- progesterone: after high oestrogen level increases, otherwise decreases (luteal phase) LH secretion
- ovaries also produce inhibit, it probably inhibits FSH production
- days in the cycle are counted from the beginning of the menstruation, its length is taken as 28 days
- there is an overlap between two successive cycles: maturation of the new follicle starts on day 26
- in the first part of the cycle oocyte is prepared for fertilization, in the second endometrium is prepared for implantation

The menstrual cycle II.

- regression of corpus luteum at the beginning of the cycle removes negative feedback - FSH secretion increases
- several follicles starts to maturate - dominant follicle secrets oestrogen and inhibit - FSH declines, development of further follicles stops
- with the maturation of the follicle, more and more oestrogen is synthesized - together with FSH, it induces expression of LH-receptors in granulosa cells
- sensitivity of granulosa cells for LH causes progesterone production already before ovulation
- ovulation is preceded by a strong oestrogen peak (reason?) - it induces LH-surge reaching its maximum by 20-24 hours before ovulation
- body temperature increases, meiosis goes to 2n
- LH causes luteinization of granulosa cells, the secreted progesterone increases FSH production
- follicular cells produce proteolytic enzymes - ovulation because of digestion of collagen fibers
The menstrual cycle III.

- in the luteal phase following ovulation, secretion of progesterone dominates
- LH level is relatively low, but sufficient for the survival of corpus luteum and for the secretion of progesterone
- progesterone increases the number of its own receptors – positive feedback
- development of endometrium is regulated by oestrogen and progesterone
- after menstruation, thickness of endometrium is 0.5 mm, proliferation is induced by oestrogen – thickness grows to 3-5 mm by day 14
- following ovulation, secretion phase ensues because of progesterone – glands are activated
- in the absence of fertilization corpus luteum deteriorates, progesterone declines, extracellular metalloproteases digest vascular walls – bleeding and menstruation
- prostaglandin $F_{2\alpha}$ might play a role
- blood loss amounts to about 30-50 ml

Fertilization I.

- sexual act is accompanied by similar excitement in females as in males, but it is not a prerequisite of fertilization – rape
- blood flow increases in the clitoris (glans analog) and in the minor labia (analog to cavernous bodies) – vaginal secretion increases
- rhythmic stimulation of the genitalia (mostly the clitoris) leads to orgasm: rhythmic contractions in the vaginal (smooth) and pelvic (skeletal) muscles
- female orgasm cannot be linked to a single event like male orgasm, occurs after longer stimulation, lasts longer and there is no refractory period
- fertilization takes place in the oviduct – sperm cells arrive within 5 minutes, but only 50-200 out of 250 million – they survive for 48 hours
Fertilization II.

- the journey of the oocyte lasts for 1–2 days
- sperm cell penetrates zona pellucida 15–25 minutes, then attaches very fast to the membrane of the oocyte
- meiosis meanwhile terminates in the oocyte
- conjugation of the two nuclei needs 4 hours, first division within 24 hours
- implantation takes place on the seventh day after ovulation in blastocyst state - it eats itself into the endometrium using enzymes
- blastocyst consists of two cell layers, from the inner one develops the embryo, from the outer one (trophoblast) the placenta
- endometrial cells are transformed by progesterone to decidual cells - interdigitation with trophoblast cells

Hormones of the placenta

- placenta is the largest endocrine organ producing many different hormones
- most important hormones:
  - oestrogens - synthesized from androgen hormones produced by the fetal adrenal cortex
  - progesterone - synthesized from cholesterol provided by maternal LDL - important by the end of week 8, its production is 250 mg/day by the end of the pregnancy
  - hCG - (human chorionic gonadotropin hormone) ensures survival of corpus luteum in the first few weeks (it is a relative of FSH, LH, TSH glycoprotein hormones) - pregnancy tests
  - human placental lactogen (somatomammotropin - belongs to the PRL/GH family) - production reaches 1 g/day, function is not well known - acromegaly, diabetes are cause probably by this hormone
- many other hormones: GnRH, ACTH, TRH, TSH, inhibin, etc. with unknown functions
Delivery

• pregnancy lasts for 280 days in humans, delivery is started probably by the fetus
• termination of pregnancy can be divided into three phases:
  - preparatory phase: more extensive appearance of gap junctions between uterine muscle cells, number of oxytocin receptors increase
  - rhythmic uterine contractions, cervical canal dilates, fetus and placenta are squeezed through the vagina
  - tonic uterine contractions to stop bleeding
• factors regulating birth:
  - oestrogen secretion of the placenta – fetal adrenal cortex starts to produce glucocorticoids instead of androgens – oestrogen production replaces progesterone
  - increased production of prostaglandins (E\textsubscript{2}, F\textsubscript{2α}) (F\textsubscript{2α} can be used to induce abortion)
  - oxytocin – strongly increases uterine contractions, but its role is permissive only as normally it increases towards the end of the second phase – timed delivery

Breast feeding I.

• breast feeding has no real alternative – it is the best, most hygienic nutrition for babies
• its effect is still detectable at age 6-7
• several sociological and psychological factor influences the length of nursing – in general it shows negative correlation with industrialization
• breasts show no sexual dimorphism before puberty – both sexes have functioning mammary glands at birth – some secretion might occur: “witch milk”
• regression after birth because the absence of intrauterine hormones
• during puberty oestrogen causes proliferation of the glandular tissue and accumulation of adipose and connective tissue in females with great individual variations
Breast feeding II.

- during pregnancy breasts develop further - for this to occur, several hormones should be present simultaneously: oestrogen, progesterone, PRL, GH, glucocorticoids, insulin - secretion is inhibited by the sexual steroids
- following delivery, secretion is induced by the high PRL and low steroid levels, ejection requires oxytocin as well
- breasts should be emptied, otherwise secretion stops - suckling and/or massage
- PRL is increased considerable (5-10-fold) by mechanical stimuli during the nursing act
- oxytocin is also increased by mechanical, but also by psychological stimuli - milk ejection during changing diaper

Female development

- takes several years, consists of six periods: postnatal (few months), prepubertal, pubertal, reproductive, climacteric, postmenopausal
- largest changes in pubertal and climacteric
- pubertal: secondary sexual characteristics develop (adipose tissue, pubic hair), breasts, internal and external sexual organs, regular cycles
- inhibition of GnRH cells disappear: menarche - first menstrual period (average: 12.8 yrs)
- climacteric: after the age of 45, menstrual periods become irregular or fail, then there are no more periods: menopause (50-51 yrs)
- follicles disappear because of maturation and atresia - no granulosa and theca cells to produce sexual steroids - strong increase in FSH and LH
- uncomfortable negative symptoms: “flushes”, emotional lability, depression, regression of oestrogen.-dependent tissues (breasts, uterus, vagina) osteoporosis, LDL/HDL ratio increases
Regulation of testicular functions

Production of gonadotropic hormones

Eckert: Animal Physiology, W.H.Freeman and Co., N.Y.,2000, Fig. 9-30.

Berne and Levy, Mosby Year Book Inc, 1993, Fig. 51-6
Anatomy of the testicle (testis)

Fonyó: Orvosi Élettan, Medicina, Budapest, 1997, Fig. 33-4.

- plexus pampiniformis
- arteria spermatica interna
- vas deferens
- caput epididymidis
- ductus deferens
- septum
teste
corpus
epididymidis
tunica albuginea
tubuli seminiferi
cauda epididymidis
epididymis

Spermatogenesis

lumen of seminiferous tubule

adluminal compartment
basal compartment
tight junction (blood-testis barrier)

Fonyó: Orvosi Élettan, Medicina, Budapest, 1997, Fig. 33-5.
Endometrial cycle

Eckert: Animal Physiology, W.H. Freeman and Co., N.Y., 2000, Fig. 9-32.