PATHOPHYSIOLOGY OF THE REPRODUCTIVE SYSTEM AND SEX HORMONES

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Infertility and male or female phenotype disorders represent the main disorders of reproductive system.

Sex hormones

Estrogens
- **estron (E1), estradiol (E2), estriol (E3)**
- steroid hormones (precursors – androstenedione, testosterone)
- sources: ovary, placenta, testes, fat tissue in case of estrone (after menopause, the estrone constitutes the main estrogen), exogenous estrogens, phytoestrogens, endocrine active tumors

Estrogens are feminizing hormones and their production and plasma levels fluctuate during the ovarian cycle. Estradiol, the main estrogen in fertile females, is produced by cells of theca interna and granulosa (follicular) cells (+ corpus luteum). Its secretion is regulated by gonadotrophin hormones of the adenohypophysis (FSH and LH).

Effects of estrogens:
- Development and growth of reproductive organs
- Increase blood flow in reproductive organ and stimulate lubrication of the vagina
- Stimulate neuroplasticity processes and affects mood
- Neuroprotective action
- Increase of NO and prostacyclin production → short-term vasodilatation
- ↓ cholesterol and vasodilatation by local increase of NO production
- Stimulation of blood coagulation (higher concentrations increase the risk of thrombosis)
- Mildly increase of water and salt retention; increases angiotensinogen production
- stimulate osteoblasts, inhibit osteoclasts. As a result, they prevent osteoporosis, accelerate body growth but also stimulate epiphyseal closure.
- ↓ erythropoietin

Estrogens elimination: conjugation in the liver, excreted by the urine (partially also by bile)

Gestagens
- progesterone
- an endogenous steroid that is synthesized from pregnenolone

The progesterone is produced by *Corpus luteum* (and by placenta during pregnancy)

Effects of the progesterone:

- the main hormone in the pregnancy, creating suitable conditions for the embryo
- initiates pre-gestation changes of the endometrium to prepare the uterus for implantation
- ↑ cervical mucus viscosity, ↓ contractibility of the uterus
- inhibits the effect of the estrogen → ↓ sensitivity to oxytocin
- increases body temperature
- inhibits LH and FSH → blocks ovulation during the pregnancy
- stimulates hypertrophy of the mammary gland

Progesterone elimination: to pregnanediol (in liver) → conjugation → excreted by the urine

Androgens
- testosterone, dihydrotestosterone, dehydroepiandrosterone, androstenedione
- steroids

Source of the androgens
- men: adrenal cortex (until puberty) and testes (from puberty)
- women: 60 % adrenal cortex, 40 % ovary (androstenedione, testosterone in smaller extend → conversion to estrogens)
- exogenous (e.g. anabolics), cancers

Effects of androgens:
- masculinizing hormones, development of genital organs in males
- growth of genital organs in males, growth of skeleton and skeletal muscle in puberty
- anabolic effects, development of the male phenotype
- necessary for spermatogenesis
- ↑ erythropoietin

Metabolisms of testosterone: → C17-ketosteroids (androsterone, etiocholanolone) → urine or conversion to estrogens

Adrenogenital syndrome = excessive androgens production from the adrenal cortex
- lack of cortisol stimulates ACTH production, leading in turn to higher secretion of androgens from the adrenal cortex

Non-steroid sex hormones
relaxin: produced by ovaries during pregnancy. Stimulates remodeling the symphysis allowing the pelvic bones to be more flexible
inhibin: produced by ovaries and testes. Inhibits FSH secretion

Regulation of sex hormones release

The secretion of estrogen and androgens is stimulated by follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the hypophysis

Gonadoliberin (hypothalamus) → LH, FSH (adenohypophysis) → sex hormones (gonads)

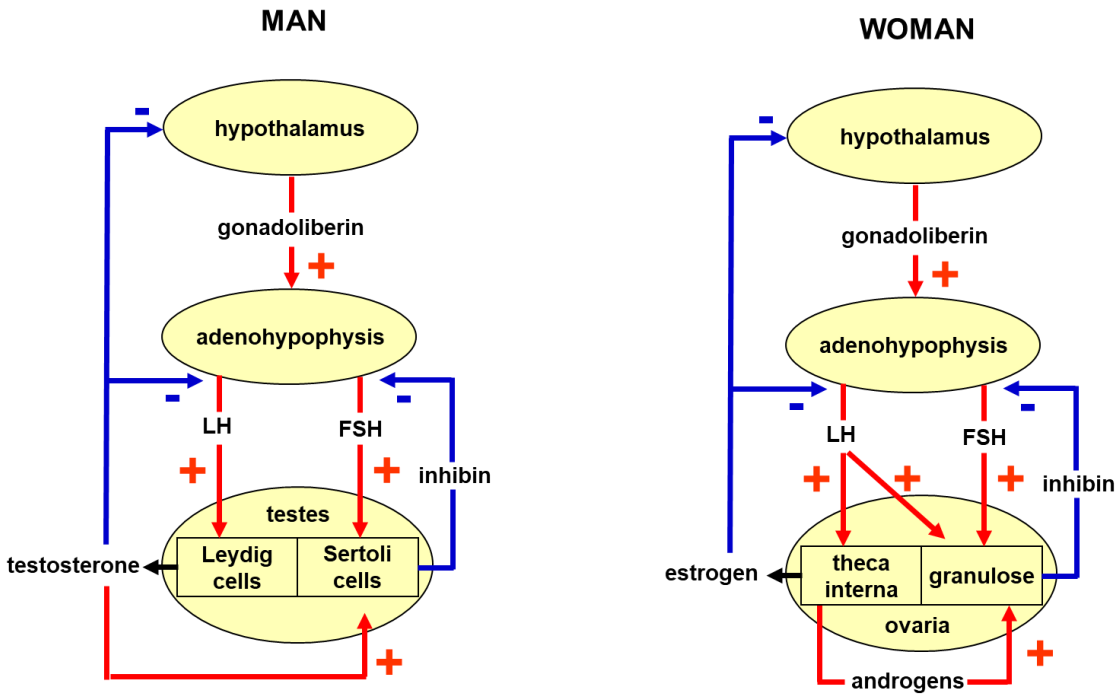
FSH
effects:

- stimulates growth and maturation of the primordial follicles of ovaries
- induces the activity of aromatase - ↑ production of estradiol
- induces receptors for LH on the cells of granulose follicles → luteinization
- trophic hormone of Sertoli cells → stimulates spermiogenesis

regulation:
- gonadotropin (in the hypothalamus) stimulates FSH
- inhibin inhibits FSH
- secretion of gonadoliberin is inhibited by prolactin (see pathophysiology of adenohypophysis – galactorrhea-amenorrhea syndrome)

LH
effects:
- trophic hormones of Leydig cells - ↑ testosterone → ↓ LH
- stimulates the secretion of androstenedione and testosterone in ovaries by the cells of theca interna
- induces progesterone secretion

regulation:
- gonadoliberin (in the hypothalamus) stimulates LH
- estradiol, progesterone, testosterone and dihydrotestosterone inhibit LH
- prolactin inhibits gonadoliberin, leading in turn to LH inhibition



Scheme of the sex hormone release regulation by gonads in males (in the left) and females (right)

Insufficient levels of sex hormones

The condition of decreased secretion of sex hormones is called hypogonadism. It may be caused by disease of the gonads (primary disease), disease of the adenohypophysis (leading

to impaired LH and FSH secretion; secondary disease) or disease of the hypothalamus (leading to impaired gonadoliberin production; tertiary disease). In cases of the secondary and tertiary diseases, the gonadotropin levels are low, leading to insufficient stimulation of the gonads to produce sex hormones (*hypogonadotropic hypogonadism*). In the case of primary insufficiency of the sex hormones, the lack of sex hormones leads to increase of the gonadotropin production due to negative feedback loop (*hypergonadotropic hypogonadism*). For these reasons, an examination of gonadotropins levels in hypogonadism represents an important diagnostic tool.

In scheme:

hypogonadotropic hypogonadism
- ↓ sex hormones, ↓ gonadotropins FSH and LH, ↓ or ↑ gonadoliberin
- causes: diseased hypothalamus, hypopituitarism, prolactinoma

hypergonadotropic hypogonadism
- ↓ sex hormones, ↑ gonadotropins FSH a LH
- primary gonads impairments (absence, disease or damage of ovaries or testes)

Symptoms of the hypogonadism vary according to the patient age and age of the disease onset.

Low levels of androgens in men
a) embryo → female-like phenotype (pseudohermaphroditism, or testicular feminization), infertility, female-like genital.
b) childhood → absent or delayed puberty, eunuchoidism (lack of secondary sexual features, prolonged growth of bones and thus taller body, weak musculature), infertility
c) adulthood → infertility, only slow regression of the secondary sexual characteristics, pathological sperm

Analogously, consequences of castration vary according to age (before or after the puberty). Before puberty, castration affects general body appearances and sexual behavior. However, castration after the puberty leads to slow and graduate regression of the male-like body appearance and behavior.

Lack of estrogens in females
a) embryo → infertility, normal female habitus
b) childhood → absent or delayed puberty, weak development of female habitus, primary amenorrhea, infertility
c) adulthood → infertility, secondary oligomenorrhea or amenorrhea, anovulation ovarian cycle, osteoporosis

Excessive levels/effects of sexual hormones

Excessive secretion of sexual hormones may come from gonads, endocrine-active tumors or exogenous endocrine-active analogues of the sexual hormones (anabolics, phytoestrogens).

Excessive androgen level can also come from the adrenal gland. The hypersecretion of the sexual hormones can be caused by overproduction of gonadoliberin from the hypothalamus (tertiary disorder), gonadotropins from the adenohypophysis (secondary disorder), or directly by primary overproduction from gonads (primary diseases; e.g. due to tumor). In cases of secondary and tertiary diseases, the gonadotropins levels are also elevated. In the case of primary disease, the gonadotropins levels will be lowered due to a negative feedback loop.

The consequences of the sexual hormones overproduction vary according to hormone implicated and age of the patient.

Excessive level of androgens in males

a) embryo → normal development
b) childhood → (pseudo)*pubertas praecox*, impaired spermiogenesis
c) adulthood → decreased fertility, the anabolic effect

Excessive level of estrogens in males

a) embryo → gynecomastia (i.e. enlarged mammillary gland)
b) childhood → gynecomastia, female-like body characteristics, impaired fertility
c) adulthood → gynecomastia, female-like body characteristics, impaired fertility

Excessive level of androgens in females

a) embryo → virilism, possibly pseudohermaphroditism, infertility
b) childhood → virilism, primary amenorrhea, infertility
c) adulthood → hirsutism, possibly virilism, secondary oligomenorrhea/amenorrhea

Excessive level of estrogens in females

a) embryo → normal development
b) childhood → *(pseudo)pubertas praecox*, impaired maturation of the primordial follicles, infertility
c) adulthood → hyperplasia of endometrium, menorrhagia, metrorrhagia, increased risk of endometrium and breast carcinoma, higher risk for thrombosis, water retention

Puberty disruption

Premature puberty = before 9 years of age

Pubertas praecox

- premature release of gonadotropins usually due to impairments in the hypothalamus
- mimics normal puberty and include activation of gonads functions and inducing the fertility

Pseudopubertas praecox

- premature development of secondary sexual characteristics but without premature gametogenesis; caused by an increased level of androgens in boys and estrogens in girls
- the hormone secretion does not depend on the activity of the adenohypophysis as the hormones are usually released by tumors. As a result, gonads are not activated by the gonadotropins.

Premature thelarche = premature breast development at girls

Delayed or absent puberty
- in boys = eunuchoidism (see above)
- in girls → primary amenorrhea

Pathophysiology of the female reproductive system

The female reproductive system is regulated by hypothalamus-hypophysis-ovaries axis (or fetus-placenta during pregnancy). Impaired fertility might have numerous causes, including an imbalance in sex hormones level, disturbances in the ovarian cycle, anatomical malformations in the lesser pelvis, oviducts or uterus, or by other diseases (e.g. hypo/hyperfunction of the thyroid gland).

Disturbances in the ovarian cycle

Causes: abnormal development (ovarian agenesis), ovarian damage, obesity, insufficient nutrients, the long-termly high physical activity accompanied by low body fat (in sportswoman), hormonal imbalance

Anovulation cycle = no ovulation → infertility
- corpus luteum is not fully developed, an insufficient level of progesterone
- regular menstrual cycle
- commonly occurs shortly after menarche and before menopause
- mechanisms: insufficient increase of LH before ovulation

Polycystic ovary syndrome
- causes chronic absence of ovulation and is related to increased risk of cancer
- chronically increased levels of both estrogens and androgens → hyperplasia of endometrium, hirsutism, impaired maturation of the primordial follicles → ovarian cysts
- elevated LH/FSH ratio
- accompanied by metrorrhagia (intermenstrual bleeding)

Ovarian hyperstimulation syndrome
- a secondary consequence of the treatment of female infertility (hormone-induced ovulation) → dysregulation
- ovarian enlargement by cysts or edema

Dysfunctions of the menstrual cycle

Eumenorea = normal (physiological) menstrual cycle
Amenorrhea = absent menstruation
- physiological (normal): before puberty, during pregnancy and lactation, after menopauses
- primary = menstruation has never occurred
- secondary = menstruation was present but disappeared

causes:
- hormonal imbalance and related absence of the ovarian cycle
- damage of the endometrium (forming scar tissue – Asherman's syndrome), e.g. by inflammation and repeated curettage
- diseases of the ovaries
- disruption of hypothalamus-hypophysis-ovaries axis
- low body weight (due to excessive physical activity or anorexia). The effect could be due to the role of body fat in leptin release

Oligomenorrhea = decreased frequency of the menstruation (1 / more than 31 days)
- decreased intensity of the bleeding often also occurs
- the causes include decreased hormonal activity during the ovarian cycle

Hypomenorea = weakened menstrual bleeding during regular cycles with normal frequency
Menorrhagia = strong and prolonged bleeding during regular cycles
- causes: hormonal dysregulation, impairments of hemostasis

Metrorrhagia = intermenstrual uterine bleeding
- causes: hormonal dysregulation, uterine cancer

Dysmenorrhea = painful menstruation (pain in the lower abdomen)
- possible causes: ↑ prostaglandin → contraction of myometrium → ischemia, lactate acidosis
- endometriosis (part of the uterus occurs ectopically in the abdominal cavity) → inflammation

Premenstrual syndrome
- a few days before menstruation
- emotional lability, irritability, anxiety, depression, headache, flatulence, the tension in the breast, limb swelling, edema

Pathological physiology of the male reproductive system

Male infertility
- congenital or acquired
- azoospermia = absence of the sperm in ejaculate; oligospermia = decreased sperm numbers; sperm defects
- cryptorchidism = undescended testes
- other causes: increased temperature, infection, chemotherapy, irradiation, phytoestrogens, alcohol, certain medication or drugs.

Causes of the male infertility
Pretesticular
- hormonal diseases, hypogonadotropic hypogonadism
- Kallman syndrome, Laurence-Moon-Biedl syndrome, Adiposogenital dystrophy
- diseases of sexual hormones and their receptors, disorders of the adrenal cortex, diseases of the thyroid gland

Testicular
- developmental malformations, chromosomal aberrations
- castration, cryptorchidism, injuries, infection, antibodies against sperm

Post-testicular
- obstructions in ductus deferens, retrograde ejaculation to the bladder
-developmental malformations in seminal duct, urethra, hypospadias (urethra does not open from the head of the penis)
- impotency, low-quality sex intercourse

Hypogonadism = lack of testosterone and dihydrotestosterone → testicular atrophy, decreased spermatogenesis, low sexual arousal, changes in body appearance
(see above)

Congenital disorders
- tissue insensitivity to testosterone (due to mutation related to androgen receptors or 5α-reductase)
- → male pseudohermaphroditism or testicular feminization syndrome (effect of the estrogens overbeats the effect of androgens)
- hypospadias, gynecomastia (mammillary gland proliferation), azoospermia

Disease of sexual differentiation

Hermaphroditism = both ovaries and testes are present
- XX/XY mosaicism or translocation of part Y on to paternal X
- various phenotype, often malformation of genital

Pseudohermaphroditism = only one type of gonads is which corresponds to karyotype, but genital is of the opposite sex.

Female pseudohermaphroditism - 46, XX, male genital
- causes: congenital virilizing hyperplasia, androgen supplementation in gravidity (8th – 13th week)

Male pseudohermaphroditism - 46, XY, female genital
causes:
- Embryonal testicular defect → both external and internal female genital (testosterone and Müllerian-inhibiting hormone from Sertoli cells are absent → Müllerian duct does not regress)
- Resistance to androgens → abnormal sexual differentiation, the 5α-reductase defect → the testosterone does not metabolize to dihydrotestosterone, impaired receptors functioning
- Testicular feminization syndrome – complete loss of sensitivity to receptors of androgens
- normal or increased levels of testosterone
- female-like phenotype, including external female genital. However, internal female genital is not developed, primary amenorrhea

Hirsutism = excessive (male-like) body hair in females

- ↑ androgens or ↑ increased sensitivity of hair follicles to androgens
Virilization = hirsutism + deep voice, skin roughening, clitoral enlargement, high muscle mass, disorders of menstruation
Achard–Thiers syndrome = virilization + hyperglycemia with glycosuria
Cushing syndrome –overproduction of androgens

Chromosomal abberations:
Turner syndrome (45, X0)
- female phenotype, elementary ovaries, internal female genital developed, small height, breast not developed, primary amenorrhea, mental retardation

Klinefelter syndrome (47, XXY)
- eunuchoid phenotype
Superwoman (47, XXX)
- decreased fertility, normal female phenotype, mild learning impairments

Superman (47, XYY)

Dysgenesis of gonads – syndromes of prenatal castration
- disorders of gonads development in various stages

Pure dysgenesis of gonads
- eunuchoid phenotype, female genital, absent gonads
Agonadism
- eunuchoid phenotype, absence of gonads and inner genitals, undeveloped breast
Anorchism
- male genital, eunuchoid phenotype, absent testes

Eclampsia, preeclampsia

= EPH-gestosis, late gestosis
- serious pathology of gravidity, posing risk for both mother and fetus
- onset: around 20th week of gravidity

Symptoms
- edema
- proteinuria
- hypertension
- convulsions

Risks for the mother:
- malign hypertension
- abrupted placenta, bleeding
- stroke
- renal failure
- convulsions and seizures

Risks for the fetus:

- hypoxia due to placental damage
- growth retardation
- premature birth, miscarriage

Risk factors:
- the first child or carrying more than 1 child (e.g. twins)
- diabetes mellitus, hypertension
- family history of pre-eclampsia
- obesity or poor diet

Pathogenesis
An imbalance between vasoconstriction and vasodilatation, particularly constriction of small arteries, leading to hypoperfusion and system hypertension. Moreover, hypovolemia due to estrogens also contributes to hypertension. Next, aggregation of thrombocytes and increased blood coagulation also occur. These changes are induced by the placenta and mitigate after birth.