Hormonal contraception

Sexual adolescence in a woman manifests in the development of secondary signs and the onset of menstrual cycle. All the changes are conditioned by the fluctuating secretion of **estrogens** and **gestagens** from ovaries.

The endocrine function of the ovaries is controlled by regular cyclic release of pituitary hormones: **FSH** (follicle-stimulating hormone) a **LH** (luteinizing hormone). Macroscopically, the beginning of the cycle is considered to be mestruation (bleeding) caused by peeling of the upper layers of the uterine mucosa. On day 6, FSH secretion increases. Under its influence, the maturation of the follicle in the ovaries starts. The theca cells of the follicles produce estrogens. LH levels also rise in the middle of the cycle. .The follicle ruptures and releases the egg into the abdominal cavity near the uterine tube. The cavity of the follicle is filled with blood and fluid (*corpos haemorhagicum*). Later, the cavity is filled with proliferating theca cells (*corpus luteum*). At the same time, progesterone production is increasing.

In the first phase, **the endometrium** proliferates considerably under the influence of estrogens (*proliferative phase*). After ovulation with an increase in progesterone, the glands multiply and the mucosa is ready for egg nidation (*secretory phase*). If fertilization does not occur, the upper layer of the endometrioum is separated - menstrual bleeding.

Estrogens

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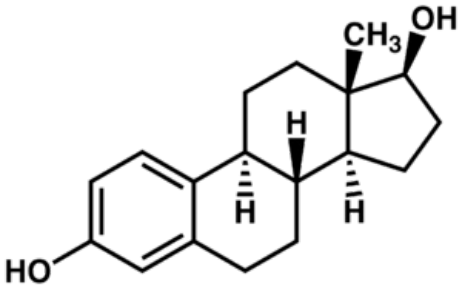
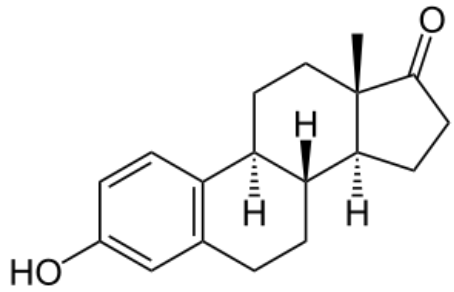
The major **estrogen** in humans is estradiol. Other physiologically active are **estrone** and **estriol** . As these substances belong to the category of steroid hormones (hydrophobic), they are almost 100% transported in the blood bound to the so-called *SHBG* (sex hormone binding protein, globulin). Although oral estradiol is active after oral administration, it is better to use semisynthetic derivatives (mainly *ethinyl estradiol*) for the high first-pass effect .



Estradiol

Effects on tissues

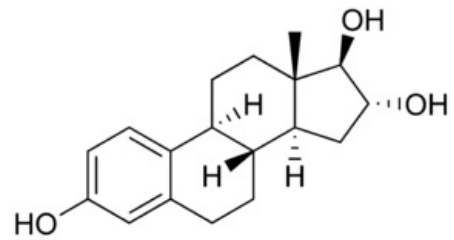
Estrogens are essential for normal *adolescence* and sexual develompmennt. Under their influence, the reproductive organs grow and secondary sexual characteristics develop. **Metabolic effect** - in the plasma reduces the amount of cholesterol - increase TAG and decrease LDL (lipoproteins of low density) particles (less incidence of cardiovascular disease in women of reproductive age), reduce osteoclast activity (preventing osteoporosis), increased coagulation(increased synthesis of fibrinogen in the liver) .



Estrone

Clinical use

- **Replacement therapy** – treatment of hypogonadism in girls, prevention of postmenopausal changes in women - beneficial effect against atrophy of the uterus (vagina, uterus) and osteoporosis, less effective in the treatment of hot flushes (attacks of redness in the face and upper torso, associated with mental instability); hypertension must be affected only by symptomatic treatment;
- **hormonal contraception** – in combination with progestagens to prevent conception or induce death of a fertilized egg; high doses are used once as the so-called *morning after contraception* (not completely accurate labeling, as it often does not prevent the conception itself, but it has an abortifiable effect and thus prevents the development of pregnancy)
- **prostate cancer** – palliative treatment.



Estriol

Toxicity

There is mainly a stimulating effect on the vagina, uterus and mammary glands. Medium doses lead to breast tension, endometrial hyperplasia and subsequent excessive bleeding . They can have a teratogenic effect when given during pregnancy. Long-term estrogen use is also associated with more frequent gallbladder disease.

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Gestagens

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Template:Infobox - hormon Progestins are a group of female sex hormones with antiestrogenic and antigonadotropic effects. The most important is **progesterone** .

Progesterone

It is formed in the corpus luteum of the ovaries and placenta (after 6-8 weeks of pregnancy ; 30-40 times more), as an intermediate in the synthesis of androgens and estrogens also in the adrenal cortex and in small amounts in testes .

It is synthesized from cholesterol via the intermediate pregnenolone, from which it differs in its arrangement on the A ring.

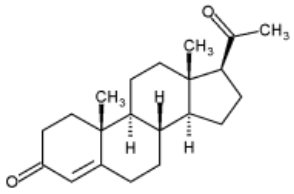
náhled|Progesteron

It binds to the protein carrier in plasma. It is rapidly metabolised in the liver - it has a very low bioavailability and a short biological half-life . Due to active metabolism in the liver, progesterone p.o. is ineffective.

After conjugation with glucuronic acid (inactivation) in the liver, it is excreted in the urine as pregnanediol.

Effect

Progestins lead to:



Progesterone

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- **development of secretory tissues in the mammary glands** (acins) - however, lactation is blocked and begins after delivery (sharp drop in progesterone levels), maintained by prolactin
- **maturation of the endometrium** in the second half of the menstrual cycle - transition from the proliferative to the secretory phase (increase in the volume and size of glandular secretion and increase in glycogen content) -> **preparation** of the uterine mucosa **for egg reception +** narrowing of the cervix and thickening of cervical mucus.
- **reducing the effect of estrogens** on the vaginal wall
- **influencing peripheral blood flow** – reduces heat loss, ie **increases body temperature** (on average by 0.5 ° C during the luteal phase of the cycle - ovulation indicator)

Compared to estrogens, progestagens have a minimal effect on the composition of plasma proteins (they do not affect plasma fibrinogen levels). They significantly affect sugar metabolism and stimulate fat storage.

Progestogens and estrogens act synergistically - estrogens initiate the formation of progesterone receptors.

Clinical use

The main indication is *contraceptive application* . Long-term application can also be used for long-term suppression of ovaries, eg in endometriosis. They have no effect on inducing abortion . *Progestin toxicity* is low, although they may cause an increase in blood pressure and a decrease in HDL.

Synthetic steroids are also used as oral contraceptives - 17alpha-hydroxyprogesterone derivatives and 17alpha-alkyl-substituted 19-nortestosterone derivatives, medroxyprogesterone acetate, etc. The inhibitory effect on cell growth is used to treat differentiated endometrial cancer.

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Contraception

History of contraception

- The attempt to separate sexual life from the conception of a child is as old as humanity itself - legendary biblical Onan – „whenever he slept with his brother's wife, he spilled his semen on the ground to keep from providing offspring for his brother" (Genesis 38:9) –the mentioned biblical hero thus became the inventor not of masturbation, but of the oldest method of contraception - **intermittent intercourse.**
- Advices of the ancient Egyptians: to introduce various substances into the vagina before intercourse: Petri papyrus, paste from crocodile droppings, elephant droppings, bovile bile,... The method based on the principle of killing sperm is still used in contraceptive suppositories (of course, does not contain mentioned substances).
- History of moders contraception: 1921 – Haberlandt (Austria) noted that extract from the ovaries of pregnant animals can be used as contraceptives. However, 80,000 ovaries would be needed to obtain a single used dose.
- Synthesis of srtificial hormones – American chemist Russel Marker from the yields of certain Mexican plant.
- 1960 – the first contraceptive pill on the market Enavid 10 - high concetration of hormones – in single tablet there were estrogens for 10 days and gestagens for 20 days.

Intermittent intercourse – coitus interruptus

- This method is not reliable – up to 20% failure per year. Causes of failure:
  - sperm leakage can occur without male orgasm;
  - expulsion of semen outside the vagina can also be a source of pregnancy;
  - after ejaculation, a small amount of sperm remains in the urethra and during repeated intercource, small amount always enters the vagina.
- The method should remain an emergency solution. Reserved for situations where nothing else is really available.

Ogino – Knaus method

- Counting fertile and infertile days. The method requires a regular menstrual cycle and it is recommended to monitor ovulation by measuring the basal temperature.

Condom

- It is also said to have been used by the famous Jacomo Casanova (1725–1798). Before World War II, more than one and half million condoms were produced annually in United States. Today's world production is at level of 8.5 trillion pieces.
- It is relatively reliable and inexpencive protection. It also protects against the transmission of sexually trransmitted diseases. So it is recommended especially for those who do not have a permanent partner.

Cervical cap

- a cup-shaped semicircular rubber cap that fits tightly over cervix. It must be of an appropriate size recommended by your doctor.

Chemical contraception

- Spermicidal creams and suppositories are inserted into the vagina before intercourse. They are harmless, easily accessible but relatively unreliable. They require an experienced user and are more suitable as a supplement to other contraceptive methods to increase reliability.

Intrauterine devices

- An effectie, long-term, comfortable and cheap method. it has beed used for many years and yet it is not really known how it works. It is especially siutable for women who have already given birth. It is not suitable for those who have heavy periods or often change partners.

Two-phase hormonal contraception

- Estrogen alone would not be enough, as the lining of the uterus would grow and there would be irregular bleeding and an increased risk of cancer. Therefore, a progestogen is added to the end of the cycle to prevent the growth of the uterine lining and at the same time close the cervix. Administration of progestogens at all times is advantageous because the lining of the uterus does not grow, the cervix is closed - this is a double protection and so it is possible to reduce the dose of estrogen.

Single-phase hormonal contraception

- Each tablet contains a dose of estrogens mixed with progestagens

Contraceptive patches

- They are based on the same principle as combined contraceptive pills. They do not increase the risk of vascular diseases and their effect is not impaired by antibiotics. However, they are still relatively expensive and technically imperfect. However, it is a very promising method with a great future.

Mini pills

- They are estrogen free and contain only small doses of progestogens. They are suitable for breastfeeding women. They are used without a week's break and can cause an irregular cycle. They show lower efficiency.

Injections and implants

- They work on the principle of maintainning the level of progestagens in the body.
- **Depot injection** – a suspension of microcrystals is applied under the skin, which dissolves slowly and thus ensures a constant level of progestogens for three months.
- **Subcutaneus implant** – hollow rods that ensures the level of progestogens for several years.
- There is some suspicion of an increased risk of osteoporosis, disrupting the menstrual cycle.

Intrauterine contraceptive complex

- combination of intrauterine devices and implent. Highly efficient method.

Postcoital contraception or Morning after pill

1. Shock administration of an increased dose of hormones. This means 4 contraceptive tablets within 72 hours after intercourse and another 4 after 12 hours (it is possible to administer 8 tablets at once, but it is almost certain that the lady would vomit it).
2. Administration of a higher dose of progestogens. If the powder was administered within an hour of contact, one tablet would suffice. Otherwise, after 12 hours, the second one follows.

Mechanism of action

Combined preparations act by several mechanisms - primary inhibition of ovulation, secondary effects may be divided into *preimplantation* (retarding tubal motility and ciliary epithelium in them), *the peri-implantation* (preventing nidation by affecting the endometrium), and *post-implantation* (prevent pregnancy from maintaining, but does not prevent nidation). All three types of secondary effects are postfertilizing, ie **abortive** - they cause **the death of an already fertilized egg** . So far, no studies have been performed that more accurately quantify the share of secondary effects in the final action of hormonal preparations.

Toxicity

The toxicityof contraceptives is important for the log-term use of contraceptives during a woman's life.

Thromboembolic events

The main dangers of using contraceptives. **Thromboembolic events** (AIM, CMP, pulmonary embolization) in elderly female smokers and in women with a familial burden of thromboembolic disorders are described in particular detail . Today, the risk of these complications during therapy is lower compared to the incidence during pregnancy .

Carcinogenic effect

There is compelling evidence that these substances **reduce** the incidence of endometrial and ovarian cancer . The results in breast cancer are inconclusive. Cervical cancer is probably unaffected. The risk was high with older preparations with a higher estrogen content.

Other risks

Nausea, breast tension, hedeache, skin pigmentation, acne, hirsutism. Side effects are significantly lower when using modern preparations with a low content of estrogens (less than 50 µg / day).

Links

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