Estrogens and Progestins 381.

Estrogens = β estradiol.
The metabolites are α-oestradiol, oestrone and oestriol. They can not be taken orally, because they will be quickly conjugated to sulphate and glucuronic acid.

Functions:

1. It is responsible for the follicular, proliferative phase of the menstrual cycle. Under it’s influence the endometrium thickens and vascularity increases. The cervical mucus increases and the pH rises to 8-9. The mucus is also enriched with protein and carbohydrate for spermatozoa.
2. An increase in oestrogen just before mid cycle leads to an increase in LH and the follicle will then rupture and ovulation will take place.
3. Once the ovum is fertilised, oestrogen will stimulate the growth of milk ducts in the breasts and maintain lactation after the baby is born.
4. It is responsible for the physical and psychological development and behaviour of a female foetus.
5. It thickens the vaginal mucosa and it promotes the cornification of the vaginal epithelium.
6. It also induces liver LDL-receptors so that serum lipoproteins are cleared more rapidly.
7. It decreases bone resorption and maintain bone mass in this way.

Preparations available:

Oestrone sulphate is a mixture of equine oestrogens and is orally active. Syntetic conjugates are available as piperazine estrone sulphate Ethinyl oestradiol differs from the natural hormone and is a very strong hormone. Mestranol and kinestrol are derivatives of ethinyl oestradiol. Stilboestrol is a synthetic stilbene derivative which takes on a steroid configuration and it can activate the oestrogen receptors. It is not a drug of choice, because of carcinogenicity. Oestriol succinate corrects oestrogen deficiency in the cervix, vagina and vulva, but does not have a significant effect on the endometrium. It is used as a local application.

Progestins.

Progesterone is secreted by the corpus luteum in the 2nd phase of the menstrual cycle under the influence of LH. It changes the endometrium from proliferative to secretory and is required for implantation and maintenance of pregnancy. It stimulates the development of alveoli in the milk ducts. It can suppress both FSH and LH and then follicle growth and ovulation can not take place.
When progesterone is withdrawn, menstruation takes place. It is metabolised in the liver to pregnanediol and pregnanolone, conjugated with glucuronic acid and excreted in the urine.

Injectable forms of progestin:

17-hydroxyprogesterone caproate is used in true progesterone deficiency and used for habitual abortion. It does not suppress ovulation or abnormal uterine bleeding. Medroxyprogesterone acetate is used as a contraceptive and is given every 3 months. Norethisterone enantate is a depot which is injected every 2 months as contraception. It is a testosterone derivative. Fertility returns after 5 – 9 months.

The 19-nortestosterone derivatives include. They have less androgenic effects:
- Norethisterone
- Norgestrel
- Norethinodrel

Newer preparations include
- Gestodene
- Levonorgestrel
These newer drugs have been associated with an increase in DVT’s.

They are structurally different and are not biotransformed with first pass through the liver. To a great extent they also do not have androgenic effects. They are used in contraception in combination with the oestrogens.

The use of oestrogens and progestins in contraception.
1. Combinations of oestrogen and progestin:
   - It prevents the release of the gonadotrophins and the mid cycle increase in LH and thus it prevents ovulation.
   - It also makes the endometrium unsuitable for implantation.
   - In the cervix it forms a thick cervical mucus which is impermeable to the sperms.

   Other forms of contraceptive preparations are:
2. Progestin alone in injections as discussed.
3. Post-coital contraception with high doses of the combination
4. Intra-uterine device which releases levonorgestrel for at least 5 years. It prevents proliferation of the endometrium and it thickens cervical mucus. It suppresses ovulation in some women

5. A patch containing a combination of oestrogen and progestin, which can be applied once a week for 3 weeks with a patch free week to induce menstruation.
6. A ring containing a combination of oestrogen and progestin inserted vaginally once a month. It must be removed after 3 weeks.

It is important to remember that we should initiate contraception with the lowest doses of hormones to reduce the possibility of side-effects. One should also evaluate the pt profile when deciding to initiate contraception, e.g. a pt smoking, older than 35 yrs would be a candidate for the insertion of an intra-uterine device containing levonorgestrel, rather than a combination of oestrogen and progestin. Progestin alone is also indicated in pts on anti-epileptic drugs, minimizing the possibility of drug interactions.

Absolute contra-indications for the use of contraception:
- Pregnancy
- Mamma and uterus Ca
- Liver disease
- Hyperlipidaemia
- A history of gestational diabetes
- A diastolic blood pressure of > 100 mm Hg
- Porphyria
- A history of thrombo-embolism

Relative contra-indications:
- Depression
- Migraine
- Big varicose veins
- Epilepsy
- Miomata and oligo- and amenorrhoea.

Adverse effects of oral contraceptives.

Mild adverse effects:
1. Nausea, mastalgia, breakthrough bleeding and oedema are all related to the amount of oestrogens in the preparation. It can be alleviated by a shift to a preparation with less oestrogen or progestins with a more androgenic effect.
2. Care should be taken with pts complaining of headaches. Ensure that it is not migraine, these pts have an increased tendency to develop CVA’s.
3. A reversible hypertension
4. Changes in lipid and carbohydrate metabolism

Moderate adverse effects:
1. Breakthrough bleeding is the most common problem in pts using progestin alone, especially lower doses. The biphasic and triphasic pills can be a good alternative, because they will decrease breakthrough bleeding without an increase in the hormone content.
5. Weight gain is seen with pt on androgen-like progestins
6. Increased skin pigmentation is observed more often in dark-skinned women. It is also exacerbated by vit B deficiency.
7. Acne can be caused by androgen-like progestins and improved with larger amounts of oestrogen.
8. Hirsutism can be aggravated by the 19-nortestosterone derivatives.
9. Urethral dilatation can cause bacteriuria more often.
10. Vaginal infections are more common and more difficult to treat.
Amenorrhoea might persist for longer than a few months (normally 2 months) after cessation of contraception. Prolactinoma should then be excluded.

**Serious adverse effects:**
1. Thrombo-embolism. Because of a lower production of antithrombin 3, increased levels of homocysteine and injury to a vessel. Genetic disorders in the production of protein C and S can also be a problem and a family history of thrombo-embolism should be taken seriously. The oestrogen content of the pill is of importance in this.
2. Myocardial infarction and CVA’s. Cigarette smoking is an important co-factor. Smoking women above 35 years using contraception have a greater chance to develop cerebral thrombosis or myocardial infarction.
3. Jaundice can occur in the first 3 cycles. It causes cholecystitis and cholangitis.
4. Oestrogen dependent mamma Ca’s and endometrium ca’s.

**Beneficial effects of the oral contraceptives.**

It is a safe and convenient method of contraception. It is associated with a reduced risk of ovarian cysts, ovarian and endometrial cancers and benign breast disease. We see less ectopic pregnancies and iron deficiencies are also less common. Rheumatoid arthritis has a lower incidence.

We treat endometriosis, dysmenorrhoea, acne and hirsutism with it.