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ASSIGNMENT

QUESTIONS;

1. Write on estrogens and progestins.
2. Drugs used as antifertility drugs.

**ESTROGEN**

Estrogen is the primary female sex hormone. It is responsible for the development and regulation of female reproductive system and secondary development. Estrogens are synthesised by the ovary and placenta, and in small amounts by the testis and adrenal cortex. The starting substance for synthesis of estrogen (and other steroids) is cholesterol. The immediate precursors to the estrogens are androgenic substances – androstenedione or testosterone . There are three main endogenous oestrogens in humans: *oestradiol*, *oestrone* and *oestriol* . Oestradiol is the most potent and is the principal oestrogen secreted by the ovary.

**BIOSYNTHESIS OF ESTROGEN**

Estrogens, in females, are produced primarily by the ovaries, and during pregnancy, the placenta. Follicle-stimulating hormone (FSH) stimulates the ovarian production of estrogens by the granulosa cells of the ovarian follicles and corpora lutea. Some estrogens are also produced in smaller amounts by other tissues such as the liver, pancreas, bone, adrenal glands, skin, brain, adipose tissue, and the breasts. These secondary sources of estrogens are especially important in postmenopausal women. The pathway of estrogen biosynthesis in extragonadal tissues is different. These tissues are not able to synthesize C19 steroids, and therefore depend on C19 supplies from other tissues and the level of aromatase.

In females, synthesis of estrogens starts in theca interna cells in the ovary, by the synthesis of androstenedione from cholesterol. Androstenedione is a substance of weak androgenic activity which serves predominantly as a precursor for more potent androgens such as testosterone as well as estrogen. This compound crosses the basal membrane into the surrounding granulosa cells, where it is converted either immediately into estrone, or into testosterone and then estradiol in an additional step. The conversion of androstenedione to testosterone is catalyzed by 17β-hydroxysteroid dehydrogenase (17β-HSD), whereas the conversion of androstenedione and testosterone into estrone and estradiol, respectively is catalyzed by aromatase, enzymes which are both expressed in granulosa cells. In contrast, granulosa cells lack 17α-hydroxylase and 17,20-lyase, whereas theca cells express these enzymes and 17β-HSD but lack aromatase. Hence, both granulosa and theca cells are essential for the production of estrogen in the ovaries.

Estrogen levels vary through the menstrual cycle, with levels highest near the end of the follicular phase just before ovulation.

Note that in males, estrogen is also produced by the Sertoli cells when FSH binds to their FSH receptors.

**MECHANISM OF ACTION**

Estrogens in the blood and interstitial fluid are bound to sex hormone–binding globulin (SHBG), from which they dissociate to cross the cell membrane, enter the nucleus, and bind to their receptor. Two genes code for two estrogen receptor isoforms, α and β, which are members of the superfamily of steroid, sterol, retinoic acid, and thyroid receptors. Unlike glucocorticoid receptors, estrogen receptors are found predominantly in the nucleus, where they are bound to heat shock proteins that stabilize them. Binding of the hormone to its receptor alters the receptor’s conformation and releases it from the stabilizing proteins (predominantly Hsp90). The receptor-hormone complex forms dimers (usually ERα-ERα, ERβ-ERβ, or ERα-ERβ) that bind to a specific sequence of nucleotides, called **estrogen response** **elements (EREs)**, in the regulatory regions of various genes and regulate their transcription. The ERE is composed of two half-sites arranged as a palindrome separated by a small group of nucleotides called the spacer. The interaction of a receptor dimer with the ERE also involves a number of nuclear proteins, the coregulators, as well as components of the transcription machinery. Complex interactions with various coregulators appear to be responsible for some of the tissue-specific effects that govern the actions of **selective estrogen receptor modulators** (**SERMs**). The receptor may also bind to other transcription factors to influence the effects of these factors on their responsive genes. Interestingly, although ERβ has its own separate actions from ERα, it also acts as a dominant negative inhibitor of ERα. Thus, while ERα has many growth-promoting properties, ERβ has antigrowth effects. Many phytoestrogens act via the ERβ protecting cells from the pro-growth effects of ERα. The relative concentrations and types of receptors, receptor coregulators, and transcription factors confer the cell specificity of the hormone’s actions. The genomic effects of estrogens are mainly due to proteins synthesized by translation of RNA transcribed from a responsive gene. Some of the effects of estrogens are indirect, mediated by the autocrine and paracrine actions of autacoids such as growth factors, lipids, glycolipids, and cytokines produced by the target cells in response to estrogen. Rapid estrogen-induced effects such as granulosa cell Ca2+ uptake and increased uterine blood flow do not require gene activation. These appear to be mediated by nongenomic effects of the classic estrogen receptor-estrogen complex, influencing several intracellular signaling pathways.

Recently, all steroid receptors except the mineralocorticoid receptors were shown to have palmitoylation motifs that allow enzymatic addition of palmitate and increased localization of the receptors in the vicinity of plasma membranes. Such receptors are available for direct interactions with, and effects on, various membrane-associated or cytoplasmic proteins without the need for entry into the nucleus and induction of transcriptional actions.

**METABOLISM**

Estrogens are metabolized via hydroxylation by cytochrome P450 enzymes such as CYP1A1 and CYP3A4 and via conjugation by estrogen sulfotransferases (sulfation) and UDP lucuronyltransferases (glucuronidation). In addition, estradiol is dehydrogenated by 17β hydroxysteroid dehydrogenase into the much less potent estrogen estrone. These reactions occur primarily in the liver, but also in other tissues.

**FUNCTIONS OF ESTROGEN**

Estrogen acts in concert with progesterone, and induces synthesis of progesterone receptors in uterus, vagina, anterior pituitary and hypothalamus. Conversely, proges­terone decreases estrogen receptor expression in the reproductive tract. *Prolactin* also influences estrogen action by increasing the numbers of estrogen receptors in the mammary gland, but has no effect on estrogen receptor expression in the uterus.

Effects of exogenous estrogen depend on the state of sexual maturity when the estrogen is administered:

* In primary hypogonadism: estrogen stimulates development of secondary sexual characteristics and accelerates growth.
* In adults with primary amenorrhoea: estrogen, given cyclically with a progestogen, induces an artificial cycle.
* In sexually mature women: estrogen (with a progestogen) is contraceptive.
* At or after the menopause: estrogen replacement prevents menopausal symptoms and bone loss.

Estrogens have several metabolic actions, including mineralocorticoid (retention of salt and water) and mild anabolic actions. They increase plasma concentrations of high-density lipoproteins, a potentially beneficial effect that may contribute to the relatively low risk of atheromatous disease in premenopausal women com­pared with men of the same age. However, estrogens also increase the coagulability of blood, and increase the risk of thromboembolism.

**PROGESTINS**

They are two main types of progestins which are

1. Natural progestins (progesterone)
2. Synthetic progestins
3. **Natural Progestins: Progesterone:** Progesterone is the most important progestin in humans. In addition to having important hormonal effects, it serves as a precursor to the estrogens, androgens, and adrenocortical steroids. It is synthesized in the ovary, testis, and adrenal cortex from circulating cholesterol. Large amounts are also synthesized and released by the placenta during pregnancy. In the ovary, progesterone is produced primarily by the corpus luteum. Normal males appear to secrete 1–5 mg of progesterone daily, resulting in plasma levels of about 0.03mcg/dL. The level is only slightly higher in the female during the follicular phase of the cycle, when only a few milligrams per day of progesterone are secreted. During the luteal phase, plasma levels range from 0.5 mcg/dL to more than 2 mcg/dL. Plasma levels of progesterone are further elevated and reach their peak levels in the third trimester of pregnancy.

**Biosynthesis of progesterone;** In mammals, progesterone, like all other steroid hormones, is synthesized from pregnenolone, which itself is derived from cholesterol.Cholesterol undergoes double oxidation to produce 22R-hydroxycholesterol and then 20α,22R-dihydroxycholesterol. This vicinal diol is then further oxidized with loss of the side chain starting at position C22 to produce pregnenolone. This reaction is catalyzed by cytochrome P450scc.The conversion of pregnenolone to progesterone takes place in two steps. First, the 3β-hydroxyl group is oxidized to a keto group and second, the double bond is moved to C4, from C5 through a keto/enol tautomerization reaction. This reaction is catalyzed by 3β-hydroxysteroid dehydrogenase/δ5-4-isomerase.

**Metabolism of progesterone;** The metabolism of progesterone is rapid and extensive and occurs mainly in the liver, though enzymes that metabolize progesterone are also expressed widely in the brain, skin, and various other extrahepatic tissues. Progesterone has an elimination half-life of only approximately 5 minutes in circulation. The metabolism of progesterone is complex, and it may form as many as 35 different unconjugated metabolites when it is ingested orally. Progesterone is highly susceptible to enzymatic reduction via reductases and hydroxysteroid dehydrogenases due to its double bond (between the C4 and C5 positions) and its two ketones (at the C3 and C20 positions).The major metabolic pathway of progesterone is reduction by 5α-reductase and 5β-reductase into the dihydrogenated 5α-dihydroprogesterone and 5β-dihydroprogesterone, respectively. This is followed by the further reduction of these metabolites via 3α-hydroxysteroid dehydrogenase and 3β-hydroxysteroid dehydrogenase into the tetrahydrogenated allopregnanolone, pregnanolone, isopregnanolone, and epipregnanolone. Subsequently, 20α-hydroxysteroid dehydrogenase and 20β-hydroxysteroid dehydrogenase reduce these metabolites to form the corresponding hexahydrogenated pregnanediols (eight different isomers in total), which are then conjugated via glucuronidation and/or sulfation, released from the liver into circulation, and excreted by the kidneys into the urine.

**Funtions of progesterone;**

* Progesterone is sometimes called the “hormone of pregnancy”, it is essential to maintain pregnancy, at least partly by suppressing uterine contractility.
* Progesterone plays an important role in breast development in women. In conjunction with prolactin, it mediates lobuloalveolar maturation of the mammary glands during pregnancy to allow for milk production and thus lactation and breastfeeding of offspring following parturition (childbirth).
* Progesterone plays an important role in the signaling of insulin release and pancreatic function, and may affect the susceptibility to diabetes or gestational diabetes.

1. **Synthetic Progestins (progestogens):** A variety of progestational compounds have been synthesized. Some are active when given by mouth. They are not a uniform group of compounds, and all of them differ from progesterone in one or more respects. In general, the 21-carbon compounds (hydroxyprogesterone, medroxyprogesterone, megestrol, and dimethisterone) are the most closely related, pharmacologically as well as chemically, to progesterone. A new group of third-generation synthetic progestins has been introduced, principally as components of oral contraceptives. These “19-nor, 13-ethyl” steroid compounds include desogestrel, gestodene, and norgestimate. They are claimed to have lower androgenic activity than older synthetic progestins.

There are two main groups of progestogens:

1. The naturally occurring hormone and its derivatives (e.g. **hydroxyprogesterone**, **medroxyprogesterone**, **dydrogesterone**). Progesterone itself is virtually inactive orally, because of presystemic hepatic metabolism. Other derivatives are available for oral administration, intramuscular injection or administration via the vagina or rectum.
2. Testosterone derivatives (e.g. **norethisterone**, **norgestrel** and **ethynodiol**) can be given orally. The first two have some androgenic activity and are metabolised to give oestrogenic products. Newer progestogens used in contraception include **desogestrel** and **gestodene**; they may have fewer adverse effects on lipids than ethynodiol and may be considered for women who experience side effects such as acne, depression or breakthrough bleeding with the older drugs. However, these newer drugs have been associated with higher risks of venous thromboembolic disease.

**Functions of progestogens**

* Progestogens is used in combination with estrogens mainly in hormone therapy for menopausal symptoms and low sex hormone levels in women.
* It is also used in women to support pregnancy and fertility and to treat gynecological disorders.
* Progestogens can be taken by mouth, through the vagina, and by injection into muscle or fat, among other routes.s

**ANTI-FERTILITY DRUGS**

Anti-fertility agents are drugs that control fertility and are also called oral contraceptives. These drugs affect and are involved in the menstrual cycle and ovulation in females. Estrogen and progesterone in combined form are given as birth control pills. The antifertility substance is deemed to be active in females when it prevents fertilization, prevents ovulation, implantation and destroys the zygote or causes abortion. In males it prevents spermatogenesis, inhibits testosterone or affects the gonadotropin of the organs or the mortality of sperm.

Progesterone is the most common progestin synthetic substances such as Norethindrone have been developed that the superior to progesterone when taken orally to turn off ovulation.

They induce temporary infertility. Synthetic estrogens have also been developed and they are often used in oral contraceptive in combination with progestins. A very potent synthetic estrogen is the compound called Ethenylestradiol. Mifepristone is a synthetic steroid which blocks the effects of Progesterone and is used as a “morning after pill” in many countries.

There are two main types of oral contraceptives:

1. Combinations of an estrogen with a progestogen (the combined pill).

2. Progestogen alone (the progestogen-only pill).

**THE COMBINED PILL**

The combined oral contraceptive pill is extremely effec­tive, at least in the absence of intercurrent illness and of treatment with potentially interacting drugs. The oestrogen in most combined preparations (second-generation pills) 4 is **ethinylestradiol**, although a few prep­arations contain **mestranol** instead. The progestogen may be **norethisterone**, **levonorgestrel**, **ethynodiol**, or – in ‘third-generation’ pills – **desogestrel** or **gestodene**, which are more potent, have less androgenic action and cause less change in lipoprotein metabolism, but which proba­bly cause a greater risk of thromboembolism than do second-generation preparations. The estrogen content is generally 20–50μg of ethinylestradiol or its equivalent, and a preparation is chosen with the lowest estrogen and progestogen content that is well tolerated and gives good cycle control in the individual woman. This combined pill is taken for 21consecutive days followed by 7 pill-free days, which causes a withdrawal bleed. Normal cycles of menstruation usually commence fairly soon after discon­tinuing treatment, and permanent loss of fertility (which may be a result of early menopause rather than a long-term consequence of the contraceptive pill) is rare.

The mode of action is as follows:

* Estrogen inhibits secretion of FSH via negative feedback on the anterior pituitary, and thus suppresses development of the ovarian follicle.
* Progestogen inhibits secretion of LH and thus prevents ovulation; it also makes the cervical mucus less suitable for the passage of sperm.
* Estrogen and progestogen act in concert to alter the endometrium in such a way as to discourage implantation.

They may also interfere with the coordinated contractions of the cervix, uterus and fallopian tubes that facilitate fertilisation and implantation.

Hundreds of millions of women worldwide have used this method since the 1960s, and in general the combined pill constitutes a safe and effective method of contracep­tion. There are distinct health benefits from taking the pill, and serious adverse effects are rare. However, minor unwanted effects constitute drawbacks to its use, and several important questions need to be considered.

**Common adverse effects**

The common adverse effects are:

* weight gain, owing to fluid retention or an anabolic effect, or both
* mild nausea, flushing, dizziness, depression or irritability
* skin changes (e.g. acne and/or an increase in pigmentation)
* amenorrhoea of variable duration on cessation of taking the pill.

**THE PROGESTOGEN-ONLY PILL**

The drugs used in progestogen-only pills include **nore­thisterone**, **levonorgestrel** or **ethynodiol**. The pill is taken daily without interruption. The mode of action is prima­rily on the cervical mucus, which is made inhospitable to sperm. The progestogen probably also hinders implanta­tion through its effect on the endometriu and on the motility and secretions of the fallopian tubes.

**Potential beneficial and unwanted effects**

Progestogen-only contraceptives offer a suitable alterna­tive to the combined pill for some women in whom es­trogen is contraindicated, and are suitable for women whose blood pressure increases unacceptably during treatment with estrogen. However, their contraceptive effect is less reliable than that of the combination pill, and missing a dose may result in conception. Disturbances of menstruation (especially irregular bleeding) are common. Only a small proportion of women use this form of con­traception, so long-term safety data are less reliable than for the combined pill.

**Pharmacokinetics of oral contraceptives: drug interactions**

Combined and progestogen-only oral contraceptives are metabolised by hepatic cytochrome P450 enzymes. Because the minimum effective dose of estrogen is used (in order to avoid excess risk of thromboembolism), any increase in its clearance may result in contraceptive failure, and indeed enzyme-inducing drugs can have this effect not only for combined but also for progesterone-only pills. Such drugs include **rifampicin** and **rifabutin**, as well as **carbamazepine**, **phenytoin** and others, includ­ing the herbal preparation St John’s Wort.

**OTHER DRUG REGIMENS USED FOR CONTRACEPTION**

**POSTCOITAL (EMERGENCY) CONTRACEPTION**

Oral administration of **levonorgestrel**, alone or combined with estrogen, is effective if taken within 72 h of unpro­tected intercourse and repeated 12 h later. Nausea and vomiting are common (and the pills may then be lost: replacement tablets can be taken with an antiemetic such as **domperidone**). Insertion of an intrauterine device is more effective than hormonal methods, and works up to 5 days after intercourse.

**LONG-ACTING PROGESTOGEN-ONLY CONTRACEPTION**

**Medroxyprogesterone** can be given intramuscularly as a contraceptive. This is effective and safe. However, menstrual irregularities are common, and infertility may persist for many months after cessation of treatment.

**Levonorgestrel** implanted subcutaneously in non-biodegradable capsules is used by approximately 3 million women worldwide. This route of administration avoids first-pass metabolism. The capsules release their pro­gestogen content slowly over 5 years. Irregular bleeding and headache are common.

A levonorgestrel-impregnated intrauterine system pro­vides prolonged, reliable contraception and, in contrast to standard copper containing devices, *reduces* menstrual bleeding.