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DEPT: PHARMACOLOGY

COURSE CODE: PHA306

COURSE TITLE: ENDOCRINE AND REPRODUCTIVE SYSTEM PHAMACOLOGY

ASSIGNMENT:

1. WRITE ON OESTROGEN AND PROGESTIN
2. DRUGS USED AS ANTI FERTILITY DRUGS
3. **ESTROGEN**

Estrogen is a hormone that plays various roles in the body. In females, it helps develop and maintain both the reproductive system and female characteristics, such as breasts and pubic hair.

Estrogen contributes to cognitive health, bone health, the function of the cardiovascular system, and other essential bodily processes.

However, most people know it for its role alongside progesterone in female sexual and reproductive health.

The ovaries, adrenal glands, and fat tissues produce estrogen. Both female and male bodies have this hormone, but females create more of it.

**HOW OESTROGEN LEVELS CHANGE**

Your estrogen levels change according to where you are in your menstrual cycle and also your stage in life. Estrogen levels are highest in the middle of cycle, and lowest during your. At menopause your estrogen levels begin to fall

1. **Estrone**

This type of estrogen is present in the body after menopause. It is a weaker form of estrogen and one that the body can convert to other forms of estrogen, as necessary.

1. **Estradiol**

Both males and females produce estradiol, and it is the most common type of estrogen in females during their reproductive years.

Too much estradiol may result in acne, loss of sex drive, osteoporosis, and depression. Very high levels can increase the risk of uterine and breast cancer. However, low levels can result in weight gain and cardiovascular disease.

1. **Estriol**

Levels of estriol rise during pregnancy, as it helps the uterus grow and prepares the body for delivery. Estriol levels peak just before birth.

**Function**

Estrogen enables the following organs to function:

1. **Ovaries:** Estrogen helps stimulate the growth of the egg follicle.
2. **Vagina:** In the vagina, estrogen maintains the thickness of the vaginal wall and promotes lubrication.
3. **Uterus:** Estrogen enhances and maintains the mucous membrane that lines the uterus. It also regulates the flow and thickness of uterine mucus secretions.
4. **Breasts**: The body uses estrogen in the formation of breast tissue. This hormone also helps stop the flow of milk after weaning

**Levels of estrogen**

Factors that can affect estrogen levels include:

pregnancy, the end of pregnancy, and breastfeeding

1. puberty
2. menopause
3. older age
4. overweight and obesity
5. extreme dieting or anorexia nervosa
6. strenuous exercise or training
7. the use of certain medications, including steroids, ampicillin, estrogen-containing drugs, phenothiazines, and tetracyclines
8. congenital conditions, such as Turner’s syndrome
9. Diabetes

**Estrogen imbalance**

An imbalance of estrogen leads to:

1. irregular or no menstruation
2. light or heavy bleeding during menstruation
3. more severe premenstrual or menopausal symptoms
4. hot flashes, night sweats, or both
5. noncancerous lumps in the breast and uterus
6. mood changes and sleeping problems
7. weight gain, mainly in the hips, thighs, and waist

**Estrogen sources and uses**

If a person has low levels of estrogen, a doctor may prescribe supplements or medication.

Estrogen products include:

1. synthetic estrogen
2. bioidentical estrogen
3. Premarin, which contains estrogens from the urine of pregnant mares

**Estrogen therapy**

Estrogen therapy can help manage menopause symptoms as part of hormone therapy, which people usually refer to as **hormone replacement therapy**.

The treatment may consist solely of estrogen (estrogen replacement therapy, or ERT), or it may involve a combination of estrogen and progestin, a synthetic form of progesterone.

Hormone treatment is available as a pill, nasal spray, patch, skin gel, injection, vaginal cream, or ring.

**It can help manage:**

1. hot flashes
2. vaginal dryness
3. painful intercourse
4. Food sources of estrogen

Some foods contain phytoestrogens, which are plant-based substances that resemble estrogen. Some studies suggest that these may affect levels of estrogen in the body. However, there is not enough evidence to confirm this.

**Foods that contain phytoestrogens include**:

1. cruciferous vegetables
2. soy and some foods containing soy protein
3. berries
4. seeds and grains
5. nuts
6. fruit
7. wine

**Supplements**

Some herbs and supplements contain phytoestrogens, which act in a similar way to estrogen. These may help regulate estrogen and treat symptoms of menopause.

Examples are:

1. black cohosh
2. red clover
3. soy isoflavones

**COMMON CONDITIONS LINKED WITH OESTROGEN**

Estrogen affect many parts of the body, and cause problems when its is off balance. Some medical conditions linked to estrogen.

1. **Adenomyosis:** when cells that normally line inside of the uterus[womb] also grow inside its muscular walls. Because it needs estrogen to grow, adenomyosis usually grow away after menopause.
2. **Fibroids:** lumps of muscle tissue inside the uterus fibroids are stimulated to grow by hormones and tend to go away after menopause.
3. **Osteoporosis**: a conditionwhere your bones become fragile and more easilybroken. Because estrogen helps with bone strength, women are in more risk after menopause.
4. **Vaginal dryness:** falling estrogen at menopause can cause the vaginal to become and thin causing discomfort and sometimes leading to other problems.

**ESTROGEN AND BREAST CANCER**

The cause of breast cancer is complex, involving many factors. However, it is known that estrogen can help breast cancer cell grows. Women who have exposed to estrogen for example because they reached puberty early or went through menopause late have a higher than at the normal age, but whose bodies have an increased risk. Estrogen taken inform of hormone-based medicines including HRT and the pill, can lead to an increased risk of breast cancer too.

1. **PROGESTINS**

compounds with biological activities similar to those of progesterone have been variously referred to in the literature as pregestational agents, progestogens, progestogens. These are substances which convert estrogen primed endometrium to secretory and maintain pregnancy. Progestin’s are hormones which favors pregnancy.

**NATURAL PROGESTIN:** Progesterone ( 21 carbon steroid) is derived from cholesterol , it was first isolated in 1929.

**SYNTHETIC PROGESTIN’S**: they have weak estrogenic androgenic and anabolic action but have potent anti ovulatory action. They combined contraceptive pills.

PROGESTERONE DERIVATIVES

1. Medroxyprogesterone acetate
2. Megestrol acetate
3. dydrogestrone
4. hydroxyprogesterone caproate

19- NORSTESTOSTERONE DERIVAIVES (OLD)

1. Norethindrone
2. Lynestrenol
3. Allylestrenol
4. Levonorgestrel

19-NORTESTERONE DERIVATIVES (NEW)

1. Desogestrel
2. Norgestimate
3. Gestodene

**ACTIONS**

1. **Uterus**: secretory changes in estrogen primed endometrium (hyperemia, tortuosity, of glands and increased secretion.
2. **Cervix**: converts watery secretion (estrogen produced) to viscid, scanty and cellular which is hostile to sperm penetration.
3. **Vagina** : induces pregnancy like changes in the mucosa leukocyte infiltration of cornified epithelium
4. **Breast**: It cause proliferation of acini in the mammary gland acting along with estrogen which prepares the breast for lactation.
5. **CNS**: may have sedative effect.
6. **Body temperature:** causes slight (0.5c) rise in body temperature.
7. **Respiration** : may stimulate respiration at high doses.
8. **Pituitary** : progesterone is a weak inhibitor of gonadotropins secretions.

**MECHANISM OF ACTION**

The progesterone receptor (PR) has limited distribution in the body confined mainly to the female genital tract breast CNS and pituitary. Upon hormone binding PR undergoes dimerization, attaches to progesterone response element (PRE) of target genes and regulate transcription through coactivators.

**PHARMACOKINETICS**

* Progesterone is orally inactive because of high first pass metabolism in liver. Hence mostly given by intramuscular in oily solution
* Micronized formulation has been developed for oral admistration which contains micro fine particles of progesterone suspended in oil and dispensed in gelatin capsules its absorption occurs through lymphatics
* Most synthetic progestin are orally active, metabolized slowly and have plasma t1/2 between 8-12hrs.

**ADVERSE EFFECTS**

* Breast engorgement , headache rise in body temperature, edema, esophageal reflex, acne and mood swings.
* Irregular bleeding may occur when given continuously
* Long term use in HRT may increase risk may increase breast cancer
* Blood sugar may rise and diabetes may be precipitated by long term use [levonorgestrel]
* Intramuscular injections of progesterone are painful

**USES**

* As contraceptive: postcoital contraceptive [ mifepristone 600mg within 72hrs]
* Hormone replacement therapy : used in non- hysterectomized post-menopausal women estrogen therapy is supplemented with progestin for 12-12 days each month to reduce the risk of endometrial carcinoma
* DUB[ dysfunctional uterine bleeding] : progestin in large dose [ norethindrone 20-40mg/day] promptly stops the bleeding and keeps it abeyance as long as therapy is gives.
* Threatened habitual abortion: a pure progestin without estrogenic or androgenic activity may show efficacy in preventing premature delivery in high risk pregnancy.
* Endometriosis: mainly manifest as dysmenorrhea, painful pelvic swellings and infertility. Progestin’s induce anovulatory hypoestrogenic state suppressing Gn release.
* Premenstrual syndrome : manifest as headache, irritability, fluid retention, distension and breast tenderness a few days preceding bleeding.
* Endometrial carcinoma: progestin’s are palliative in about 50% cases of advanced or metastatic endometrial carcinoma.

1. **ANTIFERTILITY DRUGS**

Antifertility drugs are chemical substances which suppress the action of hormones that promote pregnancy. These drugs actually reduce the chances of pregnancy and act as a protection. Antifertility drugs are made up of derivatives of synthetic progesterone or a combination of derivatives of estrogen and progesterone.

**CLASSIFICATION OF ANTI-FERTILITY DRUGS**

1. **GnRH antagonist**: Either Gonadotrophin- releasing hormone [GnRH] or any gonadotophin releasing hormone antagonist [ie Lupron] maybe used, GnRH stimulate the release of gonadotrophins [ LH and FSH] from the anterior pituitary in the body.
2. **Estrogen antagonist:** fertility medication inhibiting the effect of estrogen include **clomiphene and aromatase inhibitor**s
3. **Clomiphene**: [trade mark clomid] is a selective estrogen receptors modulator [SERM]. It is the most widely used fertility drug. It is used as an ovarian stimulator by inhibiting the negative feed back of estrogen at the hypothalamus as the negative feed back estrogen is inhibited, the hypothalamus secretes GnRH which in turn stimulates anterior pituitary to secrete LH and FSH which help in ovulation.
4. **AROMATASE INHIBITORS** : although primarily a breast cancer treatment, aromatase inhibitors can also work fertility medication, probably through a mechanism similar to clomiphene
5. **Gonadotrophins :** Gonadotrophins are hormones in the body that naturally stimulate the gonalds [ testes and ovaries]. For medication, they can be extracted from urine or by genetic modification. For example, the so called menotropins are extract from LH and FSH extracted from human urine and menopause women , FSH and FSH analogue are mainly used ovarian hyperstimulation as well as a reversal of an ovulation.
6. **Human chorionic gonadotrophin:** human chorionic gonadotrophin[HCG] is normally produced during pregnancy. However it can also replace LH as a ovulation inducer

**Others:** HMG is a medication containing a follicle-stimulating hormone[FSH] and a luteinizing hormone[LH]

**METHODS FOR FEMALE**

Female antifertility agents might be acting through following mechanism

1. Inhibition of ovulation
2. Prevention of fertilization
3. Interference with transport of ova oviduct to endometrium of the uterus.
4. Interference with the implantation of fertilized ovum
5. Distraction of early implanted embryo

**SIDE EFFECT AND RISK OF FERTILITY DRUGS**

Fertility drug side effect and risk depends on which modification your are taking. Oral fertility drug [ clomid or tetrazole] have milder side effects and injectable fertility drug [ like gonadotrophins or GnRH agonist and antagonist].

* **Clomid[ clomiphene] side effect and risks**: clomid works by tricking the body into thinking there enough circulating estrogen. It blocks the receptord in the body that react to estrogen hormone.

**Possible side effect of clomide include**

1. Hot flashes
2. Bloating and abdominal discomfort
3. Weight gain
4. Headaches
5. Mood swings and nausea

A rare but serious risk of clomid id blurred vision

* **Gonadotrophins side effect and risk**: Gonadotrophins fertility drugs are injectable hormones. They include drug like gonal-f[FSH], follistium and ovidrel [hcg] injectable may be used alone or in combination with other drugs during an IVF cycle

**Possible side effect ganodatrophins**

1. Acne
2. Upper respiratory tract infection
3. Abdominal menstrual bleeding
4. Dizziness
5. Injection site sore and redness

* **GnRH antagonist side effect and risk:** likeGnRH antagonist are used to shut down the body’s reproductive system during IVF treatment. They have significantly fewer side effect than GnRH agonist.

**Possible side effect of GnRH antagonist**

1. Abdominal tenderness
2. Headache
3. Nausea

**RARE BUT POTENTIAL SERIOUS RISKS OF FERTILITY DRUG**

* Vision changes
* Ectopic pregnancy
* Ovarian hyper stimulation syndrome [OHSS]
* Ovarian torsion
* Allergic reaction

**BENEFIT OF ANTI-FERTILITY DRUGS**

These drugs generally do not have many side effect. These drugs are very useful if taken in proper dose, following in the proper dose. Following are its significant benefits

* They cause no interference in sexual activity and risk of pregnancy is reduced.
* They might cause the reduction in menstrual bleeding
* They can be taken immediately after child birth .