GONADAL HORMONES AND THEIR INHIBITORS

By:
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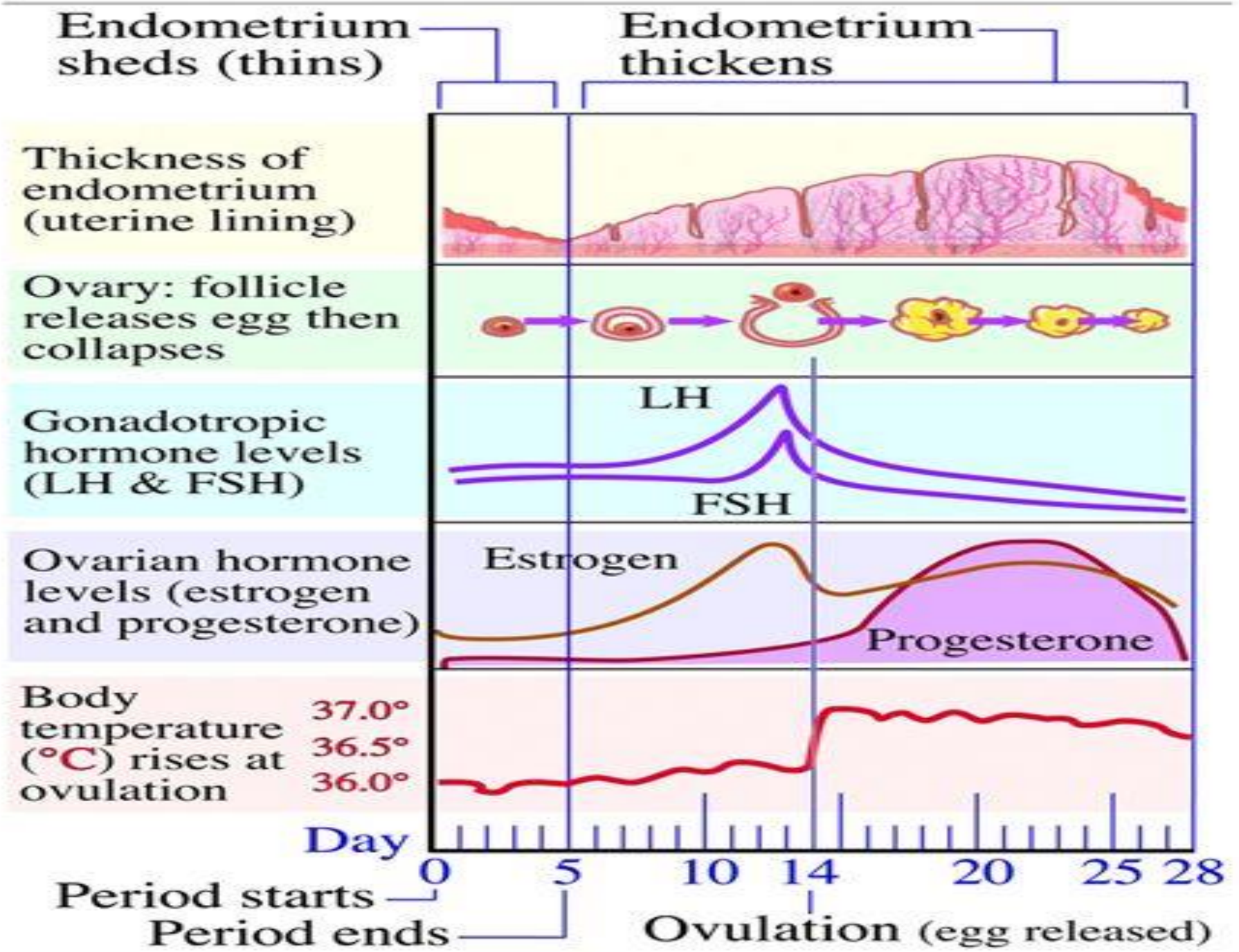
- Are the steroids produced in the ovaries and testis:
  - Estrogen
  - Progestin
  - Testosterone


Endometrium sheds (thins)
Endometrium thickens
Thickness of endometrium (uterine lining)
Ovary: follicle releases egg then collapses
Gonadotropic hormone levels (LH & FSH)
LH
FSH
Ovarian hormone levels (estrogen and progesterone)
Estrogen
Progesterone
Body temperature (°C) rises at ovulation
37.0°
36.5°
36.0°
Day
0
5
10
14
20
25
28
Period starts
Period ends
Ovulation (egg released)

- The menstrual cycle starts with menstruation.

- Hypothalamus: Gonadotrophin-releasing hormone >>>> acts on the anterior pituitary >>>> release follicle-stimulating hormone (FSH) and luteinising hormone (LH).

- FSH and LH **stimulate follicle development** in the ovary. FSH is the main hormone stimulating oestrogen release.

Follicular phase

- LH **stimulates ovulation** at mid-cycle and is the main hormone controlling subsequent progesterone secretion from the corpus luteum.

Luteal phase

- Oestrogen :controls the proliferative phase of the endometrium and has negative feedback effects on the anterior pituitary.
- Progesterone: controls the later secretory phase, and has negative feedback effects on both the hypothalamus and anterior pituitary.
- If a fertilised ovum is implanted, the corpus luteum continues to secrete progesterone.

- After implantation, human chorionic gonadotrophin (HCG) from the chorion becomes important, and later in pregnancy progesterone, HCG and other hormones are secreted by the placenta.

DRUGS AFFECTING REPRODUCTIVE FUNCTION

I) ESTROGENS

- Oestrogens : synthesized from cholesterol, by:
  - Ovaries*
  - Placenta
  - Testis and adrenal cortex (small amounts)

A) Endogenous Estrogens :

***(oestradiol**, oestrone and oestriol)*

B)Exogenous estrogens:

- **Mestranol, ethinylestradiol, diethylstilbestrol**
- Oral, transdermal, intramuscular, implantable and topical
- Single agents or combined with progestogen.

- Natural oestrogens are rapidly metabolised in the liver, whereas **synthetic oestrogens are degraded less rapidly**.

MECHANISM OF ACTION:

- Involves interaction with **nuclear receptors** (ERα or ERß) in target tissues, resulting in modification of gene transcription.

- Some of the rapid vascular and metabolic effects of oestrogens are mediated by a G protein-coupled [o]estrogen receptor (GPER).

EXOGENOUS ESTROGEN EFFECTS

Uses : Estrogens are used in the treatment of hypogonadism in young females.

- Estrogen is essential for normal female reproductive development.

Side effects : premature closure of the epiphyses of the long bones and short stature

Uses: as **contraceptives** in combination with progetins

- Continuous administration of estrogen, especially in combination with a progestin, inhibits the secretion of **gonadotropins** from the anterior pituitary.

Side effects : dose dependent nausea, breast tenderness, increased risk of **migraine** headache, **thromboembolic events** (eg, deep vein thrombosis), gallbladder disease, hypertriglyceridemia, and hypertension

- *In adults with primary amenorrhoea: oestrogen, given* cyclically with a progestogen, induces an artificial cycle.

Uses: as hormonal replacement therapy (HRT)

- Reduce bone resorption ,
- Enhances the coagulability of blood
- Increases plasma triglyceride levels while **reducing (LDL) cholesterol and increasing (HDL) cholesterol**.

Side effects : increases the risk of **endometrial cancer** , combination with progestin reduce this risk .

OVERALL SIDE EFFECTS

- Breast tenderness, nausea, vomiting, anorexia, retention of salt and water with resultant oedema, and increased risk of thromboembolism.

- Oestrogen causes endometrial hyperplasia unless given cyclically with a progestogen.

- For postmenopausal replacement

therapy, oestrogens cause menstruation-like bleeding.

- Carcinoma of the vagina was more common in young women whose mothers were given diethylstilbestrol in early pregnancy.

C) SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERM)

- Are agonist in some tissues and antagonist in others.

1. Tamoxifen :

- Antagonist at the breast tissues (To treat oestrogen-sensitive breast cancer).
- Agonist at bone :prevent from osteoporosis.
- Agonist at the uterus : increase risk of endometrial cancer.
- Increase the risk of Thromboembolic events

- 2. **Raloxifene: same as tamoxifen but has no effect on** endometrial tissue**.**

- Antagonist at the breast tissues
- Antagonist at the uterus
- Agonist at bone

- Approved for prevention and **treatment**
- **of osteoporosis**.

D) ANTI-ESTROGEN

Clomiphene:

- **Approved to induce ovulation**
- Selectively block estrogen receptors in the pituitary, reduces negative feedback and increases FSH and LH output.
- Twins are common, but multiple pregnancy is unusual.

Fulvestrant:

- Is a pure estrogen receptor antagonist (in all tissues).

II) PROGESTINS

- **Progesterone** is the major progestin in humans.

Maintain pregnancy

- Progesterone induces secretory changes in the endometrium and is required for the **maintenance of pregnancy.**

Causes significant weight gain as a Side effect

- Affect carbohydrate metabolism and stimulate fat deposition .

Used as contraceptives in combination with estrogen or alone

- Inhibit ovulation

- Progestogens act on nuclear receptors.
- The **density** of progesterone receptors is controlled by **oestrogens.**

PROGESTIN PREPARATIONS

1. **The naturally occurring hormone and its derivatives:** (e.g. **hydroxyprogesterone, medroxyprogesterone, dydrogesterone).**

- 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. (2nd generation)**

- The first two have some androgenic activity and are metabolised to give oestrogenic products.

- Newer progestogens include **desogestrel and gestodene. (3rd generation)**

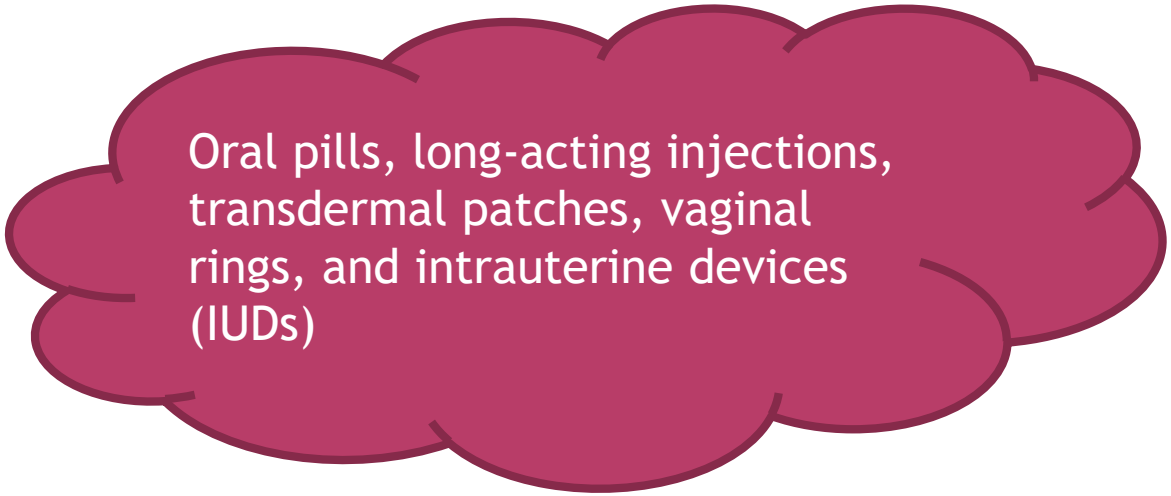
PROGESTIN ANTAGONIST:

- **Mifepristone:**
- Partial agonist at progesterone receptors.

  It sensitises the uterus to the action of prostaglandins.

- The antiprogestogen **Mifepristone, in combination** with prostaglandin analogues, is an effective medical alternative to surgical termination of early pregnancy. (abortifacient).

III) HORMONAL CONTRACEPTIVES



A. Combined oral contraceptives (COC): monophasic, biphasic and triphasic
B. Progestin only Contraceptives
C. Others: Postcoital contarception , Long acting progestin only contraception

A) COMBINED ORAL CONTRACEPTIVES (COC):

- **Ethinylestradiol, is** the oestrogen in most combined preparations.

- This combined pill is taken for 21 consecutive days followed by 7 pill-free days, which causes a withdrawal bleed.

MECHANISM OF ACTION :

- **Oestrogen:** 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.

- **Oestrogen** and **progestogen** act in concert to alter the endometrium in such a way as to discourage implantation.

- **Other uses :**
- Acne treatment, hirsutism, dysmenorrhea, and endometriosis.

- Users of combination hormonal contraceptives have reduced risks of ovarian cysts, ovarian and endometrial cancer.

SIDE EFFECTS :

- 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.

- **CVD risks:**
- With second-generation pills (oestrogen content less than 50 µg), the risk of thromboembolism is small.

- Risk increased with the 3rd generation combination (**desogestrel or gestodene),** smoking, obesity, hypertention, and long-continued use of the pill, especially in women over 35 years of age.

- **Hypertension:**
  - A small proportion of women develop **reversible** hypertension. Blood pressure is therefore monitored when oral contraceptive treatment is started.

- **Cancer risks:**
  - Ovarian and endometrial cancer risk is *reduced*.

B) PROGESTIN ONLY PILLS

- The progestogen-only pill is taken continuously. It differs from the combined pill in that the contraceptive effect is less reliable and is mainly a result of the alteration of cervical mucus. Irregular bleeding is common.

C) OTHERS:

- A) **Postcoital pill : levonorgestrel, alone or combined** with oestrogen, is effective if taken within 72 h of unprotected sexual intercourse. And repeated after 12 hrs later.

- **B) long acting progestin only :**
  - **Medroxyprogesterone>> injected IM**
  - **Levonorgestrel >>** Implanted subcutaneously>>> **5 years activity**
  - **Levonorgestrel>>>** impregnated intrauterine system provides prolonged, reliable contraception

HOME WORK

- Study the following:
- Contraceptive use in patients with epilepsy
- Androgens and the hormonal control of the male reproductive system.
- Drugs acting on the uterus (stimulant and inhibitors of contraction).
- GONADOTROPHIN-RELEASING HORMONE: (AGONISTS AND ANTAGONISTS).

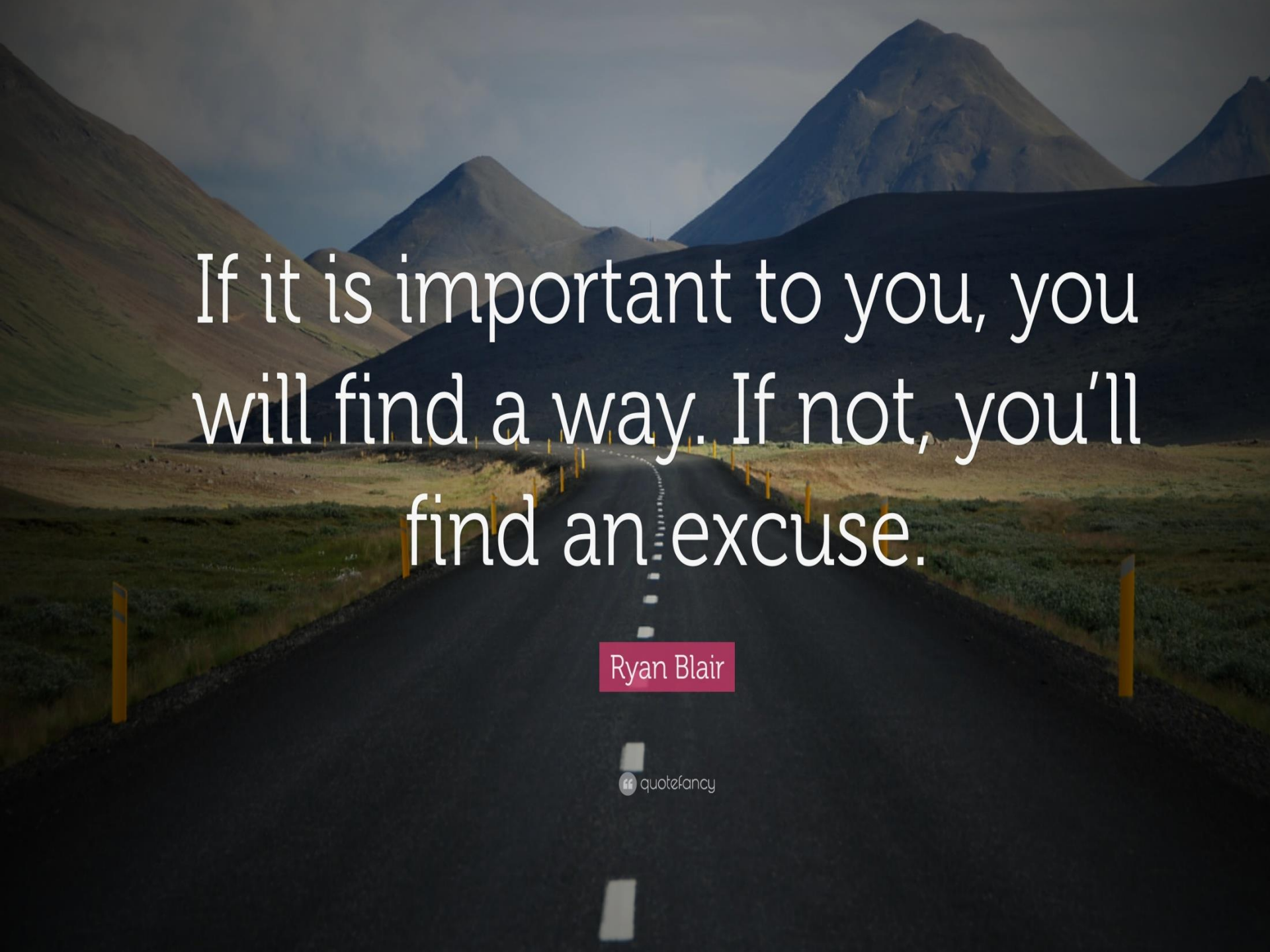
SEMINARS' GROUPS

- **Tuesday 18/2 :**
- **1-12** : Contraceptive use in females with epilepsy
- **13-24**: Androgens and the hormonal control of the male reproductive system
- **25-36**:Drugs acting on the uterus (stimulant and inhibitors of contraction)
- **37-48**:GONADOTROPHIN-RELEASING HORMONE: (AGONISTS AND ANTAGONISTS).

- **Thursday 20/2:**
- **49-61**:Pharmacokinetics
- **62-73**: Pharmacodynamics
- **74-85**:ANS (Parasympathetic and sympathetic, agonists and antagonists).
- **86-97**: Local hormaones Pharmacology

- **Tuesday 25/2:**
- **98-109**: Blood pharmacology
- **110-121**: Bone pharmacology
- **122-133**: Steroids pharmacology
- **134-146**: NSAIDs

- Summary


If it is important to you, you will find a way. If not, you'll find an excuse.
Ryan Blair
quotefancy

THANK YOU

Good luck