Medical Pharmacology

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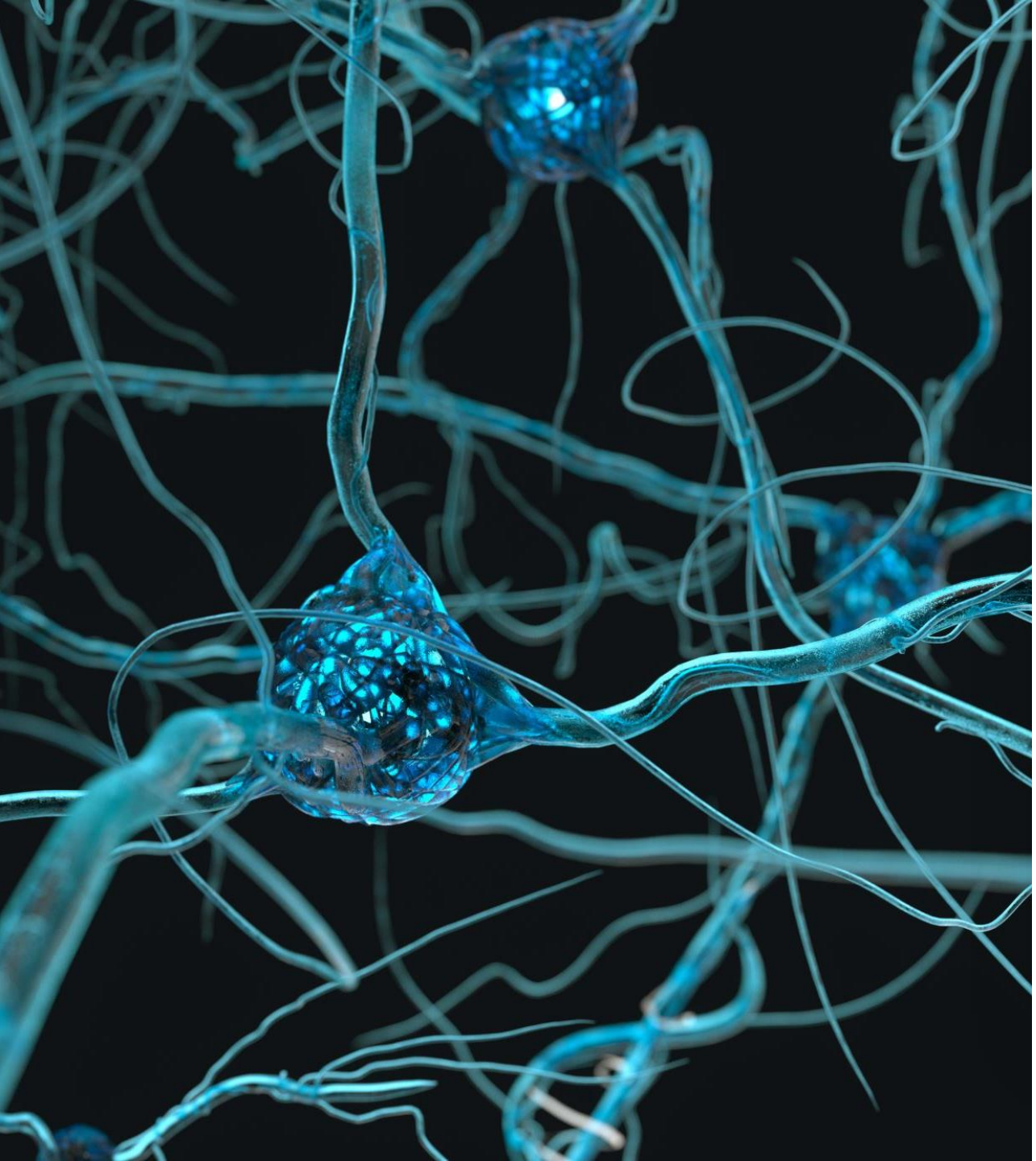
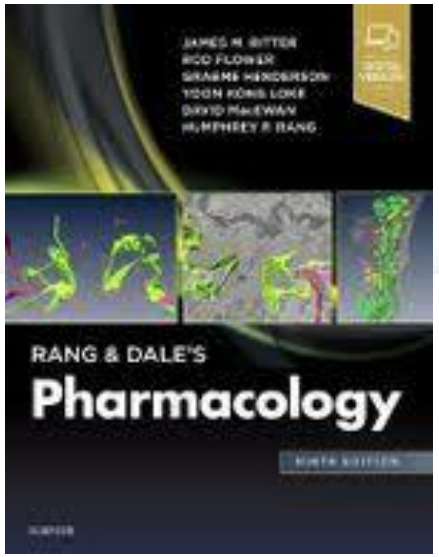
Celebrating 50 YEARS 1970 - 2020



Endocrine : Reproductive & Hormone Therapy



Rang & Dale's Pharmacology

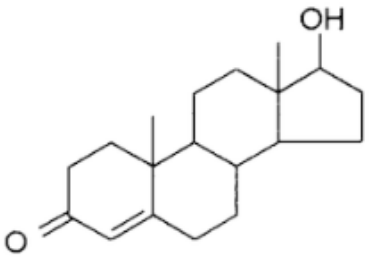
10th ed 2020

Chap 35

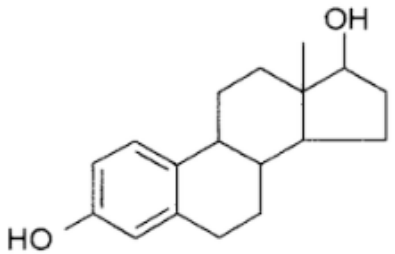
Gonadal hormones – male and female

- The primary female sex hormones are estrogen and progesterone,
- The primary men's sex hormone is testosterone.

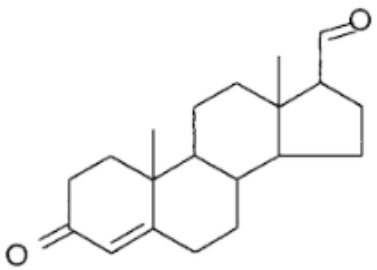
- *However, women do produce small amounts of testosterone and men also produce small amounts of estrogen and progesterone.*



Testosterone



Oestradiol



Progesterone

Hmm, they look very similar, yet they are so different!!!

Testosterone

Testosterone is produced primarily in the testes, with minimal amounts coming from the adrenal glands. testosterone helps men with:

Puberty

Penis and testes size

Facial and body hair

Sex drive

Sperm production

Fat distribution

Red cell production

Maintenance of muscle strength and mass

Testosterone plays a part on all organs within the body, including: the heart, brain, bones, liver, kidneys, skin and more. If men are low in testosterone, their symptoms can include:

Decreased mood and energy

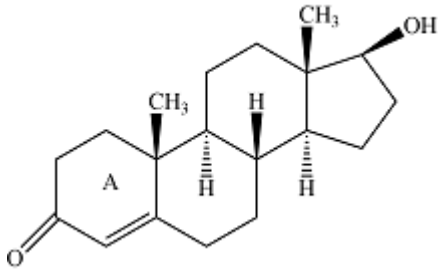
Loss of muscle mass and strength

Decreased facial and body hair

Erectile dysfunction

Loss of sex drive

Anemia



Estrogen and Progesterone

Estrogen is the main female hormone, with most being produced from the ovaries, and small amounts from the adrenal glands and fat cells.

Estrogen contributes to reproductive and sexual development. Estrogen affects every life stage of women, which are:

- Puberty
- Menstruation
- Pregnancy
- Menopause

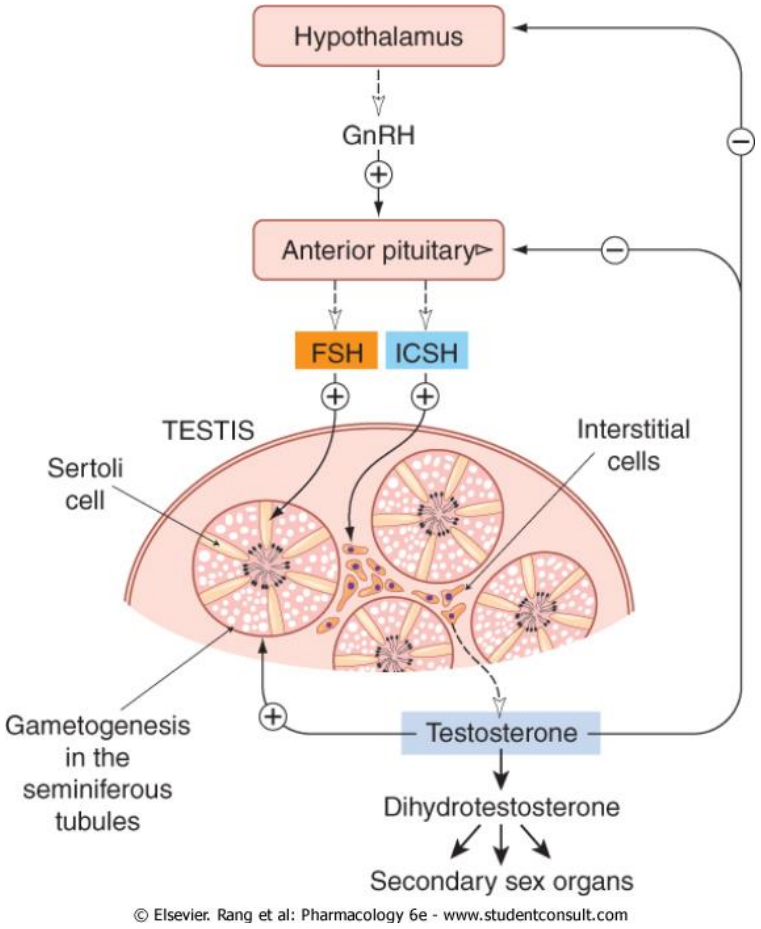
Estrogen also affects the:

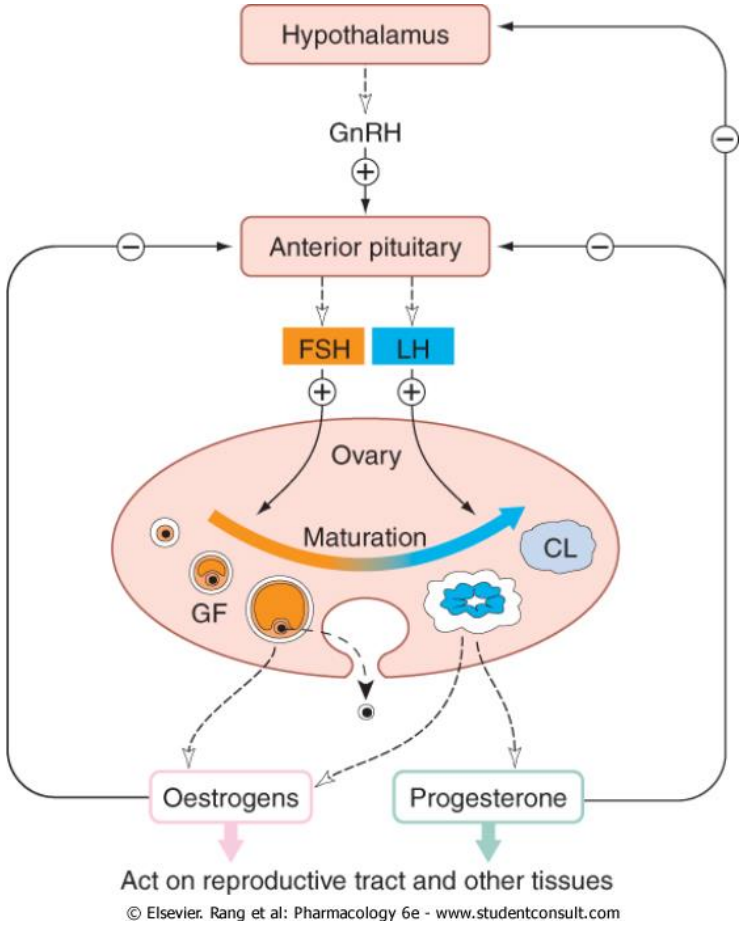
brain, cardiovascular system, musculoskeletal system, urinary tract and even hair and skin.

Progesterone:

prepares the lining of the uterus for a fertilized egg, supports pregnancy, and suppresses estrogen production after ovulation.

Gonads & Gonadal Hormones



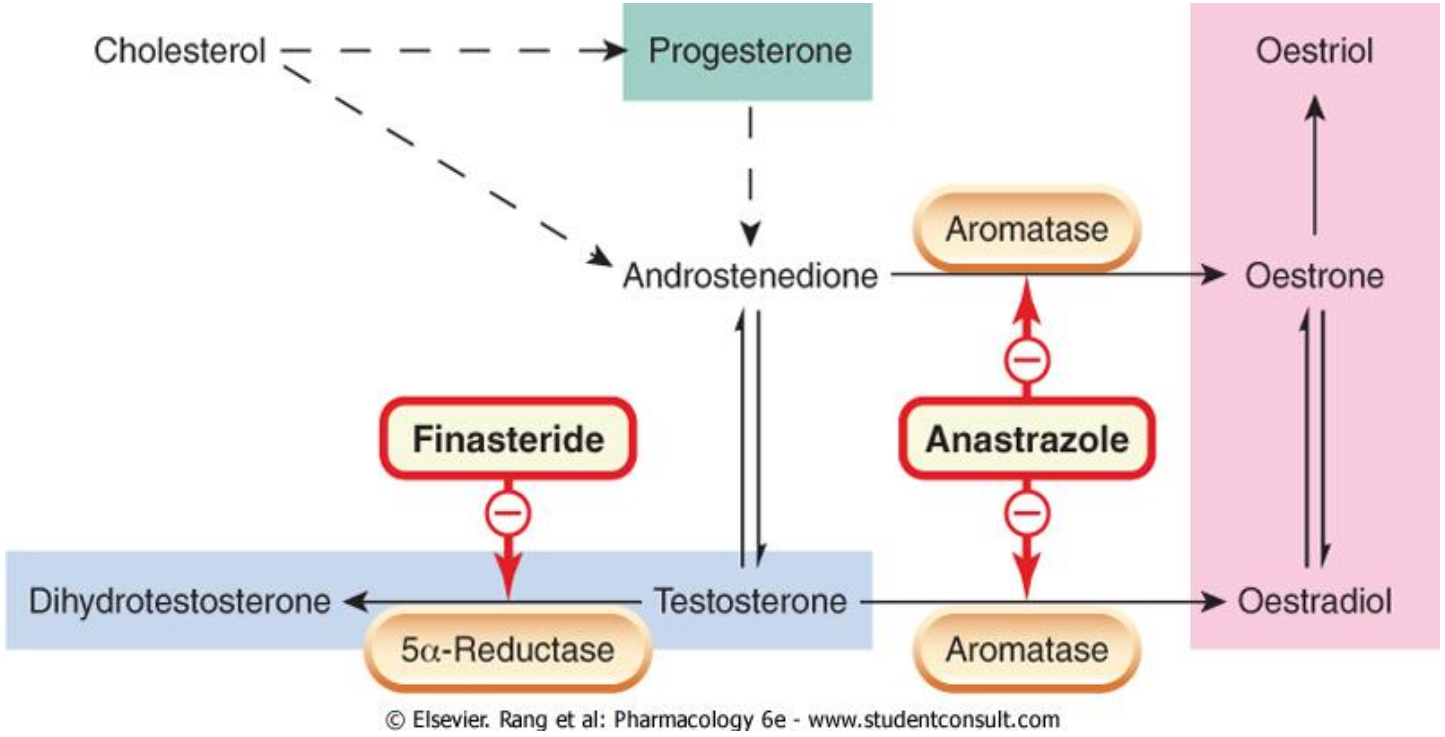


Male

Female

Gonadal Hormones

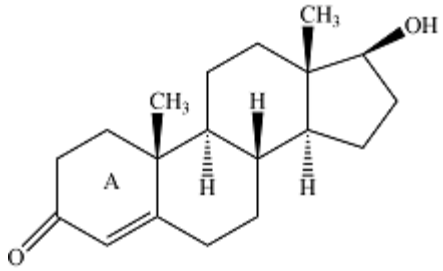
Biosynthesis



Synthetic pathway similar in ovaries, testes, adrenals

Gonadal Hormones

Androgens



Testosterone —5α-reductase→ Dihydrotestosterone

(active form in many tissues, higher affinity for receptors)

- M/A
  - Remember, testosterone is converted to active dihydrotestosterone by the enzyme 5-alpha-reductase! Testosterone is less active!
  - Testosterone and dihydrotestosterone modify gene transcription by interacting with testosterone (nuclear) receptors

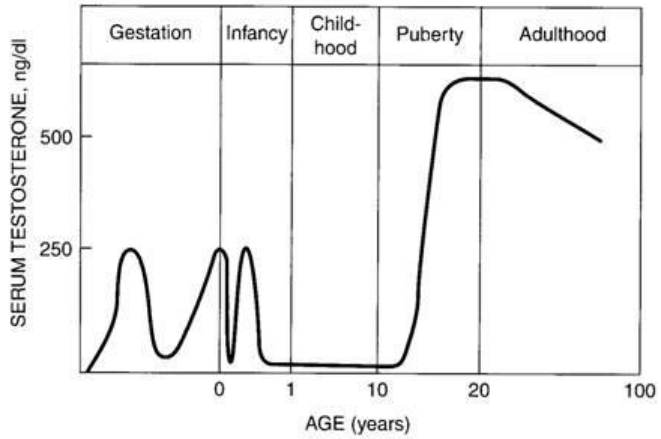


Figure 58–2. *Schematic representation of the serum testosterone concentration from early gestation to old age.*

From Goodman and Gilman's

Gonadal Hormones

Androgens

Testosterone $\xrightarrow{5\alpha\text{-reductase}}$ Dihydrotestosterone

(active form in many tissues, higher affinity for receptors)

From Goodman and Gilman's

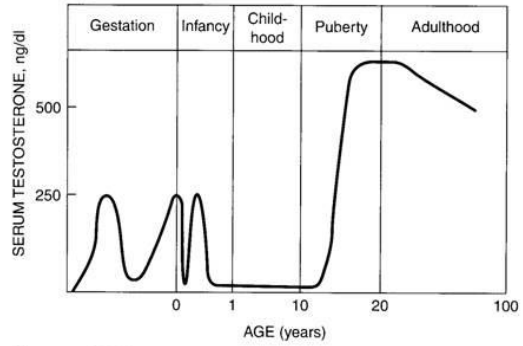


Figure 58–2. *Schematic representation of the serum testosterone concentration from early gestation to old age.*

- Circulating levels
  - In utero (during gestation)
    - Beginning of sex differentiation (> 6 weeks)
    - Lack of testosterone at 3rd trimester can lead to microphallus (small penis) and cryptorchidism (undescended testes)
  - At puberty
    - Surge in GnRH, LH, FSH & testosterone (feedback mechanism less sensitive?)
    - Development of secondary sex characteristics (hair pattern, voice deepens, skin thickens and more oilier, maturation of sexual organs)
    - Anabolic effects (skeletal and muscle growth)
    - Behavioural effects (?) including increased physical vigour, libido, aggression

Gonadal Hormones

Oestrogen in Male

Testosterone —Aromatase→ Oestradiol (anabolic effects)

- Effects on bone, spermatogenesis and behaviour
- Oestrogen deficiency (decreased aromatase or oestrogen receptors)
  - Decreases growth spurt
  - Delays epiphyseal closure (tall stature)
  - Delays skeletal maturation, malformation (“knock-kneed”, osteoporosis)
  - Increases testosterone, macro/micro-orchidism, infertility? (oestrogen involved in negative feedback)

Gonadal Hormones

Oestrogen Deficiency in Men

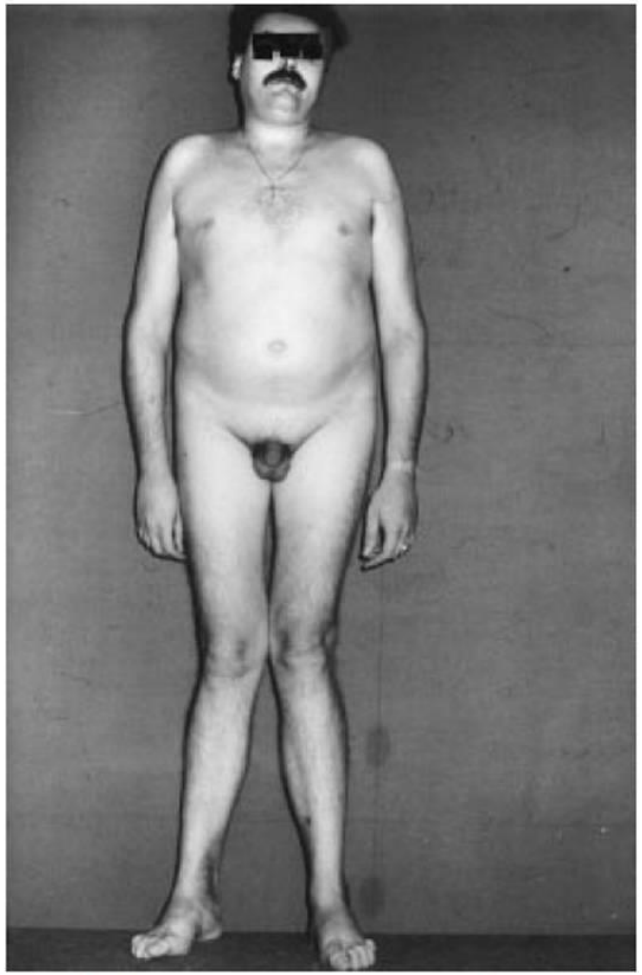


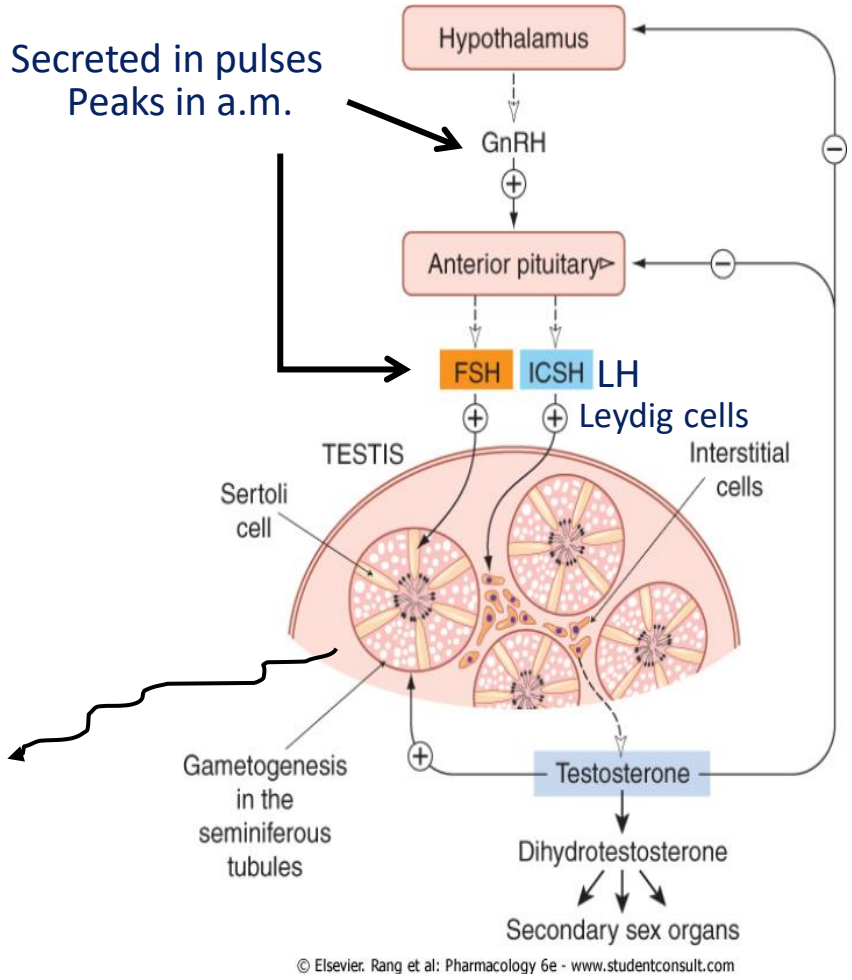
Figure 3 A 38-year-old patient with aromatase deficiency (17). He is a well-masculinized man with evident genu valgum and eunuchoid body habitus.

From Faustini-Fustini et al., (1999) European Journal of Endocrinology, 140, 111-129

Gonadal Hormones

Male Reproductive System

- Testosterone deficiency leads to infertility
- Excess testosterone inhibits FSH & LH secretions, leading to testicular atrophy and infertility



Gonadal Hormones

Male Hormone - Testosterone

Rapidly metabolised – not orally active

Testosterone undecanoate (an ester)

- Slowly hydrolysed to testosterone
- Routes of administration → po, im, scrotal or non-scrotal transdermal patch, implant, gel……

Therapeutic Uses

- As replacement therapy (hypogonadism) for:
  - Delayed puberty
  - Impotence
- Anabolic effects
  - To reverse protein loss in debilitating diseases (e.g. muscle wasting in AIDS)

Gonadal Hormones

Antiandrogens

Cyproterone acetate

- Androgen receptor antagonist with weak agonist activity at progesterone (suppresses the release of FSH, LH) and glucocorticoid receptors
- Therapeutic uses:
  - To treat masculinisation and hirsutism in female
  - To suppress excess libido $\rightarrow$ chemical castration in male sex offenders
  - Prostate cancer

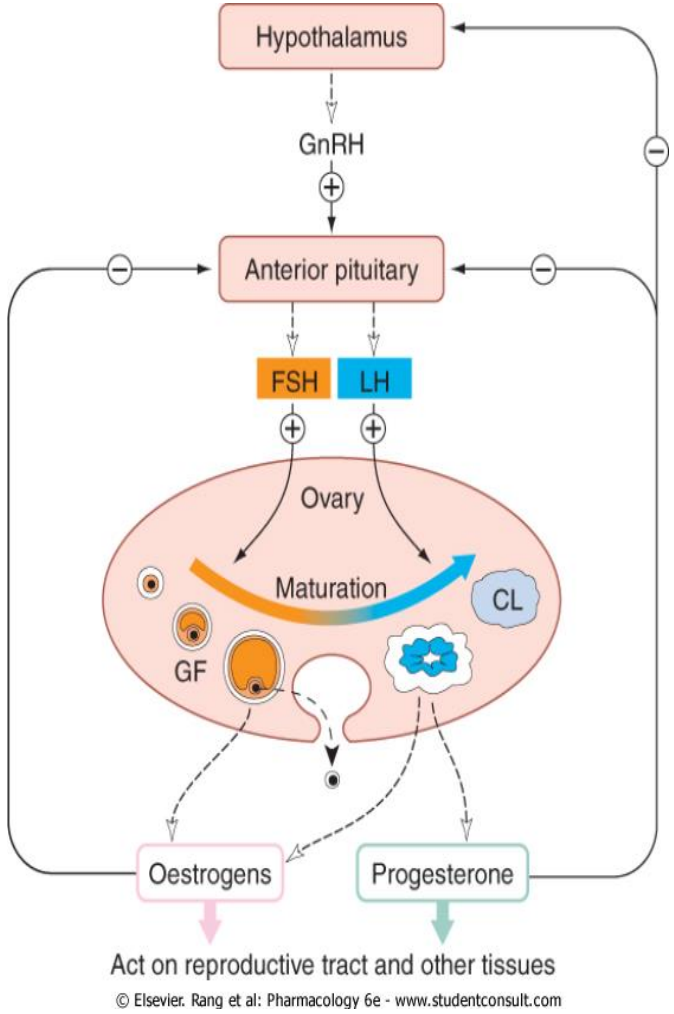
Finasteride

- Inhibits 5α-reductase $\rightarrow$ decreasing dihydrotestosterone
- Therapeutic uses:
  - Benign prostatic hyperplasia
  - Androgenic alopecia

Gonadal Hormones

Female Reproductive System - Oestrogen

- M/A - binds to oestrogen (nuclear!!) receptors, so produces genomic effects!
- "Neural switch" at puberty leading to increased secretion of GnRH and oestrogen (and somehow insensitive to feedback mechanism)
- Involves in development of:
  - Secondary sex characteristics – e.g. breast development……
  - Growth spurt (epiphysial closure after ~12 months)
  - Menstrual cycle (lasts 30-40 years until menopause)



Gonadal Hormones

Female Reproductive System - Oestrogen

- Mainly from ovarian follicular cells (or placenta in pregnancy)
- Promote development and maintenance of reproductive tissues and secondary sex characteristics
- Repair and growth of endometrium
- Increase vaginal lubrication
- Mineralocorticoid effects
- Anabolic effects, increased blood coagulability and HDL
- Progesterone receptor upregulation
- Negative feedback inhibition

Gonadal Hormones

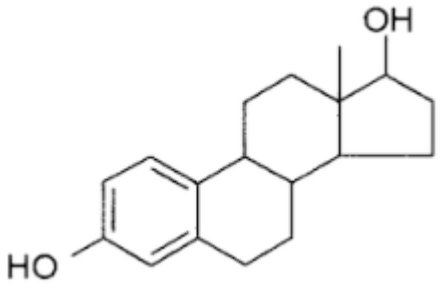
Female Reproductive System - Oestrogen

What are available in pharmacy?

- Many preparations/dosage forms (oral, transdermal, intramuscular, implantable and topical) of oestrogens are available for a wide range of indications.
- These include natural (e.g. oestradiol, oestriol) and synthetic (e.g. mestranol, ethinylestradiol, diethylstilbestrol) oestrogens.

Gonadal Hormones

Oestradiol



- Oestradiol is inactive orally (rapid metabolism) but 17-ethinyl oestradiol is orally active
- Effects:
  - Develop and maintain female sex characteristics (reproductive system, body shape, hair…)
  - Metabolic
    - Anabolic → body growth at puberty (also in male) including skin, vessels, bone (increases bone mass, osteoblasts), endometrium……
    - Uterine oedema
    - Increase blood coagulability (by increasing coagulation factors and decreasing anticoagulation factors) – risk of thromboembolism increases
    - Increase HDL and reduce LDL – risk of atheroma reduces (but studies showed no significant CV protective effects)

Effects are dose-related

Gonadal Hormones

Oestradiol – Therapeutic Uses

- As replacement therapy for deficiency
  - Hypogonadism (inadequate growth in pre-pubertal females)
  - Hormone replacement therapy (HRT) for postmenopausal women
- As contraceptive at higher doses
- Prostate and breast cancers (not use very often)

Antioestrogens – Therapeutic Uses

- To treat oestrogen-sensitive breast cancer (tamoxifen, toremifene, fulvestrant)
- Aromatase inhibitors (e.g. anastrozole) are an alternative for breast cancer in post-menopausal women
- To induce ovulation (clomiphene) in treating infertility caused by anovulation.

Gonadal Hormones

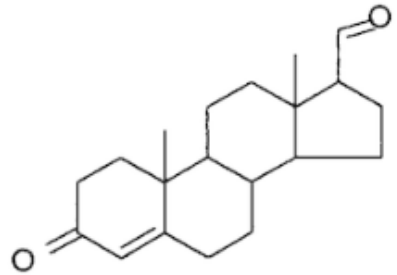
Oestradiol – Major Concerns

Risks associated with it's use

- Endometrial Carcinoma
  - Risk increases with using oestrogen alone in postmenopausal women
  - *Hysterectomy?*
- Breast Cancer
  - Small increase in risk → dose-dependent
- Metabolic effects
  - Increases risk of gallbladder disease
- Cardiovascular effects
  - Increases risk of thromboembolism

Gonadal Hormones

Female Reproductive System – Progesterone



- Mainly from corpus luteum (or placenta in pregnancy)
- Prepares endometrium for implantation (with oestrogen)
- Increases viscosity of cervical mucus
- Prepares mammary glands for milk secretion
- Thermogenic → increases body temperature (0.5°C)
- Anti-mineralocorticoid effects
- Decreases contractility of uterine smooth muscle
- Oestrogen receptor down-regulation
- Negative feedback inhibition

Gonadal Hormones

Progestogens

- Inactive orally ($t_{½}$ 5min)
- Addition of 17-ethinyl group → orally active
  - Example: norethindrone
    - Synthesised by Djerassi et al 1951
    - Enable effective mass contraception

- M/A - The mechanism of action involves intracellular/nuclear receptor so alters gene expression
- Oestrogen stimulates synthesis of progesterone receptors, whereas progesterone inhibits synthesis of oestrogen receptors

Gonadal Hormones

Progestogens

- Effects
  - Reminder: oestrogen is required to induce the formation of progesterone receptors
  - Involvement in the development of endometrium
  - Maintenance of pregnancy
  - Development of mammary apparatus
  - Carbohydrate metabolism

- Clinical Uses
  - Contraception (mostly → alone or in combination with oestrogen)
  - HRT with oestrogen (to oppose adverse effects of oestrogen)
  - Endometriosis

Gonadal Hormones

Anti-progestogens – Mifepristone (RU486)

- Progesterone receptor antagonist
- Use
  - To terminate early pregnancy by breaking down uterine lining (breaks down corpus luteum and inhibits endogenous progesterone release – luteolytic) which leads to detachment of blastocyst (~ 5 days after fertilisation of ovum)
    - Use with PGE derivatives to promote uterine contraction and soften cervix to expel the detached blastocyst
    - Effective in 95% cases
- Adverse effects
  - GI – vomiting, diarrhoea, pain……
  - Prolonged bleeding

Female Hormones & Contraception

Brief comparison

- Oestrogen
  - Inhibits FSH release via negative feedback mechanism
    - Inhibits development of follicle
- Progestogen
  - Inhibits release/surge of LH
    - Prevents ovulation
  - Thickens cervical mucus (and make it more sticky)
    - Inhibits sperm penetration and fertilisation
- Both oestrogen and progestogen
  - Alter/thin endometrium – underdeveloped
    - Inhibit implantation

Menopause and HRT (MHT)

Menopause

- cessation of ovulation - defined as the final menstrual period
- average age at menopause is 51 years, normal range 45–55 years
- results in physiological changes affecting the cardiovascular, musculoskeletal, urogenital and central nervous systems
- in perimenopausal and postmenopausal years, women often have symptoms including vasomotor symptoms (hot flushes, night sweats), muscle and joint pains, sleep disturbance, mood changes, anxiety and genitourinary symptoms

- increase in incidence of cardiovascular disease and osteoporosis after menopause

Menopausal Hormone Therapy (MHT)

- most common is combined oestrogen and progesterone
- in people with intact uterus, oestrogen increases risk of endometrial cancer

Current recommendations

- benefits of MHT outweigh risks in healthy people within 10 years of menopause or between 50 - 60 years of age
- decreased risk of osteoporosis, heart disease, bone fracture, endometrial cancer, colorectal cancer, onset of type 2 diabetes, cataracts
- slight increased risk of breast cancer, thrombosis, gallstones, ovarian cancer

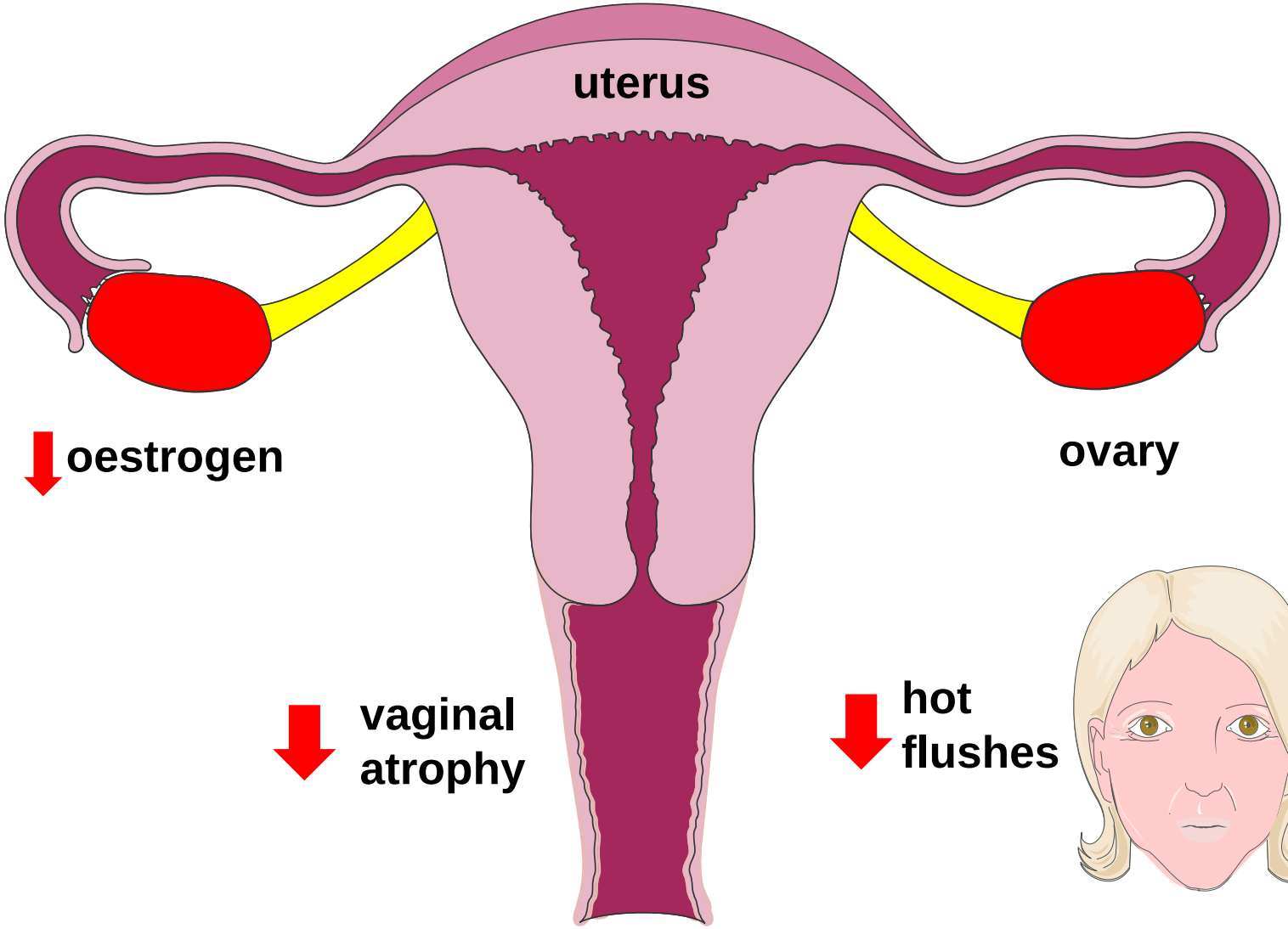
Contraindications

- breast cancer, other oestrogen-dependent cancer, undiagnosed vaginal bleeding
- thrombosis
- untreated hypertension, coronary heart disease, stroke, dementia

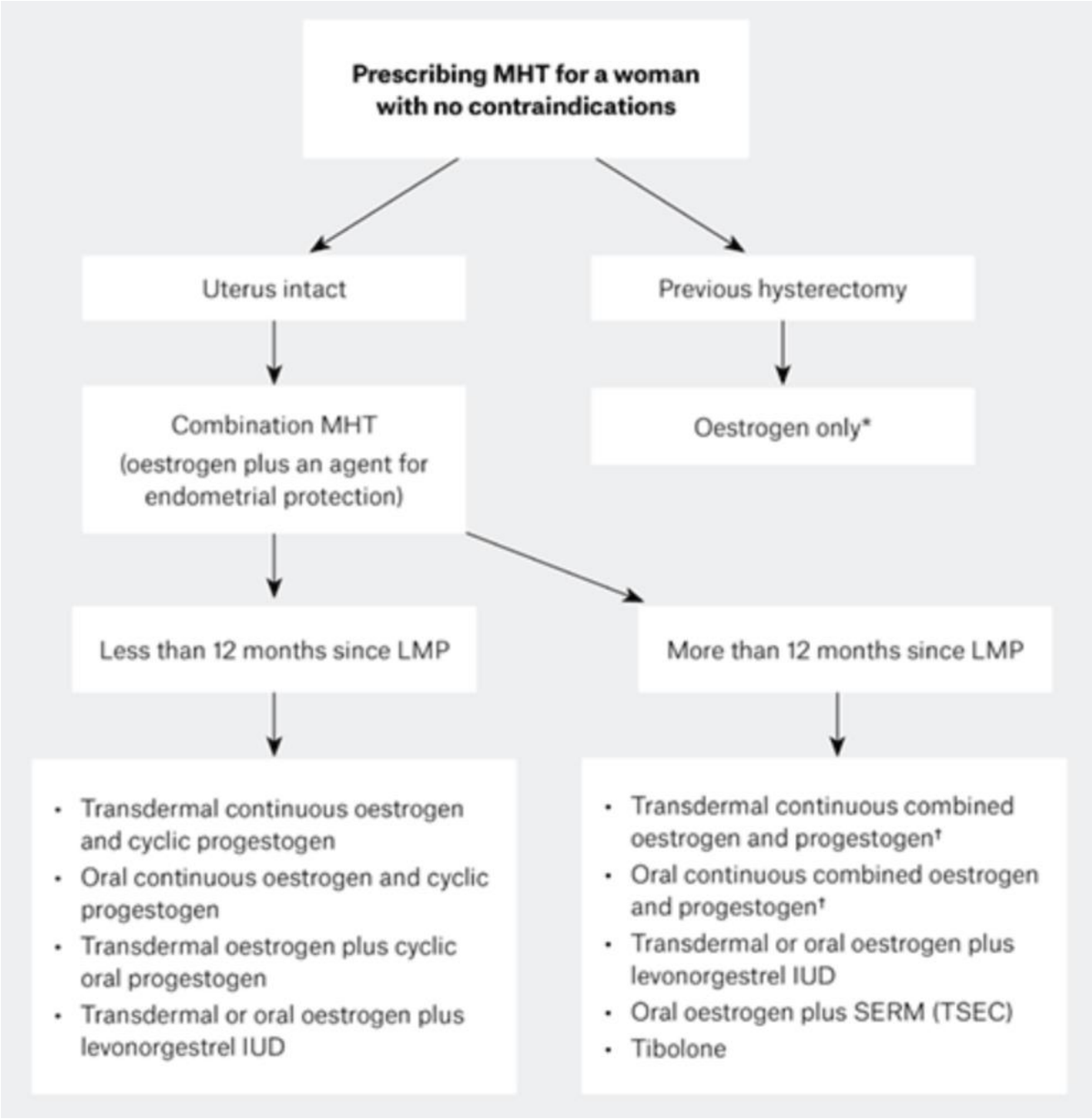
Oestrogens

Drugs for menopausal symptoms

oestrogens O

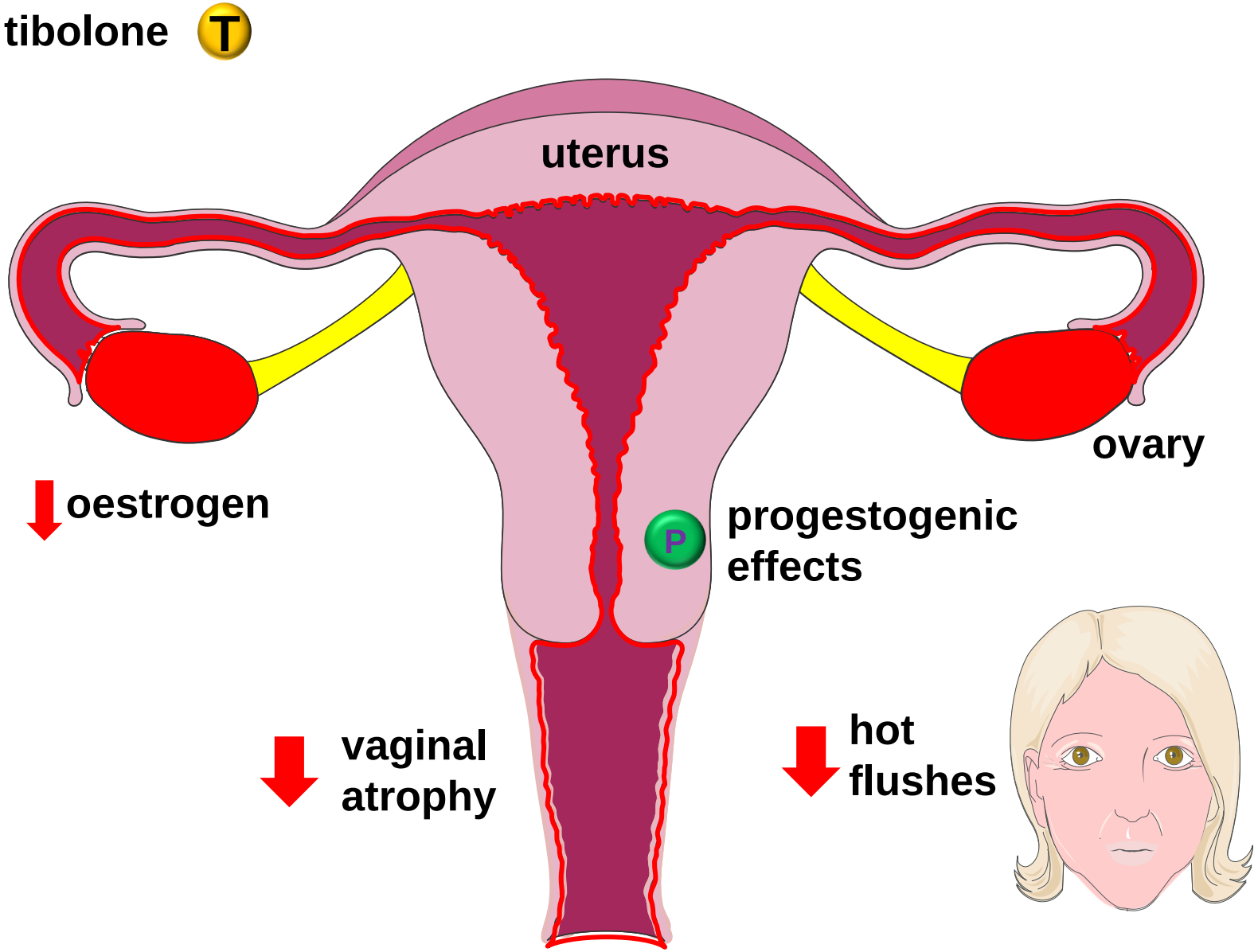


Menopausal Hormone Therapy (MHT) Guidlines



Tibolone

Drugs for menopausal symptoms



Drugs for contraception - Combined oral contraceptives

- combinations of an oestrogen with a progestogen; many variations

Mechanisms of action

- oestrogen inhibits secretion of FSH via negative feedback on the anterior pituitary, and thus suppresses development of ovarian follicles
- progestogen inhibits secretion of LH and thus can prevent ovulation; main effect is to make the cervical mucus less suitable for the passage of sperm
- oestrogen and progestogen act together to alter the endometrium to discourage implantation
- also interfere with coordinated contractions of the cervix, uterus and fallopian tubes that facilitate fertilisation and implantation

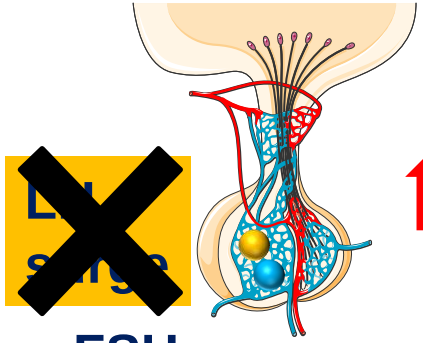
Adverse effects

- weight gain, nausea, mood changes, skin pigmentation changes / acne
- rare serious ADRs including hypertension, small increase risk of breast and cervical cancer, thromboembolism

Combined Oral Contraceptives

combined oral contraceptive E P

anterior pituitary



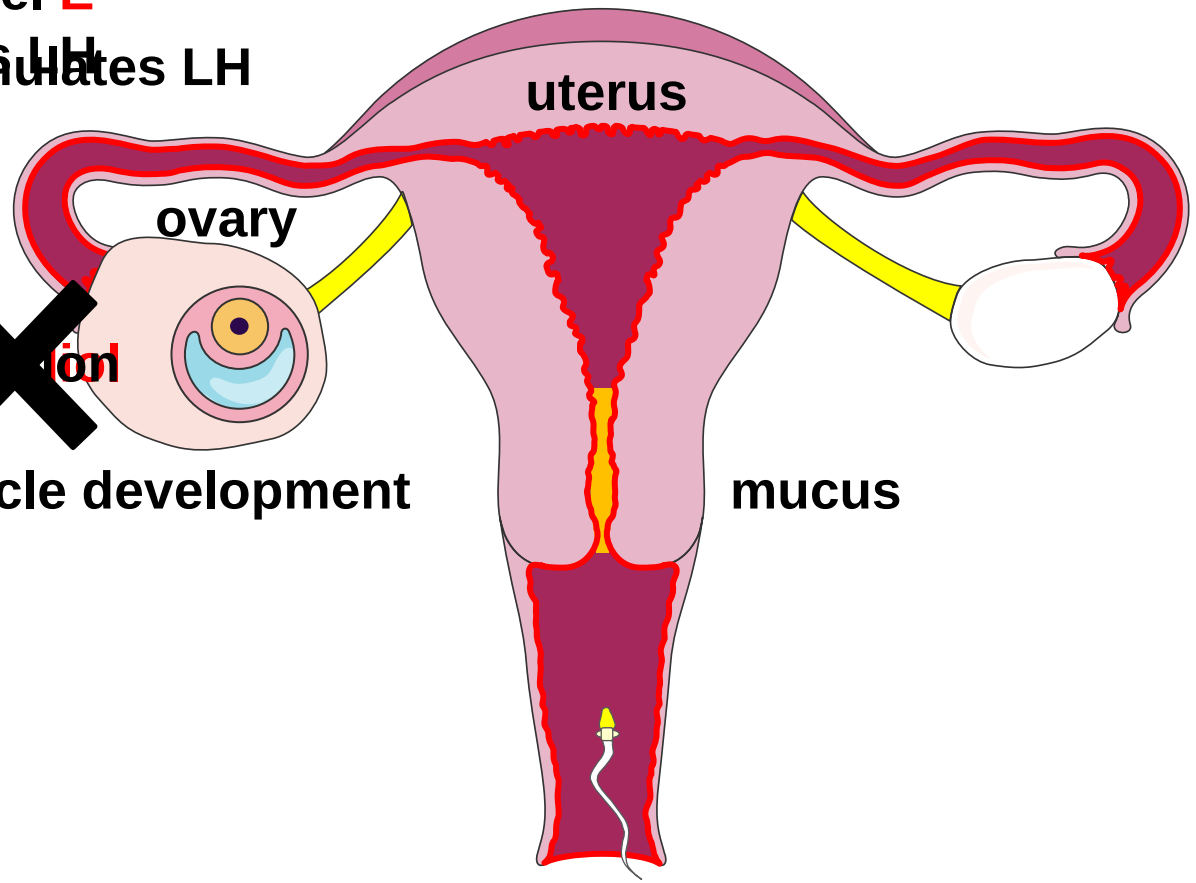
LH surge

FSH

low level E

inhibits LH

E stimulates LH



Drugs for contraception

Progesterone – only pill

- taken continuously
- less reliable contraceptive effect
- Irregular bleeding is common adverse effect

Postcoital (Emergency) Contraception

- levonorgestrel, alone or combined with oestrogen
- taken within 96 h of unprotected intercourse ~~and repeated 12 h later~~
- nausea and vomiting are common
- also intrauterine device available

Long-term contraception in Aust

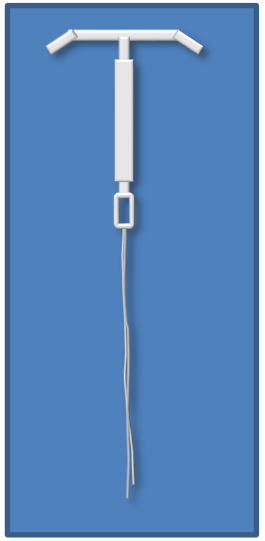
- vaginal contraceptive ring - soft plastic ring containing oestrogen and progestin - ring inserted high in vagina and worn for 3 weeks, removed for withdrawal bleed

- progestin-only (etonogestrel) implant
  - inserted subdermally (eg inside upper arm) and is effective for up to 3 years

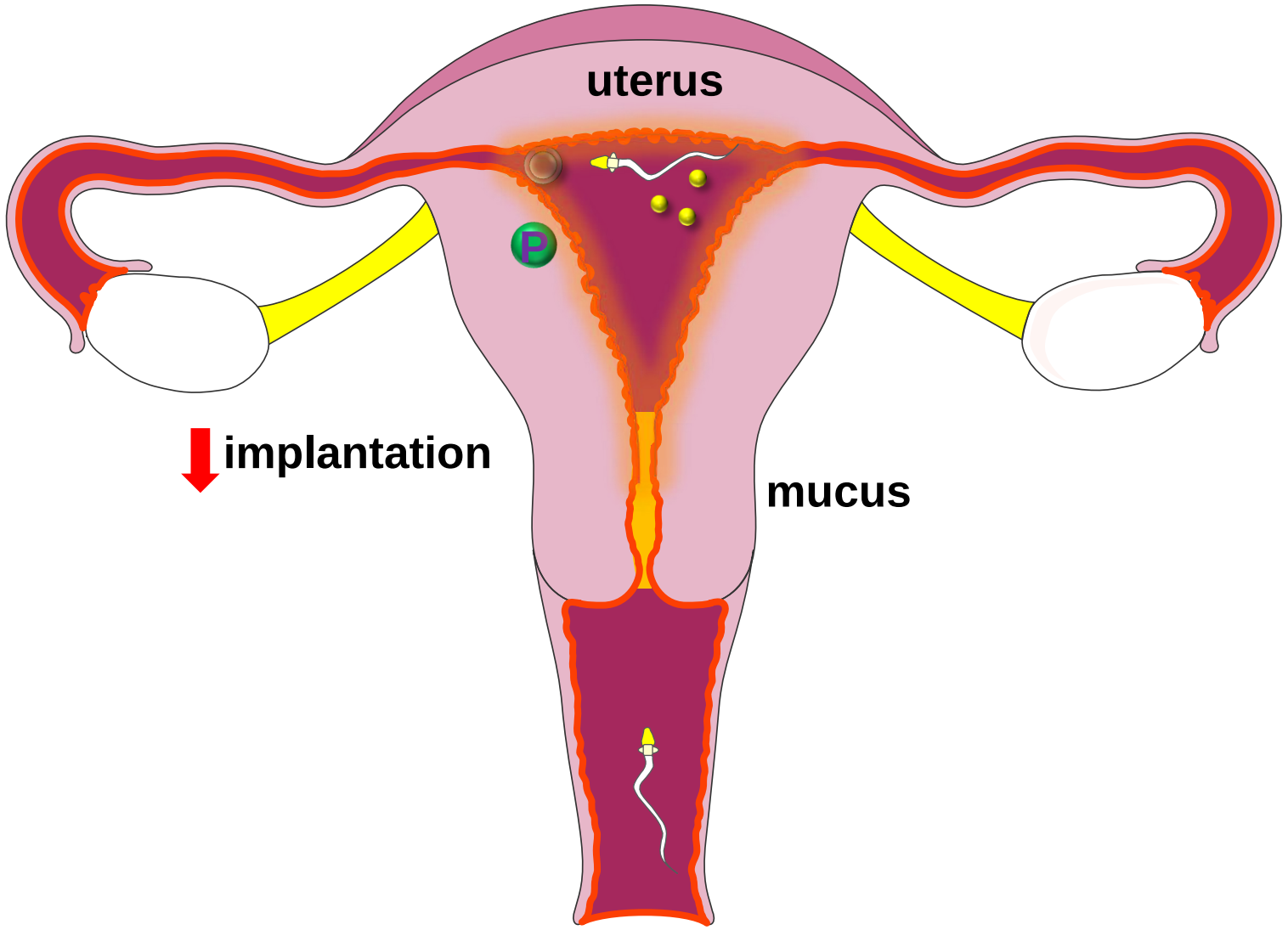
- levonorgestrel-releasing intrauterine system
  - provides effective contraception for 8 years

- depot medroxyprogesterone acetate (DMPA)
  - administered by deep intramuscular injection every 12 weeks

Levonorgestrel IUD



levonorgestrel IUD



Reference

- Chapter 36 in Rang & Dale's Pharmacolgoy 9e
- Chapter 32 & 33 in Bryant *et al* Pharmacology 5e
- Katzung et al. 12th ed Chapter 40
- Australian Medicines Handbook 2024

Practice Questions

1. What are the anabolic steroids? What health risks are associated with their use by (a) males and (b) females?
2. Describe the mechanisms of action, clinical uses and adverse effects of different types reproductive hormones and associated agents.