الجامعة السورية الخاصة
SYRIAN PRIVATE UNIVERSITY

السنة الثالثة

تأثير الأدوية2

د.رامز ونوس

4م

150

Sex hormones and drugs

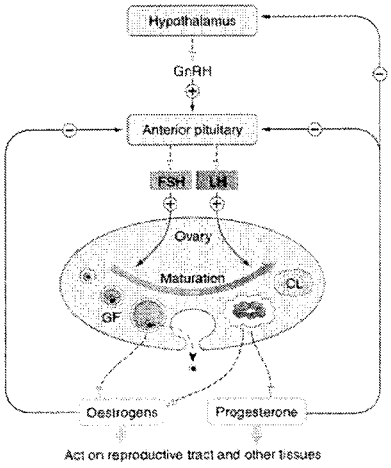
Progestins

Pharmacology II
Dr. Ramez WANNOUS
2017

- Synthetic progestogens are generally referred to as progestins. However, the terms progesterone, progestogen, and progestin are frequently used interchangeably.
- progesterone is the major natural progestogen in the body

secreted by :

- Corpus luteum in the second part of the menstrual cycle
- Placenta during pregnancy
- Testis and adrenal cortex (Small amounts)



Hormonal control of the female reproductive system.
The Graafian follicle (GF) is shown developing on the left, then involuting to form the corpus luteum (CL) on the right, after the ovum (•) has been released. FSH, follicle-stimulating hormone; GnRH, gonadotrophin-releasing hormone; LH, luteinising hormone.

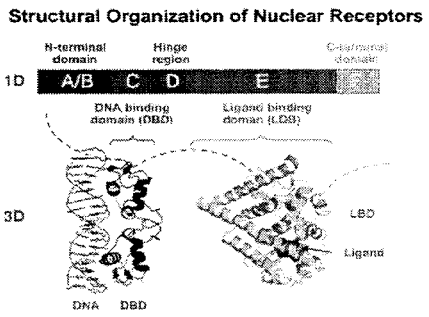
Pharmacokinetic aspects

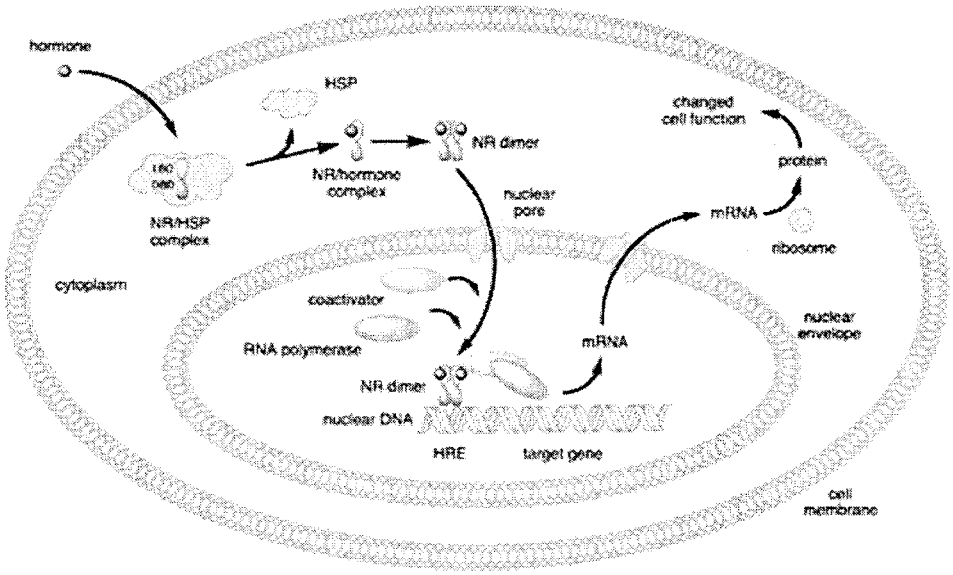
- Inactive orally with a half-life of only about 5 minutes (high first pass metabolism)
  Synthetics are active orally and metabolized slowly
  Half-life of 8-24 HRs
- Injected progesterone is bound to albumin, not to the sex hormone-binding globulin .
- Some is stored in adipose tissue.
- It is metabolised in the liver, and the products, pregnanolone and pregnanediol, are conjugated with glucuronic acid
- excreted in the urine

Physcical actions of Progesterone

- **Uterus:** Maintenance of pregnancy – nidation and maintenance of pregnancy
  - Decreases contractility of the uterine
  - Decreases the maternal immune response
- **Cervix:** viscid and cellular secretion – no sperm penetration
- **Breast:** Proliferation of acini in mammary glands
  - Prepares breast for lactation together with estrogen
- **Body temperature:** rise in temperature
- **Pituitary:** Weak Gn inhibitor, suppresses ovulation if given during follicular phase

Mechanism of Action (MOA)





NR3

Adverse Effects

The major adverse effects associated with the use of progestins are

- Headache, depression, weight gain, changes in libido and breast discomfort
- Irregular bleeding or amenorrhea
- Hyperglycaemia
- Some androgenic activities
  - acne and hirsutism.
  - Lower HDL, increased incidence of thromboembolism

Preparations

Progesterone is also available in the forms of

- Oral micronized progesterone (OMP)
- Suppositories or pessaries
- Transdermally-administered patches, gels or creams
- Intramuscular or subcutaneous injection

➢ **Progesterone Derivatives:**

Medroxyprogesterone acetate
Hydroxy progesterone caproate
Megestrol acetate
Dydrogesterone
Newer –Nomegestrol acetate

Preparations

➢ **19-nor testosterone derivatives**

a) Older

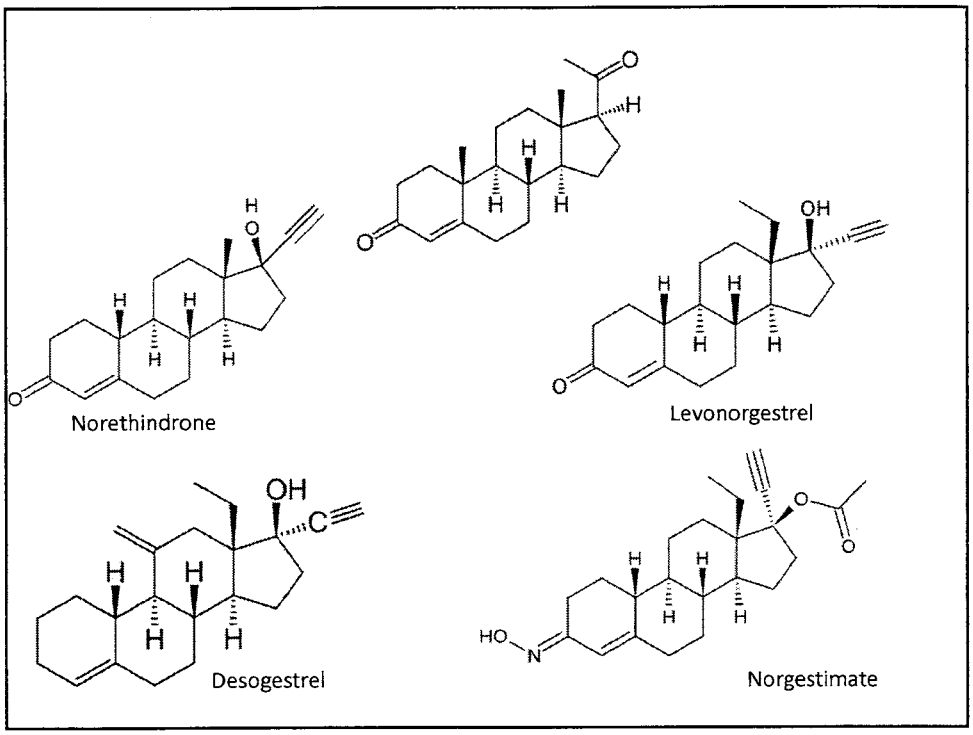
- Norethindrone
- Levonorgestrel
- Lynesternol-Ethinylesternol, Allylesternol

- The first two have some androgenic activity

b) Newer compounds (3rd Generation compounds)

- Gonanes
- Desogestrel
- Norgestimate
- Gestodene

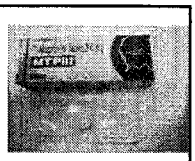
- for women who experience side effects such as acne, depression or breakthrough bleeding with the older drugs
- higher risks of venous thromboembolic disease



Uses of Progestins

- Contraceptive
- Hormonal replacement therapy
- Dysfunctional Uterine Bleeding
- Premenstrual syndrome
- Threatened and habitual abortion
- Endometrial carcinoma

Antiprogestin - Mifepristone



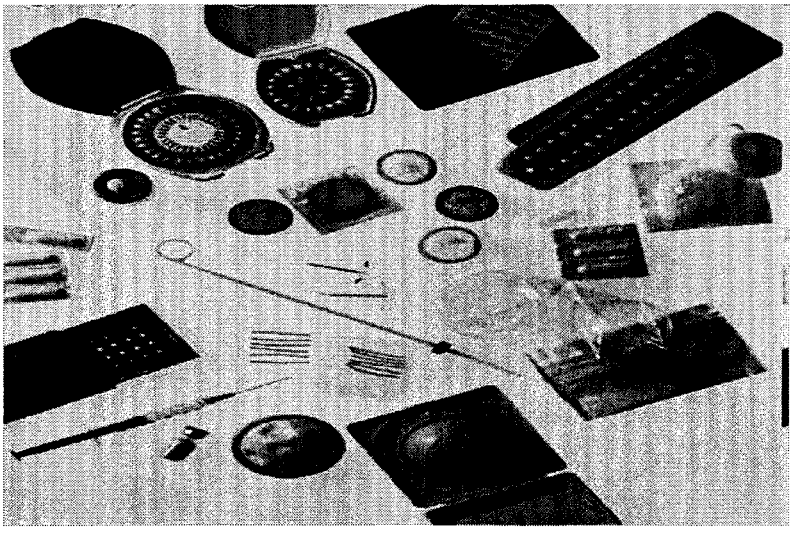
Action:

- Sensitization of endometrium to PGs
- Uses:
  - In combination with a prostaglandin (e.g. gemeprost), as a medical alternative to surgical termination of pregnancy
  - Induction of labour
  - Postcoital contraceptive

Kinetics:
Absorbed orally and bioavailability is only 25% half-life is 20-36 hrs

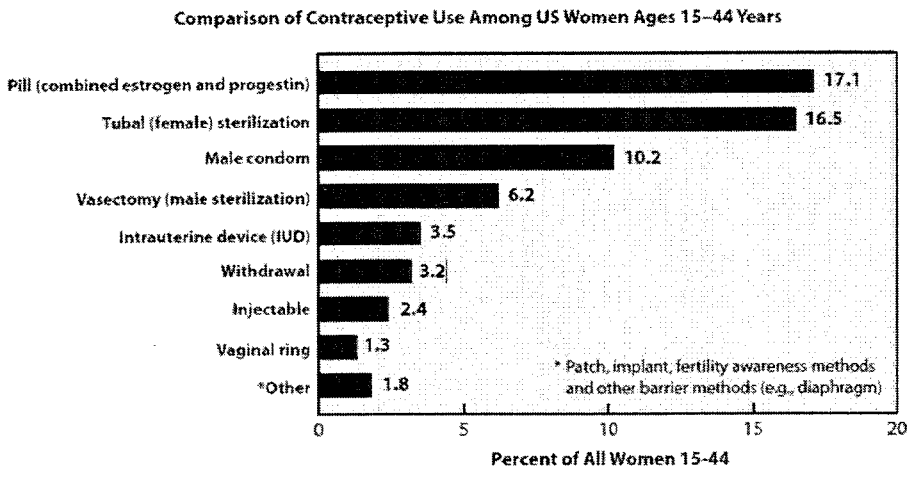
Preparations: Tablet – 200 mg

Pharmacology of Hormonal Contraception



Basic types of contraception

- Fertility awareness methods
- Situational methods
- Spermicides
- Barrier methods
- IUDs
- Hormonal contraception
- Operative sterilization



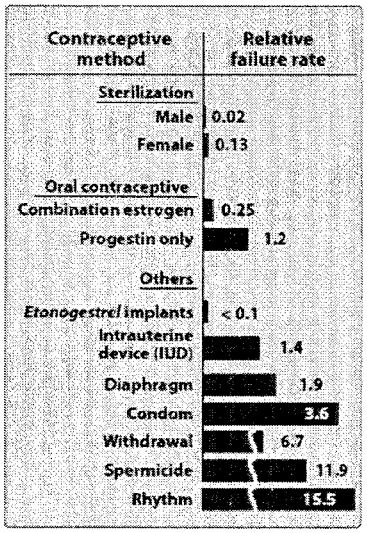


Figure 26.9
Comparison of failure rate for various methods of contraception. *Longer bars* indicate a higher failure rate—that is, more pregnancies.

Female hormonal contraception

Short acting

Oral

- Combined pill
- Mini pill
- Post-coital pill

Long acting

Injectable

– progesterone alone

– progesterone + estrogen

Implants:

– Norplant

Mechanism of action

- Combination pill, given daily for 3 of every 4 weeks:
  - Prevents ovulation by inhibiting gonadotropin secretion via effect on both pituitary and hypothalamic centers
  - Estrogenic agent ; suppresses FSH secretion (thus prevents selection and emergence of dominant follicle)
  - Progestational agent in pill ; suppresses LH secretion (thus prevents ovulation)
  - Thick Cervical mucus secretion making hostile for sperm penetration
  - Failure of implantation – hyperproliferative and hypersecretory endometrium
  - Uterine and tubal contraction – peristalsis within the fallopian tube

History

- The oral contraceptive combined pill (COCP) was first introduced in 1960
- 1970: Introduction low dose or second generation of OCs
- 1980: biphasic or triphasic regimens
- 1990: 3rd generation OCs

  (O + P has less androgenic activity,

  e.g, desogestrel 0.15 mg)

- Since then it has undergone many modifications and has been used by millions of women worldwide.

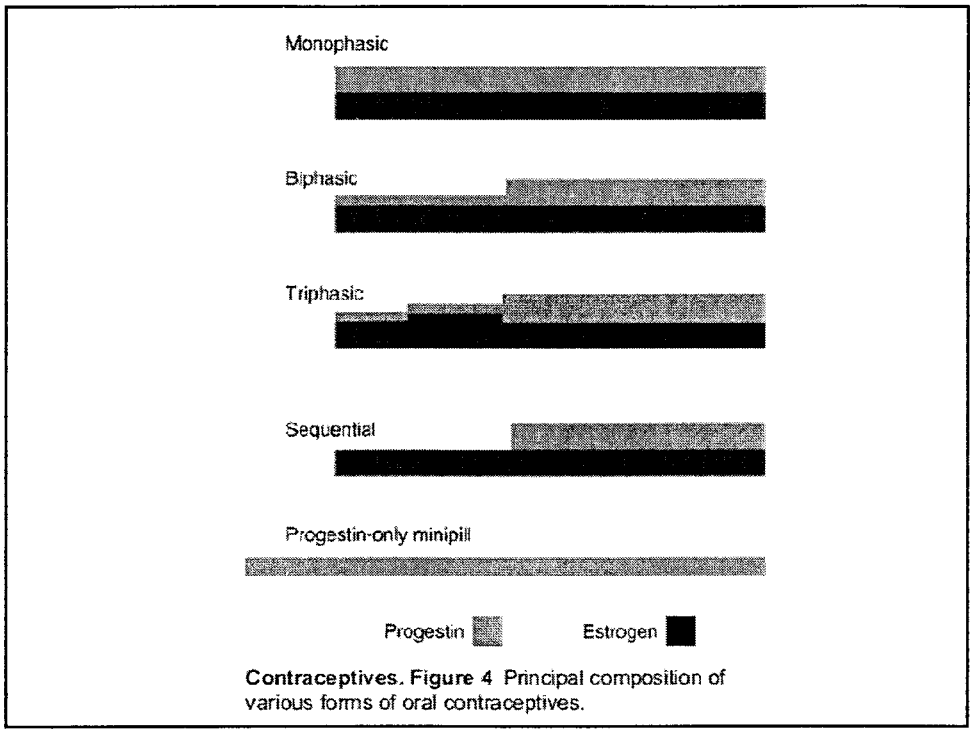
Combined Pill

- all products containing less than 50 µg ethinyl estradiol per pill are summarized as low-dose oral contraceptives.
- First generation oral contraceptives:
  - Products containing 50ug or more of ethinyl estradiol
- Second generation oral contraceptives:
  - Products containing levonorgestrel and other members of norethindrone family and 30 or 40ug ethinyl estradiol
- Third generation oral contraceptives:
  - Newer progestins (desogestrel and gestodene) which have little or no androgenic activity with 20 or 30ug ethinyl estradiol

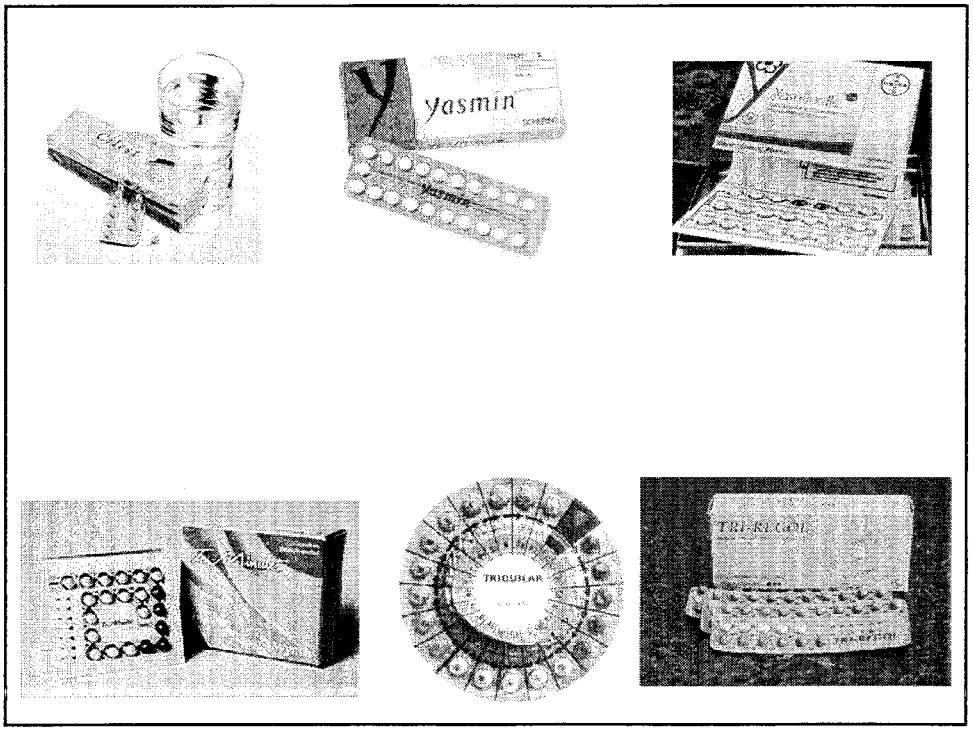
Formulations

- Formulations may be :

1. Monophasic (each tablet contains a fixed amount of estrogen and progestin); Cilest®, Jeanine®, Yasmine®, Yasminelle®
2. Biphasic (each tablet contains a fixed amount of estrogen, while the amount of progestin increases in the second half of the cycle); Anteovin®
3. Triphasic (the amount of estrogen may be fixed or variable, while the amount of progestin increases in 3 equal phases). Tri-Minulet®, Triquilar®, Tri-Regol®



Contraceptives. Figure 4 Principal composition of various forms of oral contraceptives.



Formulations

- Biphasic and triphasic formulations were initially developed with the intent of lowering the total steroid content of combined OCs (estrogen – 30 to 40 mcg)
- Two types of estrogen are used in combined OCs: ethinyl estradiol and mestranol
- Mestranol is a "prodrug" that is converted in vivo to ethinyl estradiol
- Several different progestins, of varying degrees of progestational potency, are used in combined OCs

Minipill

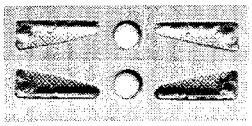
- Progesterone only pill
- To eliminate estrogen to avoid long term risks of estrogen (hypertension, venous thrombosis...)
- Low dose taken daily without gap
- Efficacy is 96-98%
- Do not affect breast milk supply (good for nursing moms)

Missed Pill Advise

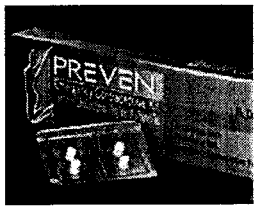
- **If 1 or 2 of 30-35mcg ethinylestradiol pill or 1 of 20 mcg**
  - Advise to take the most recent pill as soon as remembers, continue taking remaining pill at usual time, she does not require additional contraception or emergency contraception
- **If 3 or more of 30-35 or 2 or more 20 mcg**
  - Advise as above, but to use extra method of contraception until pills have been taken for 7 days in a row
  - If pill is missed in week 1 (days1-7) and unprotected sexual intercourse has taken place in pill free week or wk 1 then emergency contraception is needed
  - If pills missed in wk 3 (days 15-21), advise to finish pill in pack and start new pack the next day, omitting pill free interval
  - If one has missed > 7 consecutive days then consider as stopped COCP

Postcoital (Emergency) Contraceptives

- PLAN-B includes 2 doses of levonorgestrel separated by 12 hours (progestin-only)
- PREVEN is a 2 pill dose of a high-dose oral contraceptive (levonorgestrel and ethinyl estradiol) separated by 12 hours
- The first dose of these drugs should be taken 72 hours after intercourse
- Mifepristone – 400 mg (= 2 tablets)
- IUD



PLAN B



Injectable

- Long acting Progestin alone
  1. Depot medroxyprogesterone (DMPA) – 150 mg (1 ml vial) – half life – 50 days)
  2. Norethisterone – 200 mg (1 ml vial) – repeat at 2 months
- Long acting progestin + estrogen:
  - Medroxyprogesterone + estradol cypionate – IM injection – monthly
- Implants – norplants, progestesert etc.

Adverse Effects

- Some combined OC users will experience minor side-effects, most commonly during the first 3 cycles.
- These side-effects may lead to discontinuation of the combined OC
- The most common reason patients discontinue combined OC use is:

1. Abnormal menstrual bleeding, followed by :
2. Nausea
3. Weight gain
4. Mood changes
5. Breast tenderness
6. Headache
7. Skin changes (acne, pigmentation)

Serious Complications

- Leg vein and pulmonary thrombosis
- Coronary and cerebral thrombosis
- Hypertension
- Genital carcinoma
- Benign hepatomas
- Gallstones

Hormonal contraception

– Noncontraceptive benefits:
  - Decreased risk of ovarian and endometrial cancer
  - Relief of menstrual symptoms (e.g. fewer/less painful cramps, lighter flow)
  - Regulation of irregular menses
  - Reduced risk of ovarian cysts
  - Improvement in menstrual migraines
  - Decreased incidence of ectopic pregnancy
  - Decreased incidence of benign breast disease & iron deficiency anemia
  - Reduced symptoms of endometriosis, acne, hirsutism

Contraindications (WHO)

1. < 6 weeks postpartum if breastfeeding
2. Smoker over the age of 35 (≥ 15 cigarettes per day)
3. Hypertension (systolic ≥ 160mm Hg or diastolic ≥ 100mm Hg)
4. Current or past history of venous thromboembolism (VTE)
5. Ischemic heart disease
6. History of cerebrovascular accident
7. Complicated valvular heart disease
8. Migraine headache
9. Breast cancer (current)
10. Diabetes with retinopathy/nephropathy/neuropathy
11. Cirrhosis
12. Liver tumour