HORMONAL CONTRACEPTION

- HISTORY

Oral Contraceptive Pills

- First introduced in 1960
- Combination of:
  - 150mcg of the synthetic estrogen, mestranol
  - 9.85 mg of the synthetic progestin, norethynodrel
- Considered as a medical milestone

Oral Contraceptive Pills

- Two major types
  - Combined oral contraceptives (COCs), also called "The Pill"
    - Contain estrogen and progestin
    - Most widely used
  - Progestin only pills (POPs), also called "Mini Pill"
    - Contain no estrogen
    - Good choice for lactating women

COCs – Classification

Based on the quantities of estrogen & progestin

Monophasic - Contain fixed quantities of estrogen and progestin in all the pills

Biphasic : Contain gradually escalating doses of progestin and constant or escalating doses of estrogen throughout the 21-day pill cycle

Triphasic : Contain gradually escalating doses of progestin and constant or escalating doses of estrogen throughout the 21-day pill cycle

- Aimed to mimic the naturally occurring levels of estrogen and progesterone
- Clinically triphasic preparations not superior to monophasic OCPs in efficacy or safety

Estrogens in COCs

- Mestranol – a “prodrug” that is converted in vivo to ethinyl estradiol
  used in older formulations, not found in newer formulations
- Commonly used – ethinyl estradiol (EE), 20-35 mcg
- Contraceptive effect & cycle control
  - Inhibits FSH release from pituitary : prevents follicular growth and development
  - Stabilizes endometrium : prevents irregular or unscheduled bleeding
- Increases SHBG levels – decreases free androgen index
- Increases HDL-C, decreases LDL-C

Estrogens in COCs – Side effects

- Activation of angiotensinogen synthesis in the liver (RAAS* activation)
  - Increase in angiotensin II & aldosterone
    - Sodium & fluid retention
    - Weight gain, breast tenderness, bloating, mood changes, increase in BP
- Venous Thromboembolism (VTE) – risk lower with 20-30 mcg EE

* - RAAS – Renin angiotensin aldosterone system

Estrogen – What dose?

- Based on estrogen content, COCs are classified into:
  - **High dose : 50μg or more of ethinyl estradiol (EE)**
  - **Low dose : 30 – 35 μg of ethinyl estradiol**
  - **Ultra–low dose : 20 μg of ethinyl estradiol**
- Higher doses of EE - greater incidences of side effects (breast tenderness, bloating, nausea, thromboembolic events etc)
- The development of potent progestins facilitated use of low or ultra–low dose pills with improved safety
- Estrogen quantity used should be a balance between efficacy (endometrial stability) and side effects

Bottom Line

Lower the dose of estrogen, greater the safety

Progestins in COCs

- Mechanism of action
  - Inhibit LH surge from the pituitary : inhibit ovulaiton
  - Make endometrium unfavorable for implantation
  - Thicken cervical mucus : impede sperm transport
- Variety of progestins used in COCs with variations in progestational, estrogenic, anti-estrogenic and androgenic activities

Progestins in COCs

- 2 major advances in progestins:
  - A 10-fold reduction in the dose of the progestin
  - Introduction of more selective progestins that minimize androgenic side effects while improving contraceptive efficacy

Progestins in COCs

- Mainly 19–nor testosterone derivatives are used :
  - **First generation** : Norethisterone (norethindrone), norethisterone acetate, norethynodrel, ethynodiol diacetate, Lynestranol
  - **Second generation** : Norgestrel, Levonorgestrel
  - **Third generation** : Desogestrel, gestodene, norgestimate
- 17- hydroxy progesterone derivatives : medroxy – progesterone, cyproterone acetate
- 19-norprogesterone or 17- ∝ - spirolactone derivative: **Drospirenone**

COCs – Classification

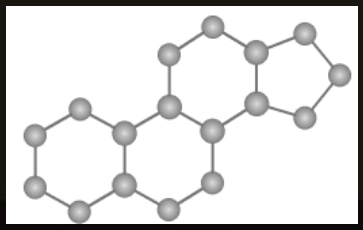
Based on historical Development

COC	ESTROGEN	PROGESTIN
1st Generation	50 μg or more of EE* or Mestranol**	• Norethynodrel • Norethindrone • Norethindrone acetate • Ethynodiol diacetate
2nd Generation	20-35 μg EE	• (dl) Norgestrel • Levonorgestrel
3rd Generation	20-35 μg EE	• Desogestrel • Norgestimate • Gestodene

* EE – Ethinyl estradiol

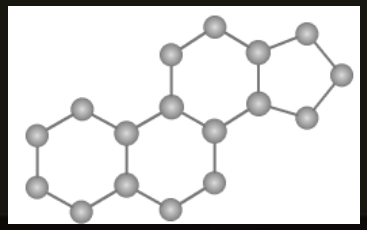
** Mestranol 50μg = 35 μg EE

Evolution of Progestins in COCs



- Parallel to a decrease in estrogen dose, the potency of the progestin increased
- Inhibition of ovulation became their primary mode of action
- Earlier progestins were developed for contraceptive use primarily – majorly focused on suppressing LH surge
- Later progestins aimed at reducing the side effects e.g. oily skin, acne, adverse lipid profile, weight gain etc
- **Ultimate objective – to develop a progestin that closely resembles progesterone!**

Natural Progesterone

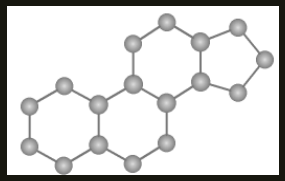


- **Antagonises action of estrogen on the endometrium** - prevents proliferation of the endometrium
- **Antigonadotrophic action** - prevents LH surge & ovulation
- **Anti-androgenic action** - Prevents conversion of testosterone to DHT as it is a natural substrate for 5-∝-reductase
- **Antimineralocorticoid effect** - prevents sodium retention and promotes excretion of sodium and water

Human Reprod Update, 2006, 12: 169-178; Ann N Y Acad Sci, 1995; 761: 311-35

Progestin	Anti-estrogenic	Andro-genic	Anti-androgenic	Anti-mineralo-corticoid
Clinical significance →	↓ SHBG & free androgen index	Seborrhea, acne, wt gain, ↓HDL-C, ↑ LDL-C	Useful in PCOS, acne, hirsutism	No wt gain, ↑ BP, bloating, breast tenderness
Progesterone	-	-	+	+
Older Progestins Medroxyprogesterone acetate	-	+	-	-
Norethisterone	+	+	-	-
Levonorgestrel	+	+	-	-
Newer Progestins Desogestrel	-	-	-	-
Cyproterone acetate	-	-	+	-
Drospirenone	-	-	+	+

Progestins vs Progesterone



- Norethisterone & levonorgestrel COCs – Androgenic side effects
- Desogestrel or other 3rd generation progestin COCs – no androgenic side effects, less wt gain or BP changes, Increase HDL-C
- **None of them** decrease fluid retention, bloating & breast tenderness or mood changes associated with menstruation
- **DROSPIRENONE – The newest progestin combines progestational, antimineralocorticoid & anti-androgenic actions – resembles natural progesterone in its actions**

Human Reprod Update, 2006, 12: 169-178; Ann N Y Acad Sci, 1995; 761: 311-35; Canad Ph Assoc CE, 2007; Pharmacology & Pharmacotherapeutics, 2005: 938-55