Oral Contraceptives

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Hormonal Contraception

A. Combinations of estrogens and progestins:

1. Monophasic forms: constant dosage of both components during the cycle.
2. Biphasic forms: dosage of one or both components is changed once during the cycle.
3. Triphasic forms: dosage of one or both components is changed twice during the cycle.

TABLE 40–3 Some oral and implantable contraceptive agents in use.[1]

	Estrogen (mg)		Progestin (mg)	
Monophasic combination tablets				
Alesse, Aviane, Lessinea, Levlite	Ethinyl estradiol	0.02	L-Norgestrel	0.1
Levlen, Levora, Nordette, Portia	Ethinyl estradiol	0.03	L-Norgestrel	0.15
Crysella, Lo-Ovral, Low-Ogestrel	Ethinyl estradiol	0.03	Norgestrel	0.30
Yasmin	Ethinyl estradiol	0.03	Drospirenone	3.0
Brevicon, Modicon, Necon 0.5/35, Nortrel 0.5/35	Ethinyl estradiol	0.035	Norethindrone	1.0
Ortho-Cyclen, Sprintec	Ethinyl estradiol	0.035	Norgestimate	0.25
Necon 1/35, Norinyl 1+, Nortrel 1/35, Ortho-Novum 1/35	Ethinyl estradiol	0.035	Norethindrone	1.0
Ovcon-35	Ethinyl estradiol	0.035	Norethindrone	0.4
Demulen 1/50, Zovia 1/50E	Ethinyl estradiol	0.05	Ethynodiol diacetate	1.0
Ovcon 50	Ethinyl estradiol	0.05	Norethindrone	1.0
Ovral-28	Ethinyl estradiol	0.05	D,L-Norgestrel	0.5
Norinyl 1/50, Ortho-Novum 1/50	Mestranol	0.05	Norethindrone	1.0
Biphasic combination tablets				
Ortho-Novum 10/11, Necon 10/11				
Days 1–10	Ethinyl estradiol	0.035	Norethindrone	0.5
Days 11–21	Ethinyl estradiol	0.035	Norethindrone	1.0
Triphasic combination tablets				
Enpresse, Triphasil, Tri-Levlen, Trivora				
Days 1–6	Ethinyl estradiol	0.03	L-Norgestrel	0.05
Days 7–11	Ethinyl estradiol	0.04	L-Norgestrel	0.075
Days 12–21	Ethinyl estradiol	0.03	L-Norgestrel	0.125
Ortho-Novum 7/7/7, Necon 7/7/7				
Days 1–7	Ethinyl estradiol	0.035	Norethindrone	0.5
Days 8–14	Ethinyl estradiol	0.035	Norethindrone	0.75
Days 15–21	Ethinyl estradiol	0.035	Norethindrone	1.0
Ortho-Tri-Cyclen				
Days 1–7	Ethinyl estradiol	0.035	Norgestimate	0.18
Days 8–14	Ethinyl estradiol	0.035	Norgestimate	0.215
Days 15–21	Ethinyl estradiol	0.035	Norgestimate	0.25
Daily progestin tablets				
Nora-BE, Nor-QD, Ortho Micronor, Jolivette, Camila, Errin	...		Norethindrone	0.35
Ovrette	...		D,L-Norgestrel	0.075
Implantable progestin preparation				
Implanon	...		Etonogestrel (one tube of 68 mg)	

[1]The estrogen-containing compounds are arranged in order of increasing content of estrogen. Other preparations are available. (Ethinyl estradiol and mestranol have similar potencies.)

Hormonal Contraception

B. **Continuous progestin therapy without concomitant administration of estrogen, orally or by implantation under the skin.**

Hormonal Contraception

- **Estrogens:**

  Ethinyl estradiol, Mestranol.

- **Progestins:**

  L-Norgestrel, Drospirenone, Norethindrone, Norgestimate, Ethynodiol diacetate.

Some oral and implantable contraceptive agents

	Estrogen	mg	Progestin	mg
Monophasic Combination Tablets	Ethinyl estradiol	0.02	L-Norgestrel	0.1
	Ethinyl estradiol	0.03	L-Norgestrel	0.15
	Ethinyl estradiol	0.02	Norethindrone	1
	Ethinyl estradiol	0.035	Norethindrone	1
	Mestranol	0.05	Norethindrone	1
Biphasic Combination Tablets				
Days 1–21	Ethinyl estradiol	0.02	Desogestrel	0.15
Days 22–27	Ethinyl estradiol	0.01	None	
Days 1–10	Ethinyl estradiol	0.035	Norethindrone	0.5
Days 11–21	Ethinyl estradiol	0.035	Norethindrone	1
Triphasic Combination Tablets				
Days 1–6	Ethinyl estradiol	0.03	L-Norgestrel	0.05
Days 7–11	Ethinyl estradiol	0.04	L-Norgestrel	0.075
Days 12–21	Ethinyl estradiol	0.03	L-Norgestrel	0.125

Days 1–7	Ethinyl estradiol	0.035	Norgestimate	0.18
Days 8–14	Ethinyl estradiol	0.035	Norgestimate	0.215
Days 15–21	Ethinyl estradiol	0.035	Norgestimate	0.25
4-Phasic Combination Tablet				
Days 1–2	Estradiol valerate	3	None	
Days 3–8	Estradiol valerate	2	Dienogest	2
Days 9–25	Estradiol valerate	2	Dienogest	3
Day 26–27	Estradiol valerate	1	None	
Daily Progestin Tablets	None	-	Norethindrone	0.35
Contraceptive Transdermal Patch (Apply 1 Patch per Week)	Ethinyl estradiol	0.02/24 h	Norgestromin	0.150/24 h
Implantable Progestin Preparation	None	-	Etonogestrel	(one tube of 68 mg)

Combination Oral Contraceptives

Mechanism of Action:

- **Inhibition of ovulation by inhibiting pituitary function.**
- **Changes in cervical mucus, endometrium, and motility and secretions of uterine tubes decrease the likelihood of conception and implantation.**

Combination Oral Contraceptives

Pharmacologic effects:

1. **Ovary:**

- **Depression of ovarian function with chronic use, and the ovaries get smaller. This is reversible in most cases.**

2. **Uterus:**

- **Hypertrophy of the cervix and polyp formation with chronic use.**

Combination Oral Contraceptives

- **Cervical mucus becomes thick and less copious.**
- **Effects on endometrium are related to hormonal content.**

3. **Breast:**

- **Enlargement.**
- **Suppression of lactation.**
- **Small amounts cross to breast milk.**

Combination Oral Contraceptives

4. **CNS:**

- **Low changes in mood, affect and behavior.**
- **Estrogens may be useful for premenstrual tension syndrome, postpartum depression and climacteric depression.**
- **Progestins have central thermogenic action.**

Combination Oral Contraceptives

5. **Endocrine function:**

- **Estrogens increase plasma corticosteroid-binding globulin.**
- **Increase plasma renin activity and aldosterone secretion.**
- **Increase thyroxine-binding globulin**
- **Estrogens increase plasma levels of SHBG → decrease plasma levels of free androgens.**

Combination Oral Contraceptives

6. **Blood:**

- **Serious thromboembolism.**
- **Estrogens increase clotting factors VII, VIII, IX, and X and decrease antithrombin III.**
- **Increase serum iron and total iron binding capacity.**
- **Some patients develop folic acid deficiency anemia.**

Combination Oral Contraceptives

7. **Liver:**

- **Estrogens reduce serum haptoglobins.**
- **Cholestasis and cholelithiasis**

8. **Lipid metabolism:**

- **Haptoglobin is an acute phase protein capable of binding haemoglobin, thus preventing iron loss and renal damage. Haptoglobin also acts as an antioxidant**

Combination Oral Contraceptives

8. **Lipid metabolism:**

- **Estrogens increase triglycerides, phospholipids, and HDL; while size of LDL particles is decreased.**
- **This effect may be modified by progestins.**
- **Progestins with androgenic properties and synthetic progestins diminish the beneficial effects of estrogens on lipoprotein metabolism, and lower HDL.**

Combination Oral Contraceptives

- **The mechanism of increased cardiovascular disease in combined hormonal contraceptoion (CHC) users may be due to thromboembolic and thrombotic changes, rather than atherosclerosis.**
- **Women with controlled dyslipidemia can use low-dose CHCs, with periodic fasting lipid profiles.**
- **Women with uncontrolled and additional risk factors should not take CHCs.**

Combination Oral Contraceptives

9. **Carbohydrate metabolism:**

- **Reduced rate of absorption of carbohydrate from GIT.**
- **Progesterone increases basal insulin levels and the rise in insulin induced by carbohydrate ingestion.**
- **Potent progestins may produce a reversible progressive decrease in carbohydrate tolerance over years.**

Combination Oral Contraceptives

- **Therefore, nonsmoking women younger than 35 years with diabetes but no associated vascular disease can safely use CHCs.**
- **Diabetic women with vascular disease (nephropathy, retinopathy, neuropathy, or other vascular disease) or diabetes of more than 20 years duration should not use CHCs.**

Combination Oral Contraceptives

10. **Cardiovascular system:**

- **Increase blood pressure, heart rate and slightly increase cardiac output.**

11. **Effects on the skin:**

- **Increase skin pigmentation especially in women with dark complexions.**
- **Androgen-like progestins increase formation of sebum and may produce acne.**

Combination Oral Contraceptives

- **The sequential agents and estrogens alone often decrease sebum production.**
- **Many patients may show suppression of sebum production, acne and hair growth because of suppression of ovarian androgens.**

Combination Oral Contraceptives

Therapeutic uses:

1. **Oral contraception:**

- **Failure rate of pregnancy ~ 0.5-1 per 100 women-years.**
- **Contraception failure has been observed in women missing one or more doses, those taking phenytoin or those taking antibiotics.**

2. **Endometriosis.**

Combination Oral Contraceptives

Adverse effects:

A. Mild:

1. **Nausea, mastalgia, breakthrough bleeding and edema (related to estrogen content of the pill).**
2. **Increased sedimentation rate (ESR) due to increased fibrinogen.**
3. **Changes in serum proteins should be taken into account when evaluating endocrine functions.**

Combination Oral Contraceptives

4. **Headache is often mild and transient, but migraine is made worse.**
5. **Failure of withdrawal bleeding (change prep).**

Combination Oral Contraceptives

B. Moderate: (may require discontinuance of oral contraception).

1. **Breakthrough bleeding is common (25% of patients) with the use of progestational agents alone**
2. **Weight gain with combination agents containing androgen-like progestins.**
3. **Increased skin pigmentation exacerbated by vitamin B12 and folic acid deficiency. It is slowly reversible.**

Combination Oral Contraceptives

4. **Acne with agents containing androgen-like progestins. Agents containing high estrogens improve acne.**
5. **Hirsutism may be aggravated by 19-nortestosterone derivatives.**
6. **Ureteral dilation.**
7. **Vaginal infections are more common and more difficult to treat.**

Combination Oral Contraceptives

8. Amenorrhea occurs in some patients and persist for several years and is often associated with galactorrhea.

- **This is specially true in women who had menstrual irregularities before taking oral contraceptives.**
- **These patients may have prolactinomas.**

Combination Oral Contraceptives

C. Severe (contraindications):

1. **Venous thromboembolic disease.**
2. **Myocardial infarction.**
3. **Cerebrovascular disease.**
4. **Ischemic bowel disease.**
5. **Cholestatic jaundice (progestin, 17-alkyl substituted agents), cholecystitis and cholangitis.**

Combination Oral Contraceptives

6. **Increased incidence of hepatic adenomas.**
7. **Depression (6%).**
8. **Cervical infection with the human papillomavirus may increase incidence of cervical cancer.**

Contraception with Progestins Alone

- **Suitable in patients for whom estrogen administration is undesirable.**
- **Injection of depot medroxyprogesterone acetate (DMPA) every 3 months, which inhibits ovulation for 14 weeks.**
- **All users experience episodes of spotting and bleeding.**
- **Amenorrhea is common.**

Contraception with Progestins Alone

- **Not suitable for women planning a pregnancy because ovulation may be suppressed for 18 months after the last dose.**
- **Long-term DMPA reduces menstrual blood loss and is associated with a decreased risk of endometrial cancer.**

Contraception with Progestins Alone

- **Suppression of endogenous estrogens may be associated with a reduction in bone density and changes in plasma lipids and increased risk of atherosclerosis.**
- **The progestin implants utilizes the subcutaneous implantation of capsules with an effect lasting up to 6 years.**

Contraception with Progestins Alone

- **Associated with irregular bleeding rather than predictable menses.**
- **May be associated with intracranial hypertension and papilledema.**
- **Adverse effects: headache, dizziness, bloating, weight gain, and reversible reduction of glucose tolerance.**