The Gonadal Hormones & Inhibitors

Yacoub M. Irshaid, MD, PhD, ABCP
Department of Pharmacology

Estrogens

- **The major estrogens produced by women are estradiol, estrone and estriol.**
- **Estradiol is the major secretary product of the ovary.**
- **Most estrone and estriol are formed in the liver from estradiol, or in peripheral tissues from androstenedione and other androgens.**

Estrogens

Synthetic estrogens:

1. **Steroidal: Ethinyl estradiol, mestranol.**
2. **Nonsteroidal: drugs that have estrogenic activity**

- **These compounds, in contrast to natural estrogens, are orally effective.**

Estrogens

Pharmacokinetics:

- **Estradiol in the circulation binds to sex hormone-binding globulin (SHBG, an α_2-globulin) and albumin with lower affinity.**
- **Estrogens hydroxylated derivatives and conjugated metabolites are excreted in bile, and reabsorbed after hydrolysis within the gut.**
- **Estrogens are excreted in small amounts in breast milk.**

Estrogens

Therapeutic uses:

1. **Primary hypogonadism: Replacement therapy for estrogen deficient patients is usually begun at 11-13 years of age in order to stimulate development of secondary sex characteristics and menses, to stimulate optimal growth, to prevent osteoporosis, and to improve psychology of the patient.**

Estrogens

2. **Postmenopausal hormonal therapy (hormonal replacement therapy [HRT]).**

- **It has a beneficial effect on circulating lipids and lipoproteins.**
- **No cardiovascular benefit from estrogen plus progestin replacement in perimenopausal or postmenopausal women.**
- **There have been an increased risk of breast cancer in patients receiving HRT.**

Estrogens

- **Therefore, routine HRT in postmenopausal women is currently not recommended.**
- **HRT may be beneficial in young women with premature menopause.**

Estrogens

- **For prevention of osteoporosis, estrogen can be used with the addition of calcium supplements.**
- **This may be associated with an increased risk of endometrial carcinoma, which can be prevented by the addition of progestin.**

Estrogens

3. Other uses:

Estrogens combined with progestins can be used to:

A. suppress ovulation in patients with intractable dysmenorrhea.

B. suppress ovarian function in treatment of hirsuitism and amenorrhea due to excessive secretion of androgens by the ovary.

Estrogens

Adverse effects:

1. **Uterine bleeding**
2. **Breast cancer**
3. **Endometrial carcinoma**
4. **Infertility, ectopic pregnancy and premature delivery**
5. **Breast tenderness**
6. **Hyperpigmentation**

Estrogens

7. Migraine headache
8. Cholestasis and gallbladder disease
9. Hypertension

Estrogens

Contraindications:

1. **Estrogen-dependent neoplasms: endometrium and breast.**
2. **Avoid in patients with undiagnosed vaginal bleeding, liver disease and history of thromboembolic disorders.**
3. **Avoid in heavy smokers.**

Progestins

- **Natural progestins: Progesterone**
- **Progesterone derivatives: Hydroxyprogesterone caproate, Medroxyprogesterone acetate, Megestrol acetate**

Progestins

- **Synthetic progestins:**

A. 17-ethinyl testosterone derivatives:

Dimethisterone

B. 19-nortestosterone derivatives:

Desogestrel, Norethynodrel, Norethindrone, L-norgestrel.

Progestins

Pharmacokinetics:

- **Progesterone is rapidly absorbed after administration.**
- **Undergoes extensive first pass metabolism and excreted in urine as pregnanediol glucuronide.**
- **t½ in plasma is approximately 5 minutes**
- **Most of synthetic agents are metabolized extensively to inactive products that are excreted mainly in urine.**

TABLE 40–2 Properties of some progestational agents.

	Route	Duration of Action	Activities[1]				
			Estrogenic	*Androgenic*	*Antiestrogenic*	*Antiandrogenic*	*Anabolic*
Progesterone and derivatives							
Progesterone	IM	1 day	–	–	+	–	–
Hydroxyprogesterone caproate	IM	8–14 days	sl	sl	–	–	–
Medroxyprogesterone acetate	IM, PO	Tabs: 1–3 days; injection: 4–12 weeks	–	+	+	–	–
Megestrol acetate	PO	1–3 days	–	+	–	+	–
17-Ethinyl testosterone derivatives							
Dimethisterone	PO	1–3 days	–	–	sl	–	–
19-Nortestosterone derivatives							
Desogestrel	PO	1–3 days	–	–	–	–	–
Norethynodrel[2]	PO	1–3 days	+	–	–	–	–
Lynestrenol[3]	PO	1–3 days	+	+	–	–	+
Norethindrone[2]	PO	1–3 days	sl	+	+	–	+
Norethindrone acetate[2]	PO	1–3 days	sl	+	+	–	+
Ethynodiol diacetate[2]	PO	1–3 days	sl	+	+	–	–
L-Norgestrel[2]	PO	1–3 days	–	+	+	–	+

[1] **Interpretation:** + = active; – = inactive; sl = slightly active. Activities have been reported in various species using various end points and may not apply to humans.

Progestins

- **Progestins without androgenic activity include Progesterone, dimethisterone, desogestrel, norgestimate, gestodene, norethynodrel.**

Progestins

Therapeutic uses:

1. **Hormonal replacement therapy.**
2. **Hormonal contraception.**
3. **To produce long-term ovarian suppression → prolonged anovulation and amenorrhea. This therapy has been employed in the treatment of dysmenorrhea, endometriosis and bleeding disorders when estrogens are contraindicated.**

Progestins

Adverse effects:

1. **Elevation of blood pressure.**
2. **Reduce plasma HDL levels (androgenic progestins).**
3. **Enhance effects of estrogen on breast cancer risk in postmenopausal women.**

Estrogen and Progesterone Inhibitors and Antagonists

Tamoxifen and Related Drugs

- **Is a competitive partial agonist / antagonist at estrogen receptors.**
- **The first selective estrogen receptor modulator (SERM) discovered.**
- **It is extensively used in the palliative treatment of breast cancer in postmenopausal women.**
- **It is a nonsteroidal agent that is given orally.**

Tamoxifen and Related Drugs

- **Prevents loss of lumbar spine bone density, changes in plasma lipid levels and risk for atherosclerosis after menopause.**
- **This treatment may increase risk of endometrial cancer.**

Adverse effects:

- **Hot flushes and nausea in 25% of patients.**

Tamoxifen and Related Drugs

- **Toremifene is structurally similar with similar properties, indications and toxicities.**
- **Raloxifene is similar at some but not all estrogen receptors.**
- **It has similar effects on lipid and bone, but does not stimulate endometrium or breast.**
- **It is indicated for prevention of postmenopausal osteoporosis. (not first-line)**

Mifepristone

- **19-norsteroid.**
- **Strong progesterone receptor blocker**
- **Has luteolytic properties when given in mid-luteal period → contraceptive effect.**
- **It is an emergency post-coital contraceptive.**
- **Acts also as an antagonist at glucocorticoid receptors.**

Mifepristone

- **May be useful in treatment of endometriosis, Cushing's syndrome, breast cancer, and neoplasms that contain glucocorticoid or progesterone receptors such as meningiomas.**
- **Adverse effects: prolonged bleeding, abdominal or pelvic pain, nausea and vomiting.**

Danazol

- **It is a 17α-ethinyltestosterone derivative.**
- **Has weak progestational, androgenic and glucocorticoid activities.**
- **It suppresses ovarian function by inhibiting the mid-cycle surge of LH and FSH, but does not have significant effect on basal FSH and LH in normal women.**

Danazol

Therpeutic uses:

- **Endometriosis: It inhibits gonadal function.**
- **Fibrocystic disease of the breast**

Adverse effects:

- **Weight gain, edema**
- **Decreased breast size**
- **Acne and oily skin**
- **Increased hair growth**

Danazol

- **Deepening of voice**
- **Hot flushes,**
- **Changes in libido**
- **Contraindicated in pregnancy and breast feeding as it may produce urogenital abnormalities in the offspring.**

Aromatase Inhibitors

Anastrozole, Fadrozole.

- **May be useful in women whose breast cancer has become resistant to tamoxifen.**
- **May be employed as adjuncts to androgen antagonists in the treatment of precocious puberty, and primary treatment in the excessive aromatase syndrome.**

Fulvestrant

- **Is a pure estrogen receptor antagonist.**
- **May be useful in breast cancer patients who have become resistant to tamoxifen.**

Ovulation-inducing Agents (Clomiphene)

- **Clomiphene is a partial estrogen agonist.**
- **It is active after oral administration.**

Clomiphene

Pharmacodynamics:

- **Has estrogenic activity in cases of gonadal deficiency.**
- **Inhibits the action of strong estrogens.**
- **It increases the secretion of gonadotropins by inhibiting estradiol's negative feedback effect on the gonadotropins.**
- **Thus, it stimulates ovulation in women with ovulatory dysfunction.**

Clomiphene

Therapeutic uses:

1. **Ovulatory dysfunction in women wishing to become pregnant. The drug should be given repeatedly until pregnancy occurs.**

- **Normal ovulation does not usually resume, thus it is of no value in patients with ovarian or pituitary failure.**

Clomiphene

Adverse effects:

1. **Hot flushes is the most common adverse effect.**
2. **Intensification and prolongation of after images in some occasions.**
3. **Occasionally: headache, constipation, allergy, hair loss.**
4. **Ovarian stimulation and enlargement.**
5. **Multiple pregnancies (10%).**

Clomiphene

6. **Nausea, vomiting, increased nervous tension, depression, fatigue, breast soreness, weight gain, urinary frequency and heavy menses have been reported. They may be due to hormonal changes of ovulation rather than to the drug.**

Contraindications and cautions:

1. **Patients with enlarged ovaries should receive small doses.**
2. **Caution in patients with visual symptoms.**