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Estrogens, Progestins, and Specific Estrogen Receptor Modulators (SERMs)

Jeannine S. Strobl



DRUG LIST

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Estrogens	
Estradiol	705
Estropipate	710
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Mestranol	707
Progestins	
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Megestrol	707
Norethindrone	707

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NATURAL ESTROGENS AND PROGESTINS

Biologically important natural estrogens and progestins include estradiol, estrone, estriol, and progesterone. *Estradiol-17 β is the most potent estrogen that is found naturally in women.* Estrone is one-tenth as biologically active as estradiol, and estriol is the weakest of the three. Estriol is synthesized by the placenta and is excreted at high levels in the urine of pregnant women. Progesterone is the most important naturally occurring progestin.

The ovary is the major site of estrogen and progestin biosynthesis in nonpregnant premenopausal women. In pregnant women, the fetoplacental unit is the major

source of estrogens and progestins. Peripheral sites of estrogen synthesis include the liver, kidney, brain, adipose tissue, skeletal muscle, and testes. Progesterone is secreted in small amounts by the testes and adrenal gland. The combined estrogen and progestin production by all of these peripheral sites amounts to 10% or less of ovarian synthesis in normal premenopausal women. In postmenopausal women, ovarian steroid synthesis declines and peripheral estrogen biosynthesis accounts for all estrogen produced, both in postmenopausal women and in males.

The naturally occurring estrogens and progestins are not orally active because they are rapidly metabolically inactivated. The major site of estrogen and progestin metabolism is the liver. Both are subject to first-

pass metabolism. Metabolites are also formed in the gastrointestinal tract, brain, skin, and other steroid target tissues. Estrogens and progestins are primarily excreted in the urine. Estrone, estradiol, 2-methoxyestrone, and their respective glucuronide or sulfate conjugates are the most abundant estrogen urinary metabolites. Progesterone is excreted as pregnanediol or as a pregnanediol conjugate. A small fraction (10% or less) of the estrogen metabolites enter the bile, where they may undergo enterohepatic recirculation before elimination.

Plasma proteins bind estrogens and modulate estrogenic activity. More than 90% of estradiol in the bloodstream is protein bound, with sex hormone-binding globulin (SHBG) being the major serum estrogen-binding moiety. Estrogens that are bound to SHBG are biologically inactive because of their high binding affinity, while estrogens that are bound loosely to serum albumin are available for entry into tissues and are therefore biologically active. Progesterone in plasma is 89% protein bound. Progesterone binds with a relatively high affinity to the serum protein corticosteroid-binding globulin and also to albumin.

MECHANISMS OF ACTION

Estrogens and progestins exert their effects in target tissues by a combination of cellular mechanisms. High-affinity estrogen and progestin receptors are found in target tissues. There are two forms of the estrogen receptor, ER- α and ER- β , and two forms of the progesterone receptor, PR- α and PR- β . Receptor binding by estrogens and progestins can activate a classic pathway of steroid hormone gene transcription. Gene activation is mediated by the ability of steroid hormone receptor complexes to recruit nuclear coactivator proteins to the transcription complex. Gene repression occurs in a ligand-dependent fashion by the recruitment of nuclear corepressor proteins to the transcription complex. This latter effect is an important mechanism of action of estrogen antagonism. Activation of steroid hormone receptors by their cognate ligands proceeds through receptor phosphorylation events. It is well established that estrogen and progesterone receptor activation also takes place in a ligand-independent fashion. As a result of cross-talk among cell signaling pathways, ER and PR are activated by phosphorylation events triggered by such diverse stimuli as epidermal growth factor, insulinlike growth factor, protein kinase A, and protein kinase C.

An additional mode of estrogen and progesterone action is classified as nongenomic effects. Nongenomic mechanisms for steroid hormone action are attributed to responses to estrogens and progestins that occur in a very short time (seconds to several minutes) such that they are difficult to explain by transcriptional activa-

tion. The role of the ER and PR receptors in these responses is incompletely understood. One important example of a nongenomic estrogen action that is mediated by ER- α is the rapid stimulation of endothelial nitric oxide synthase (eNOS). This enzyme produces nitric oxide. Nitric oxide has vasodilatory activity, and activation of eNOS may be an important mediator of the cardioprotective effects of estrogens.

Estradiol can augment target tissue responses to progesterone by inducing an increase in the concentration of progesterone receptors. Progesterone, on the other hand, appears to limit tissue responses to estrogen by decreasing the concentration of ERs.

ACTIONS OF ESTROGENS AND PROGESTINS IN FEMALES

The Menstrual Cycle

Secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus stimulates the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary. FSH and LH regulate the production of estrogen and progesterone by the ovary. Ovarian estrogen and progesterone secretion proceed in a cyclical manner. It is this cyclical release of estrogen and progesterone that determines the regular hormonal changes in the uterus, vagina, and cervix associated with the menstrual cycle. Cyclical changes in blood levels of estrogen and progesterone, together with FSH and LH, modulate the development of ova, ovulation, and the corpus luteum in the ovary.

During the first, or *follicular*, phase of the menstrual cycle, estradiol blood levels rise slowly and then fall quite rapidly. Estradiol blood levels peak around midcycle (days 12–14). The midcycle estrogen peak is thought to be important in triggering a midcycle surge of LH and FSH secretion. Estrogens have a biphasic effect on LH and FSH release, with high levels of estrogen at midcycle triggering LH and FSH release; subsequently they suppress LH and FSH secretion. This suppression is mediated by inhibition of GnRH release from the hypothalamus.

The *luteal* phase of the menstrual cycle follows the LH and FSH surge (days 14–28). The brief elevation of the LH level stimulates production of the ovarian corpus luteum. The high levels of estradiol and the FSH surge at midcycle inhibit estradiol biosynthesis by the ovarian granulosa cells. As a consequence, during the luteal phase, estrogen production is reduced and androgens produced by the ovarian thecal cells accumulate. Androgens, together with low levels of FSH, stimulate the production of progesterone by the granulosa cells in the corpus luteum. The menstrual cycle ends about 14 days later with the regression of the corpus luteum and

a concomitant fall in estrogen and progesterone production. The triggering mechanism for this regression may involve both estrogens and prostaglandins. In the event that pregnancy occurs, human chorionic gonadotropin secretion by the embryo maintains the corpus luteum through stimulation of progesterone and estrogen synthesis.

Control of Pregnancy

Ovulation

During the follicular phase of the menstrual cycle, one or more follicles are prepared for ovulation. FSH and estrogens are the most important hormones for this developmental process. Complete follicular maturation cannot occur in the absence of LH. Rupture of a mature follicle follows the midcycle peak of LH and FSH by about 24 hours. In humans, usually one mature ovum is released per cycle. During the luteal phase of the menstrual cycle and under the influence of LH, the ovarian granulosa cells of the corpus luteum become vacuolated and accumulate a yellow pigment called *lutein*.

Implantation

The lining of the uterus, that is, the endometrium, is critical for implantation of the fertilized ovum. The endometrium consists of a layer of epithelial cells overlying a layer of vascularized stromal cells. Under the influence of estrogen and progesterone, the endometrium undergoes cyclical changes that prepare it for the implantation of a fertilized ovum. The follicular phase of the menstrual cycle also may be called the *proliferative phase* when referring to changes that occur in the uterus. Estrogens induce endometrial cell division and growth.

During the luteal phase, when the uterus is exposed to high concentrations of progesterone and moderate estradiol levels, the mitotic activity in the endometrial cells is suppressed. The action of progesterone on the endometrium converts it from a proliferative state to a secretory state. The epithelial cell structure assumes a more glandular appearance. Vascularization of the stroma increases, and some stromal cells begin to look like the decidual cells of early pregnancy. Estrogens and progesterone are key hormones in the maintenance of pregnancy. Estriol is produced in high concentrations by the placenta in pregnant women.

Cervical mucus is secreted by the endocervical glands and is regulated by estrogens and progestins. Under the influence of high levels of estrogen or progesterone, the physicochemical composition of cervical mucus may reduce sperm motility and provide a barrier to fertilization.

When implantation of the ovum does not occur, estrogen and progesterone levels fall and menstrual

bleeding ensues. The endometrial lining, but for a single layer of epithelial cells, is shed.

Growth and Development

Estrogens cause the growth of the uterus, fallopian tubes, and vagina. Stimulation of proliferation of the vaginal epithelium is checked by the cyclical exposure to progesterone during the luteal phase in the mature female. Estrogens also are responsible for the expression of female secondary sex characteristics during puberty. These include breast enlargement, the distribution of body hair, body contours as determined by subcutaneous fat deposition, and skin texture. During development, estrogens stimulate proliferation of the ductal epithelial cells in breast tissue. Progesterone mediates lobuloalveolar development at the ends of these mammary ducts. In women, cyclical changes in the breast cell proliferation occur during the menstrual cycle, with the highest levels of proliferation occurring during the luteal phase, when circulating levels of both estrogen and progesterone are high. This has led to the idea that progesterone, as well as estrogens, exerts mitotic effects in adult human breast tissue. The effects of estrogens and progesterone on breast development are most noticeable during puberty and pregnancy.

Estrogens can stimulate the release of growth hormone and exert a positive effect on nitrogen balance. These effects contribute to the growth spurt during puberty. Closure of the bone epiphyses signaling the end of long bone growth is also estrogen mediated.

Bone remodeling occurs throughout adult life. Osteoblasts are the bone cells that are responsible for increasing bone mass. Bone loss occurs through the activity of other bone cells, called osteoclasts. Normal bone remodeling takes place when there is a balance between osteoblast and osteoclast activities. Estrogens maintain bone mass by inhibiting bone resorption by the osteoclasts. Estrogens inhibit the production of cytokines by peripheral blood cells and the osteoblasts that stimulate osteoclast activity. In postmenopausal women, declining estrogen levels give rise to a net increase in osteoclast activity and loss of bone mass resulting in the serious condition osteoporosis. Also, progestins antagonize loss of bone.

Other Actions of Estrogens and Progestins

The high levels of estrogens and progesterone associated with pregnancy may alter liver function and glucose metabolism. High circulating levels of estrogen can cause mild glucose intolerance. Estrogens increase the synthesis of many liver proteins, including transferrin, SHBG, corticosteroid-binding globulin, thyroid-binding globulin, and proteins involved in blood clotting.

Estrogens lower serum cholesterol levels by stimulating the formation of high-density lipoproteins and reducing low-density lipoproteins. Reductions in serum albumin and antithrombin III synthesis can occur in the presence of elevated female sex steroids.

In males, estrogens stimulate the growth of the stromal cells in the accessory sex organs.

SYNTHETIC AGENTS ACTING VIA ESTROGEN AND PROGESTERONE RECEPTORS

Long-acting semisynthetic estrogens and progestins contain esterified lipophilic substituents. Esterification of steroids prolongs their release from depot injection sites. Medroxyprogesterone acetate (*Amen*, *Cytin*, *Provera*, *Depo-Provera*) is a widely used long-acting synthetic progestin.

Synthetic steroid hormones retain the common steroid nucleus, but they may contain novel substituents that affect their pharmacological activity. The two most widely used synthetic steroid estrogens are ethinyl estradiol (*Estinyl*) and mestranol, found in oral contraceptives. Synthetic steroids containing an ethinyl substitution are metabolized more slowly. Thus, *these synthetic steroid hormones have better oral absorption properties and extended biological half-lives than the natural estrogens.*

Approximately 50% of a dose of mestranol is demethylated to form ethinyl estradiol. Ethinyl estradiol also can be deethinylated. Subsequently, the metabolism of these two synthetic estrogens proceeds by means of the same pathways as the natural steroid hormones. The principal metabolites of mestranol and ethinyl estradiol are hydroxylated derivatives that are conjugated with either glucuronic acid or sulfate. The synthetic steroid estrogens, in contrast to the natural estrogens, are excreted primarily in the feces.

One chemical class of synthetic progestins is derived from testosterone and is referred to as the 19-nortestosterones. These compounds have progestational activity yet retain some androgenic activity. Norethindrone (*Micro-nor*, *Nor-QD*) and norethindrone acetate (*Aygestin*) are two synthetic progestins derived by the addition of an ethinyl group at the C17 position of 19-nortestosterone. There is little difference between the pharmacological activity of norethindrone and norethindrone acetate because in humans the acetate group is very readily cleaved to yield norethindrone. Norethindrone is metabolized by hydroxylation and conjugation, just as are the natural progestins. The majority of the 19-nortestosterone metabolites are conjugates that are excreted in the urine.

A second chemical class of synthetic progestins contains the pregnane nucleus structure of progesterone along with some additional substitutions. Alkyl chain additions to the C17 position increase the biological

half-life of these compounds. Modifications at positions C6 and C7 increase their progestational activity. Examples of these synthetic progestins include medroxyprogesterone and megestrol acetate (*Megace*). These compounds are metabolized in the same manner as progesterone and are excreted in the urine.

SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMs)

Selective ER modulators (SERMs) are nonhormonal pharmacological agents that bind to ERs. A characteristic feature of the SERMs is that a given agent will act as an estrogen agonist in one or more tissues and as an estrogen antagonist in one or more other estrogen target organs. Tamoxifen citrate (*Nolvadex*), clomiphene citrate (*Clomid*, *Serophene*) and raloxifene (*Evista*) are examples of nonsteroidal SERMs. The best studied SERM is tamoxifen citrate, a drug formerly characterized as an antiestrogen.

Tamoxifen is a partial estrogen agonist in breast and thus is used as a treatment and chemopreventative for breast cancer. Tamoxifen is a full agonist in bone and endometrium, and prolonged use of tamoxifen leads to a fourfold to fivefold increase in the incidence of endometrial cancer. See Chapter 56 for a detailed discussion of the use of tamoxifen in breast cancer.

Raloxifene (*Evista*) is a new SERM approved for use in the treatment and prevention of osteoporosis because it has estrogenic activity in bone. Raloxifene is an estrogen antagonist in both breast and endometrial tissues. The estrogenlike properties of raloxifene result in the maintenance of a favorable serum lipid profile (decreased low-density lipoprotein levels with no change in either high-density lipoproteins or triglycerides). Raloxifene is 95% bound to plasma proteins. Absorption of raloxifene is impaired by cholestyramine.

Tamoxifen, clomiphene, and raloxifene are orally active. The primary route of excretion of all three drugs is in the feces. The undesirable effects common to all three of these SERMs are increased frequency of hot flashes and increased risk of thromboembolism. Both effects are attributable to their estrogenic activity.

Faslodex (*Fulvestrant*) is a SERM with no known agonist activity on the ER. It is administered as a monthly injection. In phase III clinical trials faslodex showed good activity against advanced breast cancer.

CLINICAL USES

The chief therapeutic uses of estrogens and progestins are as oral contraceptives and hormone replacement therapy. Progestins and SERMs are also important agents in the treatment of osteoporosis, breast cancer, endometrial cancer, and infertility.

Oral Contraception

Oral contraceptives are among the most effective forms of birth control (Table 61.1). The most widely used type of oral contraceptive in the United States today is the *combination* preparation, that is, a combination of estrogen and progestin (Table 61.2). Users take a tablet daily that contains both an estrogen and a progestin for 20 to 21 days of the menstrual cycle and then nothing or a placebo for the remainder of the cycle or the next 7 to 8 days. Withdrawal bleeding occurs 2 to 3 days after discontinuation of this regimen. Combination preparations vary in the dose of synthetic estrogen and progestin they contain. The use of sequential and triphasic oral

contraceptives minimizes the overall dose of hormone delivered. These preparations are designed to more closely simulate estrogen-to-progestin ratios that occur physiologically during the menstrual cycle. *Ethinyl estradiol and mestranol are the only two estrogen constituents used for oral contraception in the United States.* The use of ethinyl estradiol is favored. Mestranol is inactive until it is metabolized to ethinyl estradiol.

Several progestins are used in combination products. Norgestrel (*Ovrette*) is a mixture of active and inactive enantiomers; levonorgestrel (*Norplant*) is the active enantiomer. Levonorgestrel and norethindrone are the most potent synthetic progestins in oral contraceptive preparations.

Inhibition of ovulation is the primary mechanism of the contraceptive action of sequential and combination birth control preparations. Ovulation is prevented by the suppression of the midcycle surge of FSH and LH. Estrogens are most active in inhibiting FSH release, but at high enough doses, they also inhibit LH release. In low-dose combination products, the progestin causes LH suppression. The progestin component is also important in causing withdrawal bleeding at the end of the cycle.

Combination oral contraceptive drugs having the lowest effective concentration of both estrogen and progestin should be prescribed. These preparations are known as low-dose oral contraceptive agents. Adverse effects of both estrogen and progestin are minimized with the use of these agents.

Clinical experience with the low-dose combination drugs indicates that the estrogen-to-progestin ratio is critical in achieving maximum contraceptive activity. In certain combinations (*Ortho-Novum 7/7/7*, *Tri-Norinyl*, *Tri-Levlen*, *Triphasil*), the estrogen-to-progestin ratio is varied in three phases over the initial 21 days by changing the progestin content of the tablets. An example of the estrogen and progestin doses found in this type of oral contraceptive is shown in Table 61.3.

Progestin-only oral contraceptive formulations consist of a low dose of either norethindrone or norgestrel

TABLE 61.1 Pregnancy Rates vs. Contraceptive Method

Method	Pregnancies (%) ^a
Male sterilization	0.15
Norplant System	0.20
Female sterilization	0.40
Oral contraceptives	3.00
Intrauterine device	3.00
Condom	12.00
Diaphragm or sponge	18-28
Spermicide	21.00
None	85.00

^aAccidental pregnancy rate during a 1-year period.
Data from Trussell J and Kost K. *Stud Fam Plann* 1987;18:237.

TABLE 61.2 Some Oral Contraceptive Preparations Available in the United States, with Estrogen-Progestin Content

Estrogen	Progestin	Trade name
Ethinyl estradiol (20 µg)	Norethindrone acetate (1 mg)	Loestrin
Ethinyl estradiol (30 µg)	Norgestrel (300 µg)	Lo-Ovral
Ethinyl estradiol (30 µg)	Levonorgestrel (150 µg)	Nordette, Levlen
Ethinyl estradiol (35 µg)	Norethindrone (0.5 mg)	Brevicon, Modicon
Ethinyl estradiol (50 µg)	Norgestrel (0.5 mg)	Ovral
Ethinyl estradiol (50 µg)	Ethinodiol diacetate (1 mg)	Demulen
Mestranol (50 µg)	Norethindrone (1 mg)	Ortho-Novum, Norinyl, Norethin
None	Norethindrone (0.35 mg)	Micronor, Nor-QD
None	Norgestrel (0.075 mg)	Ovrette

TABLE 61.3 Estrogen and Progestin Composition of Tri-Levlen 28, a Triphasic Oral Contraceptive

	Estrogen	Progestin	Days
Phase I	Ethinyl estradiol (30 µg)	Levonorgestrel (50 µg)	1-6
Phase II	Ethinyl estradiol (40 µg)	Levonorgestrel (75 µg)	7-11
Phase III	Ethinyl estradiol (30 µg)	Levonorgestrel (125 µg)	12-21
Blank tablets	0	0	22-28

(Table 61.2). Because of an increased incidence of certain side effects and slightly decreased contraceptive activity, progestin-only oral contraceptives are not extensively used. The undesirable side effects associated with progestin-only contraceptives are irregular bleeding episodes, headache, weight gain, and mood changes. Progestin-only contraceptive *devices* are used. The *Norplant System* for contraception consists of a series of levonorgestrel-filled pliable plastic tubes that are implanted subcutaneously on the inside of the upper arm by a physician. While one set of six tubes can remain effective for up to 5 years, the contraceptive effects are readily reversible with removal of the implant. Adverse effects are similar to those seen with other progestin-only contraceptives; however, accidental pregnancy is less frequent.

Mirena is a relatively new intrauterine contraceptive device that releases levonorgestrel into the uterine cavity for 5 years. Use of this contraceptive device is associated with fewer systemic progestin side effects and is at least as effective as *Norplant*.

Abortifacients and Emergency Contraceptives

Progesterone is a hormone required for the maintenance of pregnancy. Termination of early pregnancy is effected using the steroidal antiprogesterin drug, mifepristone (RU486), which acts by blocking progestin binding to the progesterone receptor. A single oral dose of RU486 followed by a single dose of a prostaglandin (*Misoprostol*) 48 hours later is 90 to 95% effective in terminating pregnancy. The side effects are generally mild except for heavy bleeding. Severe cardiovascular complications have occurred and may be due to the prostaglandin component of this treatment. The use of RU486 is therefore contraindicated in women at risk for cardiovascular disease, including smokers and women over 35 years of age.

High-dose estrogen and high-dose progestin are effective in emergency contraception when given immediately following unprotected coitus. *Plan B* is an emergency contraceptive kit consisting of two tablets of the progestin levonorgestrel (0.75 mg). The first tablet must be taken as soon as possible but no later than 3 days after coitus, and the second tablet is taken 72 hours later. This regimen is more effective and better tolerated than the *Preven* emergency contraceptive kit, an estrogen-progestin combination (two tablets of 50 µg ethinyl estradiol and two tablets of 0.25 mg of levonorgestrel). The high doses of estrogen in the *Preven* regimen are associated with severe nausea and vomiting.

Hormone Replacement Therapy

The beginning of menopause is marked by the last menstrual cycle. This is the result of declining ovarian func-

tion and reduced synthesis of estrogens and progesterone. Estrogen production in postmenopausal women is usually only about 10% of that in premenopausal women. Almost no progesterone is synthesized in postmenopausal women. Hormone replacement therapy (HRT) generally refers to the administration of estrogen-progestin combinations. Estrogen replacement therapy (ERT) consists of the use of an estrogen alone, usually in the form of conjugated equine estrogens or an estrogen transdermal patch.

The four most common symptoms associated with menopause are vasomotor disorders, or hot flashes; urogenital atrophy; osteoporosis; and psychological disturbances. A varying proportion of women may have one or more of these symptoms.

Osteoporosis

One in four postmenopausal women have osteoporosis. *Osteoporosis, a decrease in bone mass, constitutes the most serious effect of menopause.* It has been estimated that following cessation of ovarian function, the loss of bone mass proceeds at a rate of 2 to 5% per year. As a result of osteoporosis, as many as 50% of women develop spinal compression fractures by age 75, and 20% will have hip fractures by age 90.

Estrogen replacement therapy can prevent bone loss and actually increase bone density in postmenopausal women. *Estrogen treatment is the most effective therapy for osteoporosis* and significantly reduces the incidence of bone fractures in postmenopausal women. The usual dose of estrogen prescribed is 0.625 mg/day of conjugated equine estrogens (*Premarin*). Alternatively, a transdermal estrogen patch can be used.

Endometrial cancer is not a concern in women who have undergone hysterectomy. However, in women with an intact uterus, there is a risk of endometrial cancer with ERT. A preliminary endometrial biopsy should be performed before instituting therapy to rule out endometrial hyperplasia or cancer, and biopsies should be repeated at 6- to 12-month intervals in women receiving ERT. When endometrial cancer is a concern, patients should consider HRT. Estrogens should be given in an intermittent fashion followed by at least 7 to 10 days of treatment with a progestin alone. Oral norgestimate, norethindrone acetate, and medroxyprogesterone acetate are progestins given to postmenopausal women receiving estrogens to control endometrial proliferation.

Alternatives to steroid hormone therapy for osteoporosis include raloxifene, bisphosphonates, sodium fluoride, vitamin D and calcium supplementation, calcitonin, and parathyroid hormone. Tamoxifen has estrogenic effects on bone and delays bone loss in postmenopausal women. However as a result of estrogenic activity in the uterus, long-term tamoxifen administration has been associated with an increased risk of

endometrial cancer. Raloxifene has estrogenic activity on bone but antiestrogenic activity in uterus and breast tissue. Raloxifene is a SERM that was specifically approved for the prevention and treatment of osteoporosis.

Cardiovascular Actions

Declining estrogen levels associated with menopause are correlated with an increased risk of cardiovascular related deaths in women. The protective effects of estrogens on the lipid profile are well recognized. There is a relationship between elevated levels of cholesterol, triglycerides, very low density lipoproteins, low-density lipoproteins, and coronary artery disease; in contrast, the elevation of high-density lipoproteins appears to be related to a reduced incidence of cardiovascular effects. The hormonal effects produced by estrogen and progestin therapy vary with the dosage, duration, route of administration, and particular preparation. In general, estrogenic compounds lower levels of “bad cholesterol” (low-density lipoproteins), while progestins raise low-density lipoproteins and triglycerides.

The use of HRT for mitigation of cardiovascular disease is not supported by the most recent clinical studies. The use of estrogen–progestin combinations in postmenopausal women was associated with a slight increase in coronary artery disease and a threefold elevation in thromboembolic episodes.

Conjugated equine estrogens (*Premarin*) are the most commonly used estrogens in the treatment of menopause-associated vasomotor symptoms and osteoporosis. *Premarin* is a mixture of estrogen sulfates, including estrone, equilin, and 17- β -dihydroequilin. The sulfate derivatives are orally active and are cleaved within the body to yield the active, unconjugated estrogen.

Premphase is an estrogen–progestin combination that introduces a cyclic progestin component. *Premphase* packets consist of a 2-week regimen of daily 0.625-mg conjugated equine estrogens followed by a 2-week period of a combination of conjugated equine estrogens and daily medroxyprogesterone. Esterified estrogens, primarily sodium estrone sulfate (*Estratab*), and estropipate (*Ogen*) are also used. Several transdermal patches deliver estradiol continuously. These products differ in their dose of estradiol: *Climara*, 0.025 mg/day; *Estraderm*, 0.05 mg/day; and *Vivelle*, 0.0375 mg/day.

Vasomotor Symptoms

Vasomotor disorders (hot flashes) are common, affecting 70 to 80% of postmenopausal women. The cause of the vasomotor changes appears to be associated with the release of LH after normal female estrogen levels have fallen. These symptoms occur with variable frequency but generally disappear without treatment within 2 to 3

years of onset. Estrogen or progestin therapy is often effective in suppressing vasomotor symptoms. Short-term estrogen therapy (2 years) for these symptoms is recommended and is not associated with increased cancer risk. Continuous therapy is usually not required.

Urogenital Atrophy

The tissues of the distal vagina and urethra are of similar embryonic origin, and both are sensitive to the trophic action of estrogens. Postmenopausal atrophy of these tissues may result in painful sexual intercourse, dysuria, and frequent genitourinary infections. Unlike the vasomotor complaints, these symptoms seldom improve if untreated. Treatment with a combination of minimally effective dosages of an estrogen and a progestin is recommended. Estrogen can be administered orally or in a topical preparation with equivalent efficacy. Progestins are given orally.

Replacement Therapy in Premenopausal Women

Oophorectomy causes many of the symptoms seen in menopause. The onset and intensity of vasomotor symptoms and osteoporosis, however, may be more severe than in women proceeding into the more gradual age-associated process of menopause. The regimens for estrogen–progestin replacement therapy in oophorectomized patients are comparable to those recommended for postmenopausal women.

Several genetic conditions lead to a failure of ovarian development. These genetic alterations lead to a failure in the synthesis of normal amounts of estrogen or progesterone, so that female secondary sex characteristics do not appear at puberty. Only with estrogen treatment is there stimulation of the growth of the genitalia, breast enlargement, and development of female body contours and distribution of body hair. Some increases in body height also occur with estrogen therapy, but this is more marked after androgen treatment. Replacement estrogens can be administered using a transdermal patch formulation or micronized estradiol (*Estrace*, *Gynodiol*).

Central Nervous System Effects

Insomnia and fatigue in many postmenopausal women may be related to reduced estrogen levels; there is a correlation between the incidence of waking episodes and low levels of estrogen. Estrogen replacement therapy may be used to treat severe cases.

There is considerable interest in the role of estrogen hormone replacement therapy as a cognitive enhancer in postmenopausal women. Although there is some evidence for improved cognitive abilities in postmenopausal women receiving estrogen replacement therapy, the effects reported thus far are modest.

Infertility

Anovulation, often related to altered ratios of estrogen to progestin, can be treated with a variety of agents, including estrogen–progestin replacement, clomiphene citrate, bromocriptine, FSH, LH, human chorionic gonadotropin, and GnRH. Clomiphene citrate (*Clomid*, *Serophene*) and bromocriptine (*Parlodel*) are the two most widely used agents.

Induction of Ovulation

Anovulation can be due to an insufficient release of LH and FSH during the mid phase of the menstrual cycle. Induction of ovulation by clomiphene citrate is the result of stimulation of FSH and LH release. The mechanism of this action is probably related to the *estrogen antagonist* properties of clomiphene citrate. Although estrogens generally exert a negative-feedback inhibition on FSH and LH secretion by means of a suppression of GnRH from the hypothalamus, clomiphene exerts its action by stimulating secretion of these hormones. Antagonism of this feedback system results in a surge of FSH and LH secretion, hence ovulation.

Patients with normal or elevated estrogen levels and normal pituitary and hypothalamic function respond most frequently to treatment with clomiphene citrate. In this group, the ovulation rate following clomiphene citrate may be 80%. Clomiphene citrate is administered on a cyclic schedule. First, menstrual bleeding is induced; next drug is given orally for 5 days at 50 mg/day. Ovulation is expected 5 to 11 days after the dose of clomiphene citrate. Pregnancy rates approach 50 to 80% after six such treatment cycles, with most pregnancies occurring during the first three treatment cycles. Clomiphene is also used in conjunction with gonadotropins to induce ovulation for in vitro fertilization.

CANCER

Certain tissues of the female reproductive tract, which are subject to the trophic action of hormones, exhibit a high frequency of neoplasia. Cancer of the breast, the second most common form of cancer in American women, and the rarer endometrial cancer in women, are often responsive to treatments with estrogens or progestins. The toxicity of these hormonal treatments compared with standard cancer chemotherapy is low.

Breast Cancer

Early breast cancer is usually treated by surgery and local irradiation. Hormonal therapy is reserved for patients with advanced metastatic breast cancer. Breast cancer occurs in both premenopausal and postmeno-

pausal women. Approximately one-third of patients have a complete or partial remission with a mean duration of 9 to 12 months after hormonal therapy. Hormonal therapy of advanced breast cancer is not curative, but extended control of disease is possible by the use of different hormonal therapies sequentially.

Estrogen receptor–positive breast cancer in premenopausal and postmenopausal women responds equally to tamoxifen therapy (see Chapter 58). In addition, daily tamoxifen administration for 5 years is a successful therapy for the prevention of breast cancer in the contralateral breast in women who have already had one episode of breast cancer.

Progestins have been used with some success in the treatment of breast cancer, and the response rate is approximately the same as with tamoxifen. Most clinical experience has been obtained using oral megestrol acetate.

The successful response of breast cancers to tamoxifen or progestin treatment depends on the presence of high-affinity receptors for estrogen, progesterone, or both. Fewer than 10% of mammary tumors that lack detectable ER levels will respond to hormonal therapies. *Determination of hormone receptor levels in tumor samples is highly recommended before selecting a therapy.*

Although estrone is a weak estrogen, breast tissue metabolizes estrone and estrone sulfate to estradiol, providing a trophic signal for tumor growth. *The newest drug introduced for the hormonal control of breast cancer is letrozole (Femara).* It is a nonsteroidal aromatase inhibitor that dramatically reduces serum levels of estradiol, estrone, and estrone sulfate in postmenopausal women by blocking the conversion of adrenal androgens, androstenedione, and testosterone to estrone and estradiol. The duration of remission in breast cancer patients treated with letrozole exceeds that of tamoxifen, and the drug can be used even in tumors that have developed resistance to tamoxifen. Letrozole is orally active and is excreted primarily in the urine. The incidence of side effects is rare. It does not change serum corticosteroid, aldosterone, or thyroid hormone levels. Anastrozole (*Arimidex*) is another promising third-generation aromatase inhibitor.

Endometrial Cancer

Progesterone administration induces remissions in approximately one-third of patients with metastatic endometrial cancer. The mean duration of response is 27 months. Almost 60% of endometrial adenocarcinomas contain progesterone receptors. Preliminary data show a correlation between progesterone receptor status and response rates in this disease. The mechanism of the effect of progesterone on endometrial cancer is not known.

OTHER USES

Other clinical uses of estrogens and progestins include the treatment of dysfunctional uterine bleeding, dysmenorrhea, endometriosis, and rarely, metastatic prostate cancer.

Breast Cancer

Administration of estrogen alone or estrogen–progestin combinations multiplies by 1.2 to 1.8 the relative risk of breast cancer in postmenopausal women. The risk is slightly greater in women taking estrogen–progestin (conjugated equine estrogens plus medroxyprogesterone acetate) compared with women taking estrogen alone (conjugated equine estrogens). In addition, the risk is greater for lean women (low body mass index) with either therapy. Thus, the ability of progestins to protect the endometrium from cancer risk is not observed in breast tissue. Oral contraceptive use in younger women does not seem to be associated with an increased breast cancer risk.

Ovarian Cancer

Oral contraceptive use lessens the incidence of ovarian cancer.

Hepatic Cancer

Hepatocellular carcinoma and benign hepatomas are rare complications of oral contraceptive and tamoxifen use.

Cardiovascular Complications

Estrogen replacement therapy is associated with an increased risk of thromboembolic disease, and alternative therapies for osteoporosis and cardiovascular protection are recommended for individuals with prior thromboembolic episodes. The problems generally are more severe and/or more frequent when either of the synthetic estrogens, ethinyl estradiol or mestranol, is used. These preparations alter liver function more significantly than do the natural estrogens, such as the sulfate conjugates or esterified estrogens. Alterations in the synthesis of specific liver proteins, such as coagulation factors and fibrinogen, are implicated in the formation of thromboembolisms. Conjugated estrogens, tamoxifen, clomiphene and raloxifene also increase the frequency of thromboembolic disease.

Current estimates are that oral contraceptive use doubles to triples the overall risk of thromboembolic disease. The increased use in recent years of oral contraceptives with lower estrogen content probably contributes to the decreased risk. However, the risk is

greater in women who smoke, who are over age 35, or who are diabetic.

Mild hypertension and fluid retention frequently occur in oral contraceptive users. Systolic blood pressure is elevated 5 to 6 mm Hg; diastolic blood pressure increases are on the order of 1 to 2 mm Hg. Hypertension is not commonly a problem in postmenopausal women receiving conjugated estrogens.

Migraine Headaches

A 0.5% incidence of migraines has been reported among users of oral contraceptives. Migraine headaches may be a warning signal for an oncoming stroke, and immediate discontinuation of oral contraceptive use is recommended.

Teratogenesis

Diethylstilbestrol (DES) was once given to prevent spontaneous abortion, but it no longer has such a medical indication. There is a 0.01 to 0.1% incidence of a rare vaginal and cervical clear cell adenocarcinoma among the daughters of mothers who received DES during their first trimester of pregnancy. An increased cancer incidence in male offspring of mothers who had received DES has also been noted.

Progestins may be teratogenic during the first trimester of pregnancy. Therefore, if pregnancy is suspected, oral contraceptive use should not be initiated or use should be stopped promptly.

Fertility

There is some delay in the return of fertility after discontinuation of oral contraceptive use. Gonadotropin profiles should be normal 3 months after combination oral contraceptive use is stopped. The incidence of prolonged amenorrhea extending beyond 6 months is 2 to 3%. This reaction is especially a problem with the use of progestin-only minipills.

Breast Feeding

The use of oral contraceptives may interfere with lactation. In addition, the hormones may be present in the mother's milk, hence be taken in by the nursing child. If breast feeding is planned, the use of oral contraceptives should be discontinued until after weaning.

Gallbladder Disease

There is a 2.5-fold increased incidence of gallbladder disease in postmenopausal women receiving estrogens. This occurrence may be related to changes in plasma lipid metabolism.

Glucose Tolerance

Estrogen usage is associated with a mild decrease in glucose tolerance. Estrogens do not cause diabetes, but their concurrent use in the diabetic patient may necessitate adjustment in insulin dosage.

ADVERSE EFFECTS

Common side effects associated with estrogen use include nausea, weight gain, and edema. Progestin use is associated with weight gain and mild depression. Tolerance to these effects usually develops over several months.

Low-dose estrogen combination oral contraceptives result in irregular midcycle bleeding episodes in some patients. High-progestin preparations, especially the progestin-only minipill, can cause irregular bleeding and prolonged amenorrhea.

Endometrial hyperplasia frequently develops in premenopausal and postmenopausal women receiving estrogens alone. This reaction is generally regarded to be a premalignant state, because individuals reported to have endometrial hyperplasia later have a higher than normal incidence of endometrial carcinoma. *Administration of estrogens only is associated with a 1.7- to 15-fold increased risk of endometrial carcinoma.* The relative risk rises with increased dosage and duration of estrogen use. Women receiving progestins 10 days per month during estrogen therapy generally do not develop endometrial carcinoma. Women taking combination oral contraceptives have slightly less risk of developing endometrial carcinoma than nonusers. This may be related to the constant exposure of the endometrium to both progestin and estrogen.

Adverse Reactions to SERMs

Ovarian enlargement is the most common side effect of clomiphene use. The occurrence of multiple births following ovulation induction with clomiphene is 4 to 9%; 90% of these multiple births are twins. Since clomiphene is teratogenic, therapy should be discontinued if there is a chance that conception has occurred. Rarely, irreversible ocular toxicities have been reported with clomiphene use.

Nausea, vomiting, and hot flashes may accompany tamoxifen administration. Tamoxifen may cause a transient flare of tumor growth and increased pain due to bone metastases. These reactions are thought to be due to an initial estrogenic action of this drug. Mild or tran-

sient depression of platelet counts often occurs in patients receiving tamoxifen. At very high doses, generally no longer used in cancer treatment, ocular toxicity has been reported. There is a slight risk of hepatocellular carcinoma in humans receiving long-term (5 years) tamoxifen therapy as well as a slightly (0.4%) elevated incidence of endometrial cancer.

Raloxifene and clomiphene use is associated with an increased frequency of vasomotor disturbances (hot flashes) and thromboembolism formation.

CONTRAINDICATIONS AND DRUG INTERACTIONS

Some of the contraindications to the use of estrogens, progestins, and estrogen-progestin combinations are presented in Table 61.4.

Certain concomitantly administered drugs may interfere with the effectiveness of the oral contraceptives or lead to an increased incidence of breakthrough bleeding. These include rifampin, isoniazid, ampicillin, neomycin, penicillin V, chloramphenicol, sulfonamides, nitrofurantoin, phenytoin, barbiturates, primidone, analgesics, and phenothiazines.

The oral contraceptives also may decrease the effectiveness of anticoagulants, anticonvulsants, tricyclic antidepressants, guanethidine, and hypoglycemic agents. The causes of such drug interactions include alterations in hepatic microsomal drug-metabolizing enzymes, competition for binding sites on plasma proteins, and enhanced excretion.

Raloxifene absorption is inhibited by cholestyramine.

TABLE 61.4 Contraindications for Drug Use

Formulation

Estrogens	Breast or endometrial cancer or vaginal bleeding of unknown origin
	Pregnancy
	Hepatic dysfunction or liver cancer
	Preexisting cardiovascular disease
Progestins	Pregnancy
	Depression
Oral contraceptives	Pregnancy
	Smokers over age 35
Antiestrogens	Pregnancy
	Endometrial cancer

Study QUESTIONS

1. Raloxifene is a SERM. A characteristic of SERMs is that they
 - (A) Act as estrogen agonists at all ERs
 - (B) Antagonize estrogens at all ERs
 - (C) Act as agonists at some and antagonists at other ERs
2. The most widely used type of oral contraceptive in the United States is
 - (A) Estrogen only
 - (B) Progestin only
 - (C) Combination of estrogen and progestin
3. Osteoporosis is the most serious effect of menopause. All of the following statements about osteoporosis are true EXCEPT
 - (A) Estrogen is an effective treatment.
 - (B) If endometrial cancer is a concern, a combination of estrogen and progestin should be considered.
 - (C) Vitamin D and calcium supplementation are alternatives to steroid hormone therapy.
 - (D) Bisphosphonates are ineffective in prevention of osteoporosis.
 - (E) Calcitonin is a useful alternative agent.
4. Breast cancer is the second most common cancer in women. All of the following statements concerning breast cancer are true EXCEPT
 - (A) Hormonal therapy is reserved for patients with advanced metastases.
 - (B) Estrogen treatment is an acceptable form of hormonal therapy.
 - (C) Progestin treatment is an accepted form of hormonal therapy.
 - (D) Tamoxifen is an accepted form of nonhormonal therapy.
5. The mechanism of action of the compound RU486 is to
 - (A) Block estrogen binding to ERs
 - (B) Block progestin binding to progesterone receptors
 - (C) Act as an estrogen agonist
 - (D) Act as a progesterone agonist

ANSWERS

1. **C.** Raloxifene is a recently approved SERM. It is a partial estrogen agonist in breast tissue but was initially characterized as an antiestrogen. It, like the best-studied SERM, tamoxifen, has estrogen agonist properties in some tissues and estrogen antagonism properties in others.
2. **C.** Although progestin-only oral contraceptive formulations are available, the combination of estrogen and progestin is considered the safest and most desirable type.
3. **D.** The bisphosphonates are a useful alternative therapy to steroid hormones. Estrogen treatment is effective, but in some patients the risks outweigh the benefits.
4. **B.** Estrogen therapy is contraindicated in the presence of breast cancer. Normal breast growth is stimulated by estrogens, and estrogen administration is therefore contraindicated. Hormonal therapy is normally reserved for patients with advanced metastases. Surgery and local irradiation are the preferred therapy for early breast cancer. Progestin treatment and tamoxifen therapy are both accepted forms of therapy. Both are more effective in treatment of cancers with high-affinity receptors for estrogen, progesterone, or both.
5. **B.** RU 486 acts as a competitive progesterone antagonist and blocks progesterone binding at its receptors. It has no activity at estrogenic receptors.

SUPPLEMENTAL READING

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CASE Study Use of Hormones in Menopause

Joan Jenkins is a 56-year-old woman who comes to your office complaining of hot flashes, increased irritability, and inability to concentrate on day-to-day tasks. She indicates that she is undergoing menopause but that she does not want to take any hormones because her mother had breast cancer and she was afraid that this would increase her risk. She says the symptoms are almost unbearable. What do you advise?

ANSWER: You should try to allay her fears but point out that she is correct in being concerned. Tell her that there is an increased risk of breast cancer after estrogen or estrogen–progestin combination therapy but that the risk is relatively small. Inform her

that her severe symptoms will be relatively short-lived and suggest trying hormone replacement therapy for a short time to see if the condition is greatly improved. The use of estrogen replacement for short periods (up to 2 years) is not associated with an increased incidence of breast cancer. You should also point out that osteoporosis is the most serious menopausal symptom and that there are alternatives to hormone therapy in preventing the decrease in bone mass associated with menopause. She should be encouraged to take calcium and vitamin D supplementation immediately. She should be scheduled for baseline determination of her bone density so that any evidence of loss of bone mass can be ascertained.