anterior pituitary gland. Progesterone also may help maintain pregnancy by decreasing uterine contractility. This, in turn, decreases the risk of spontaneous abortion.

Progesterone, in general, has opposite effects on lipid metabolism compared with estrogen. That is, progestins decrease high-density lipoprotein (HDL) cholesterol and increase low-density lipoprotein (LDL) cholesterol, both of which increase risks of cardiovascular disease. Physiologic progesterone increases insulin levels but does not usually impair glucose tolerance. However, long-term administration of potent synthetic progestins, such as norgestrel, may decrease glucose tolerance and make diabetes mellitus more difficult to control. Like estrogen, progesterone is metabolized in the liver.

ESTROGENS AND PROGESTINS USED AS DRUGS

- When exogenous estrogens and progestins are administered for therapeutic purposes, they produce the same effects as endogenous (naturally occurring) hormones.
- Several preparations of estrogens and progestins are available for various purposes and routes of administration:
  - *Naturally occurring, nonconjugated estrogens* (estradiol, estrone) *and natural progesterone* are given intramuscularly (IM) because they are rapidly metabolized if administered orally. Some crystalline suspensions of estrogens and oil solutions of both estrogens and progesterone prolong drug action by slowing absorption.
  - *Conjugated estrogens* (eg, Premarin) and some synthetic derivatives of natural estrogens (eg, ethinyl estradiol) and natural progesterone (eg, norethindrone) are chemically modified to be effective with oral administration. The most widely used synthetic steroidal estrogen is ethinyl estradiol, which is used in hormonal contraceptives. Ethinyl estradiol is well absorbed with oral administration and reaches peak plasma levels within 2 hours. It is 98% bound to plasma proteins and its half-life varies from 6 to 20 hours. Ethinyl estradiol undergoes extensive first-pass hepatic metabolism and is further metabolized and conjugated in the liver; the conjugates are then excreted in bile and urine.
  - *Nonsteroidal, synthetic preparations* are usually administered orally or topically. They are chemically altered to slow their metabolism in the liver. They are also less bound to serum proteins than naturally occurring hormones.
- Most hormonal contraceptives consist of a synthetic estrogen (eg, ethinyl estradiol) and a synthetic progestin (eg, norethindrone). Norethindrone undergoes first-pass metabolism so that it is only 65% bioavailable. It reaches peak plasma levels in 0.5 to 4 hours and has a half-life of 5 to 14 hours. It is metabolized in the liver and excreted in urine and feces. Monophasic contraceptives contain fixed amounts of both estrogen and progestin components. Biphasics and triphasics contain either fixed amounts of estrogen and varied amounts of progestin or varied amounts of both estrogen and progestin. Biphasic and triphasic preparations mimic normal variations of hormone secretion, decrease the total dosage of hormones, and may decrease adverse effects.

  These contraceptives are dispensed in containers with color-coded tablets that must be taken in the correct sequence. Dispensers with 28 tablets contain seven inactive or placebo tablets of a third color. A few contraceptive products contain a progestin only. These are not widely used because they are less effective in preventing pregnancy and are more likely to cause vaginal bleeding, which makes them less acceptable to many women.
- Several combination products and alternative dosage forms are available to help individualize treatment and promote compliance. For example, several noncontraceptive combination oral tablets are available for treatment of menopausal symptoms and osteoporosis. Two combination products (Combi-Patch and Ortho Evra) are available in transdermal patches for topical application. Also, along with several cream formulations, a vaginal tablet (Vagifem) and a vaginal ring (Estring) of estrogen are available for topical application in treating atrophic vaginitis.

Mechanisms of Action

The precise mechanisms by which estrogens and progestins produce their effects are unknown. Estrogens circulate in the bloodstream to target cells, where they enter the cells and combine with receptor proteins in cell cytoplasm. The estrogen–receptor complex is then transported to the cell nucleus where it interacts with deoxyribonucleic acid (DNA) to produce ribonucleic acid (RNA) and new DNA. These substances stimulate cell reproduction and production of various proteins. Progestins also diffuse freely into cells, where they bind to progesterone receptors.

Hormonal contraceptives act by several mechanisms. First, they inhibit hypothalamic secretion of gonadotropin-releasing hormone, which inhibits pituitary secretion of FSH and LH. When these gonadotropic hormones are absent, ovulation and, therefore, conception cannot occur. Second, the drugs produce cervical mucus that resists penetration of spermatozoa into the upper reproductive tract. Third, the drugs interfere with endometrial maturation and reception of ova that are released and fertilized. These overlapping mechanisms make the drugs highly effective in preventing pregnancy.

Indications for Use

Estrogens

- **As replacement therapy in deficiency states.** Deficiency states usually result from hypofunction of the pituitary gland or the ovaries and may occur anytime during the life cycle. For example, in the adolescent girl with delayed sexual development, estrogen can be given to produce the changes that normally occur at puberty. In the woman of reproductive age (approximately 12 to