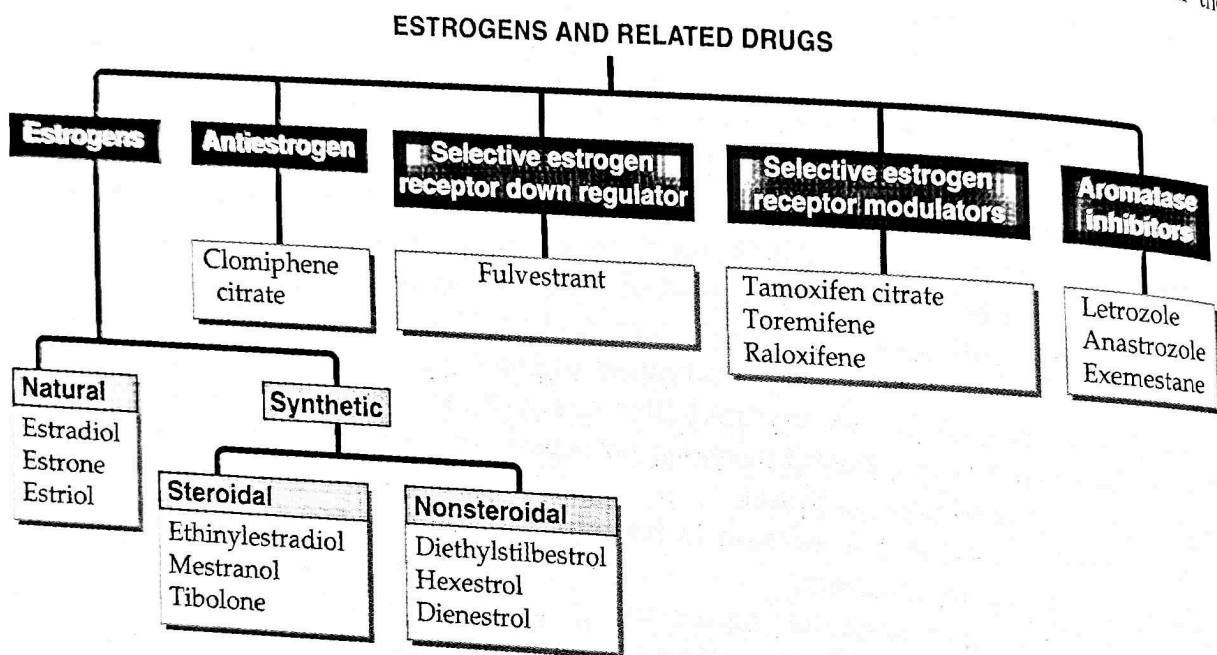


Chapter 22

Estrogens, Progestins and Contraceptives

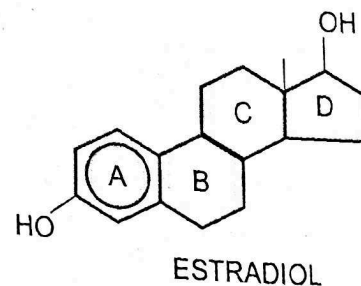
The estrogens, its receptor agonists and antagonists, and synthesis blockers are classified in the following chart:



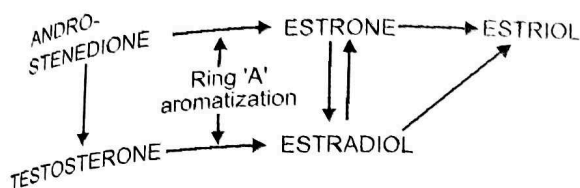
ESTROGENS (Female Sex Hormones)

These are substances which can induce estrus in spayed (ovariectomized) animals.

It was established in the year 1900 that ovaries control female reproductive function through a hormonal mechanism. Allen and Doisy (1923) found that an alcoholic extract of ovaries was capable of inducing estrus in rodents, and devised a simple bioassay method. The active principle estradiol was obtained in pure form in 1929 and soon its chemical structure was worked out.



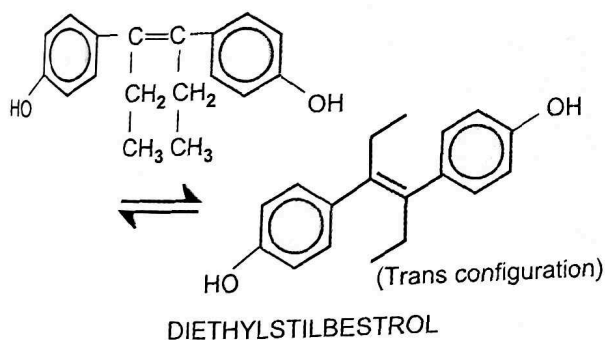
Natural estrogens *Estradiol* is the major estrogen secreted by the ovary. It is synthesized in the graafian follicle, corpus luteum and placenta from cholesterol. Steps depicted on the right hand side in Fig. 20.1 are carried out. Further steps are shown below.



Estradiol is rapidly oxidized in liver to *estrone* which is hydroxylated to form *estriol*. All three are active and circulate in blood, but estradiol is the most potent estrogen. Estrone and estriol have much lower affinity for the estrogen receptor (ER) than estradiol. Small quantity (2–20 µg/day) of estradiol is produced in human males also from aromatization of testosterone in the testes and extraglandular tissues. In the mare, large quantity of *equilin* is produced which has 1/5 estrogenic potency of estradiol.

Synthetic estrogens Natural estrogens are inactive orally and have a short duration of action due to rapid metabolism in liver. To overcome this, steroidal and nonsteroidal synthetic compounds have been produced (see chart).

The nonsteroidal compounds assume a trans configuration as depicted below and sterically resemble natural estrogens.



Regulation of secretion The daily secretion of estrogens in menstruating women varies from 10–100 µg depending on the phase of the cycle. Its secretion starts from the graafian follicle under the influence of FSH and the blood level rises gradually during the follicular phase. Due to the modest preovulatory FSH surge, estrogens further rise transiently. After ovulation, corpus luteum continues to secrete estrogens till about two days before menstruation. Estrogens exercise feedback inhibition of FSH (also of LH at higher

concentrations) by direct action on pituitary as well as through hypothalamus (see p. 262).

During pregnancy, placenta secretes large quantities of estrogens, (mainly estrone and estriol) reaching a peak of upto 30 mg/day at term. Their level declines sharply after delivery. In the postmenopausal women, daily production of estrogen has been estimated as 2–10 µg—derived primarily by extraglandular aromatization of adrenal androgens.

Actions

1. Sex organs The estrogens bring about pubertal changes in the female including growth of uterus, fallopian tubes and vagina. Vaginal epithelium gets thickened, stratified and cornified. They are responsible for the proliferation of endometrium in the preovulatory phase, and it is only in concert with estrogens that progesterone brings about secretory changes.

In the absence of progesterone (anovulatory cycles) withdrawal of estrogens alone produces menstruation. If modest doses of estrogen are given continuously without added progesterone—endometrium hypertrophies and menstruation is delayed, but breakthrough bleeding occurs at irregular intervals. However, the normal event which triggers menstruation is progesterone withdrawal. The progesterone withdrawal bleeding cannot be suppressed even by high doses of estrogens.

Estrogens augment rhythmic contractions of the fallopian tubes and uterus, and induce a watery alkaline secretion from the cervix. This is favourable to sperm penetration. They also sensitize the uterus to oxytocin. Deficiency of estrogens is responsible for atrophic changes in the female reproductive tract that occur after menopause.

2. Secondary sex characters Estrogens produced at puberty cause growth of breasts—proliferation of ducts and stroma, accumulation of fat. The pubic and axillary hair appear, feminine body contours and behaviour are influenced.

Acne is common in girls at puberty as it is in boys—probably due to small amount of androgens produced simultaneously. Administration of

estrogens to suppress pituitary-gonadal axis causes regression of acne.

3. Metabolic effects Estrogens are anabolic, similar to but weaker than testosterone. Therefore, small amount of androgen may be contributing to the pubertal growth spurt even in girls, as estrogens do in boys. Continued action of estrogen promotes fusion of epiphyses both in girls and boys.

Estrogen is important in maintaining bone mass primarily by retarding bone resorption. Osteoclast pit formation is inhibited and there is increased expression of bone matrix proteins such as osteonectin, osteocalcin, collagen and alkaline phosphatase. It promotes positive calcium balance, partly by inducing renal hydroxylase enzyme which generates the active form of Vit D₃.

Both osteoblasts and osteoclasts express estrogen receptors (ERs). The major action of estrogens is to reduce maturation and activity of osteoclasts by modifying regulatory cytokine signals from osteoblasts (see Ch. 24 for bone remodeling mechanisms).

Pharmacological doses of estrogens can cause mild salt and water retention—edema occurs in predisposed patients, but it can be treated with diuretics. BP may rise after prolonged use. Combination contraceptives containing higher doses of estrogens and progestins impair glucose tolerance. Normal blood sugar is not affected but diabetes may be precipitated or its control vitiated. However, amounts used for HRT and low dose contraception do not affect carbohydrate metabolism.

Estrogens decrease plasma LDL cholesterol while HDL and triglyceride levels are raised. The raised HDL : LDL ratio is probably responsible for rarity of atherosclerosis in premenopausal women. However, blood coagulability is increased due to induction of synthesis of clotting factors (factors II, VII, IX and X). Fibrinolytic activity in plasma also tends to increase due to lowering of plasminogen-activator inhibitor-1 (PAI-1).

Estrogens induce nitric oxide synthase and PGI₂ production in vascular endothelium. The increased availability of NO and PGI₂ could

promote vasodilatation. They increase lithogenicity of bile by increasing cholesterol secretion and reducing bile salt secretion. Plasma levels of sex hormone binding globulin (SHBG), thyroxine binding globulin (TBG) and cortisol binding globulin (CBG) are elevated—but without any change in hormonal status.

Mechanism of action

Estrogens bind to specific receptors located normally within the nucleus of target cells and produce effects by regulating protein synthesis. Estrogen receptors (ERs) have been demonstrated in female sex organs, breast, pituitary, liver, bone, blood vessels, heart, CNS and in certain hormone responsive breast carcinoma cells. The ER is analogous to other steroid receptors: agonist binding to the ligand binding domain brings about receptor dimerization and interaction with 'estrogen response elements' (EREs) of target genes. Gene transcription is promoted through certain *coactivator proteins*. On binding an estrogen antagonist the receptor assumes a different conformation and interacts with other *corepressor proteins* inhibiting gene transcription.

Two distinct ERs designated ER α and ER β have been identified, cloned and structurally characterized. Most tissues express both subtypes, but ER α predominates in uterus, vagina, breast, bone, hypothalamus and blood vessels, while ER β predominates in prostate gland of males and ovaries in females. Estradiol binds to both ER α and ER β with equal affinity, but certain ligands have differing affinities. More importantly ER α and ER β may have a different pattern of interaction with coactivators and corepressors.

Few nongenomic rapid actions of estrogens in certain tissues (e.g. granulosa cells), mediated through the same ERs but which are located on the cell membrane, have also been observed.

Pharmacokinetics

Estrogens are well absorbed orally and transdermally, but natural estrogens are inactive by the oral route due to rapid metabolism in liver.

Estradiol esters injected i.m. are slowly absorbed and exert prolonged action. Natural estrogens in circulation are largely plasma protein bound—to SHBG as well as to albumin.

Estradiol is converted to estrone and *vice versa* in liver. Estriol is derived from estrone. All three are conjugated with glucuronic acid and sulfate, which are excreted in urine and bile. Considerable enterohepatic circulation occurs due to deconjugation in intestines and reabsorption; ultimate disposal occurs mostly in urine.

Ethinylestradiol is metabolized very slowly ($t_{1/2}$ 12–24 hours). It is orally active and more potent.

Preparations and dose

All estrogen preparations have similar action. Their equivalent *parenteral* doses are—

Estradiol 0.1 mg = Ethinylestradiol 0.1 mg
= Mestranol 0.15 mg = Conjugated estrogens 10 mg = Estriol succinate 16 mg = Diethylstilbestrol 10 mg.

The *oral* potencies differ from the above due to differing extents of first pass metabolism. Estradiol is inactive orally, conjugated estrogens and estriol succinate undergo partial presystemic metabolism, while in case of ethinylestradiol, mestranol and diethylstilbestrol the oral and parenteral doses are practically the same.

The preferred route of administration of estrogens is oral. Intramuscular injection is resorted to only when large doses have to be given.

1. Estradiol benzoate/cypionate/enanthate/valerate: 2.5–10 mg i.m.; OVOCYCLIN-P 5 mg inj, PROGYNON DEPOT 10 mg/ml inj.
2. Conjugated estrogens: 0.625–1.25 mg/day oral; PREMARIN 0.625 mg, 1.25 mg tab (for HRT), 25 mg inj (for dysfunctional uterine bleeding), 0.625 mg/g vaginal cream (for atrophic vaginitis).
3. Ethinylestradiol: for menopausal syndrome 0.02–0.2 mg/day oral; LYNORAL 0.01, 0.05, 1.0 mg tab, PROGYNON-C 0.02 mg tab.
4. Mestranol: acts by getting converted to ethinylestradiol by demethylation in the liver: 0.1–0.2 mg/day oral; in OVULEN 0.1 mg tab, with ethynodiol diacetate 1 mg.
5. Estriol succinate: 4–8 mg/day initially, maintenance dose in menopause 1–2 mg/day oral; EVALON 1, 2 mg tab, 1 mg/g cream for vaginal application in atrophic vaginitis 1–3 times daily.

6. Fosfestrol tetrasodium: (For carcinoma prostate) initially 600–1200 mg slow i.v. inj for 5 days, maintenance 120–240 mg/day oral or 300 mg 1–3 times a week i.v. HONVAN 120 mg tab, 300 mg/mL.

7. Dienestrol: 0.01% topically in vagina: DIENESTROL 0.01% vaginal cream.

Transdermal estradiol A transdermal patch (Estradiol-TTS) is available in 3 sizes, *viz.* 5, 10 and 20 cm² delivering 0.025 mg, 0.05 mg and 0.1 mg respectively in 24 hours for 3–4 days. The usual dose in menopause is 0.05 mg/day which produces plasma estradiol levels seen in premenopausal women in the early or mid follicular phase. Cyclic therapy (3 weeks on, 1 week off) with estradiol-TTS is advised with an oral progestin added for the last 10–12 days. Beneficial effects of estradiol-TTS on menopausal symptoms, bone density, vaginal epithelium and plasma Gn levels are comparable to those of oral therapy, but improvement in serum lipid profile is less marked.

Systemic side effects of estradiol-TTS are the same as with oral estrogens, but are milder. Oral therapy delivers high dose of the hormone to the liver and increases synthesis of several proteins which may have undesirable consequences. Estradiol-TTS avoids high hepatic delivery: consequently plasma levels of TBG, CBG, angiotensinogen and clotting factors are not elevated—risk of thromboembolic phenomena may not be increased or is low.

ESTRADERM-MX: Estradiol 25, 50 or 100 µg per 24 hr transdermal patches; apply to nonhairy skin below waist, replace every 3–4 days using a different site; add an oral progestin for last 10–12 days every month.

Recently a combined estradiol 50 µg + norethisterone acetate 0.25 mg patch has become available in some countries (ESTRAGEST-TTS). Two weeks of estraderm-TTS followed by 2 weeks estragest-TTS with patches changed twice weekly is used for total transdermal HRT.

A gel formulation of estradiol for application over skin is also available. OESTRAGEL, E₂ GEL 3 mg/5 g in 80 g tube, SANDRENA 1 mg/g gel; apply over the arms and spread to cover a large area once daily for HRT.

Adverse effects

Most of the adverse effects of estrogens are described with HRT and with oral contraceptives (*see* p. 350).

In addition, dose dependent adverse effects noted when use is made for other indications are—

1. Suppression of libido, gynaecomastia and feminization when given to males.
2. Fusion of epiphyses and reduction of adult stature when given to children.
3. In postmenopausal women, estrogens can increase the risk of irregular bleeding and endometrial carcinoma (5–15 fold). A progestin given concurrently blocks the risk.
4. Estrogens can accelerate the growth of existing breast cancer, but low-dose estrogen only HRT does not appear to increase the risk of developing new breast cancer (see p. 335).
5. Long-term estrogen therapy doubles the incidence of gallstones. Benign hepatomas are more common in women taking estrogens in their teens and twenties.
6. Migraine, epilepsy and endometriosis may be worsened by estrogens.

Estrogens are contraindicated during pregnancy.

Uses

Currently, the two most common uses of estrogens are as *contraceptives* and for *hormone replacement therapy* (HRT) in postmenopausal women, but there are some other indications as well.

1. Hormone replacement therapy (HRT)

Due to cessation of ovarian function at menopause women suffer a number of physical, psychological and emotional consequences.

Medical problems related to menopause are:

- *Vasomotor disturbances* Hot flashes, chilly sensation, inappropriate sweating, faintness, paresthesias, aches and pains.
- *Urogenital atrophy* Change in vaginal cytology and pH, vaginal dryness, vulval shrinkage, dyspareunia, vaginitis, itching, urinary urgency, predisposition to urinary tract infection.
- *Osteoporosis* Loss of osteoid as well as calcium → thinning and weakening of bone → minimal trauma fractures especially of femur, hip, radius, vertebrae.
- *Dermatological changes* Thinning, drying and loss of elasticity of skin, wrinkles, thin and listless hairs.

- *Psychological/Cognitive disturbances* Irritability, depressed mood, loss of libido and self confidence, anxiety and dementia.
- *Increased risk of cardiovascular diseases* Coronary artery disease, myocardial infarction, stroke. The vasomotor symptoms tend to subside over a few years, but the other changes progress continuously.

Estrogen ± progestin HRT or 'menopausal hormone therapy' (MHT) is highly efficacious in suppressing the perimenopausal syndrome of vasomotor instability, psychological disturbances as well as in preventing atrophic changes and osteoporosis. However, several recent findings have emphasized a number of risks and limitations of long-term HRT, so that HRT is now generally restricted to limited duration for control of hot flashes and other symptoms in women below 60 years or within 10 years after menopause.*

The *dose* of estrogen used in HRT is substantially lower than that for contraception. Typically, conjugated estrogens are used at 0.625 mg/day dose (equivalent to ethinylestradiol 10 µg) cyclically (3 weeks treatment 1 week gap), but there is a trend now to use lower doses (0.3–0.45 mg/day). A progestin (preferably micronized oral progesterone 100 mg/day, or medroxy progesterone acetate/norethisterone 2.5 mg daily) is added for the last 10–12 days each month. Though the progestin may attenuate the metabolic and cardiovascular benefits of estrogen, it is needed to block the increased risk of dysfunctional uterine bleeding and endometrial carcinoma due to continuous estrogenic stimulation of endometrium. Estrogen alone is used in hysterectomised women and when a progestin is not tolerated or is contraindicated. Low-dose estrogen alone may be tried, if it can control the symptoms. Transdermal estradiol appears to have certain advantages (see above) and is preferred by many.

The benefits and risks of HRT are considered below:

- a. *Menopausal symptoms and atrophic changes* The vasomotor symptoms respond promptly and almost completely. They are the primary indication for using HRT which also improves sleep disturbances, bodyache, general

* Global consensus statement on Menopausal Hormone Therapy.

physical, mental and sexual well being. Estrogen therapy tends to mitigate perimenopausal depression, but combining it with a progestin may nullify this benefit. HRT should be discontinued once the vasomotor symptoms abate. Estrogens also arrest genital and dermal atrophic changes; vulval and urinary problems resolve. Vaginal application of estrogen is effective in relieving local symptoms as well as dyspareunia and should be preferred when this is the only aim of HRT.

b. **Osteoporosis and fractures** HRT restores Ca^{2+} balance; further bone loss is prevented and the excess fracture risk is nullified. When used for this purpose, HRT should be initiated before significant bone loss has occurred, because reversal of osteoporosis is none or slight. Calcium + vit D supplements and exercise aid the beneficial effect of HRT. However, accelerated bone loss starts again on cessation of HRT. The 'Women's health, osteoporosis, progestin-estrogen' trial (2002) has shown that even lower doses of conjugated estrogens (0.3, 0.45 mg/day) increased bone mineral density in postmenopausal women, though 0.625 mg/day was more effective.

Notwithstanding the above, appreciation of the other risks of HRT (see below) has dislodged estrogen from its prime position in the treatment of osteoporosis. Bisphosphonates are more effective and the drugs of choice. If prevention and treatment of osteoporosis is the goal, HRT is not the best option, and is not recommended beyond 5 years of use or in women over 60 years of age.

c. **Cardiovascular events** Since hypertension and cardiovascular disease are rare in premenopausal women, and estrogens improve HDL:LDL ratio, retard atherogenesis, reduce arterial impedance, increase NO and PGI_2 production and prevent hyperinsulinaemia, it was believed that estrogen therapy in postmenopausal women will have a protective cardiovascular influence.

In the past two decades many large scale placebo controlled randomized interventional trials and cohort studies have yielded opposite results. The 'Heart and estrogen/progestin replacement study' (HERS and HERS II) conducted in older women with preexisting cardiovascular disease found that HRT triples the risk of venous thromboembolism, increases risk of MI in the 1st year and affords no secondary prophylaxis of CAD in the long-term. The larger 'women's health initiative' (WHI) study conducted in over 16000 younger women without CAD found 24% increase in CAD, 40% increase in stroke and doubling of venous thromboembolism with the use of combined HRT. The study was terminated prematurely in 2002. The increased risk of MI was attributed to the progestin component, since women who took estrogen alone had no increase in the incidence of MI. Reexamination of the data has revealed ~30% reduction in incidence of MI among women who took HRT within 10 years of menopause. As such, a few years of HRT just after menopause and before 60 years of age may be protective.

d. **Cognitive function and dementia:** Contrary to earlier belief, the 'women's health initiative memory study' (WHIMS) conducted among older women (65–79 years)

has failed to detect any protection against cognitive decline by either estrogen alone or combined HRT. There was in fact a slight global deterioration. Surprisingly, incidence of dementia (Alzheimer's) was doubled.

e. **Cancer:** That estrogens enhance the growth of *breast cancer* has been well recognized. However, it was contended that small replacement doses of estrogens will not induce new cancer. This appears to be supported by the estrogen alone arm of WHI study in hysterectomized women, as the occurrence of breast cancer was actually lower (but insignificantly). On the other hand, another longer term 'California Teachers study' found a slightly higher risk. In the combined HRT group, a significantly higher incidence of cancer breast occurred, indicating that medroxyprogesterone was the culprit. The prospective observational cohort 'Million women study' (MWS) in the UK found a marginally higher incidence of breast cancer with estrogen alone, but a clearly higher one with estrogen + progestin. Some other studies have also implicated the progestin, and the CSM of UK has drawn similar conclusions. Thus, the protective effect of progestin on endometrial cancer appears to be counter balanced by the procarcinogenic effect on the breast.

Estrogen is well known to induce endometrial hyperplasia and its continuous use unopposed by progestin results in irregular uterine bleeding. In the long-term it predisposes to *endometrial carcinoma*. The MWS has supported this contention. The standard practice is to give combined HRT to women with an intact uterus. However, a Cochrane Database Review has concluded that lower dose unopposed estrogen does not increase endometrial carcinoma risk. Thus, low-dose estrogen alone may be used for HRT in women with intact uterus when a progestin is contraindicated.

A small protective effect of combined HRT on *colorectal carcinoma* has been detected by the WHI study, but this needs to be confirmed.

f. **Gallstone, migraine:** Estrogens slightly increase the risk of developing gallstones, while progestins may trigger migraine.

Tibolone It is a 19-norsteroid developed specifically to be used for HRT. It is converted into 3 metabolites which exert estrogenic, progestational and weak androgenic actions in specific tissues. In a dose of 2.5 mg daily, it suppresses menopausal symptoms and lowers the raised Gn levels. No endometrial stimulation has been noted. Urogenital atrophy, psychological symptoms, libido and osteoporosis are improved similar to other forms of HRT. Contraindications are the same as for conventional HRT, but long term benefits and risks are not defined.

Weight gain, increased facial hair and occasional vaginal spotting may be noted. After the initial response, tibolone has failed to gain popularity.

Current conclusions regarding HRT

1. The main indication of HRT is vasomotor and other symptoms in women before the age of 60 years or within 10 years after menopause. It should be used at the smallest effective dose and for the shortest duration.
2. Young women with premature menopause clearly deserve HRT at least till the age of natural menopause.
3. Hysterectomized women should receive estrogen alone, while those with intact uterus be given estrogen + progestin. The option of low-dose estrogen alone may be tried, if symptomatically effective.
4. Perimenopausal women should be given cyclic HRT rather than continuous HRT.
5. HRT is not the best option to prevent osteoporosis and fractures, but may be used in women <60 years of age.
6. HRT affords protection against coronary artery disease only in early postmenopausal women. Combined HRT at conventional dose may increase the risk of venous thromboembolism, MI and stroke in elderly women.
7. HRT does not protect against cognitive decline; may increase the risk of dementia.
8. Combined HRT increases the risk of breast cancer, gallstones and migraine.
9. Transdermal HRT may have certain advantages over oral HRT.
10. The need for HRT should be assessed in individual women, and not prescribed routinely.

LIVIAL 2.5 mg tab, one tab daily without interruption; institute therapy only after the woman has been menopausal for at least 12 months.

2. Senile vaginitis Estrogens change vaginal cytology to the premenopausal pattern and are effective in preventing as well as treating atrophic vaginitis that occurs in elderly women. Oral therapy can be given but more commonly a topical preparation is used; an antibacterial may be combined. Estrogens help in overcoming vaginal infection and relieve symptoms of *Kraurosis vulvae*.

3. Delayed puberty in girls (primary hypogonadism) This may be due to ovarian agenesis (Turner's syndrome) or hypopituitarism. In both cases pubertal changes are brought about by cyclic estrogen treatment started at the age of 12–13 years, building up gradually to adult doses and then cyclic progestin is added. For rapid gain in height growth hormone and/or a small dose of androgen may be added. This treatment will have to be continued till the age of menopause (~ 50 yrs).

4. Dysmenorrhoea While PG synthesis inhibitors are the first line drugs, cyclic estrogen therapy (with added progestin to ensure withdrawal bleeding) benefits by inhibiting ovulation (anovular cycles are painless) and decreasing prostaglandin synthesis in endometrium. However, hormonal treatment should be reserved for severe cases.

5. Acne It occurs at puberty due to increased androgen secretion in both boys and girls. Estrogens benefit by suppressing ovarian production of androgen by inhibiting Gn release from pituitary. Cyclic treatment (with added progestin) is quite effective. Use of estrogen in boys is out of question. Even in girls, topical therapy with

antimicrobials, tretinoin and other drugs is preferred over estrogens (see Ch. 66).

6. Dysfunctional uterine bleeding A progestin given cyclically is the rational and effective therapy. Estrogens have adjuvant value.

7. Carcinoma prostate Estrogens are palliative; produce relief in primary as well as metastatic carcinoma prostate by suppressing androgen production (through pituitary). GnRH agonists with or without androgen antagonist are preferred over estrogens for this purpose.

ANTIESTROGEN

Clomiphene citrate It binds to both ER α and ER β and the *trans* isomer (*enclomiphene*) acts as a pure estrogen antagonist in all human tissues, but the *cis* isomer (*zuclomiphene*) and the racemate display weak agonistic action in rats. Clomiphene induces Gn secretion in women by blocking estrogenic feedback inhibition of pituitary. The amount of LH/FSH released at each secretory pulse is increased. In response, the ovaries enlarge and ovulation occurs if the ovaries are responsive to Gn. Antagonism of peripheral actions of estrogen results in hot flashes. Endometrium and cervical mucus may be modified.

The chief use of clomiphene is for infertility due to failure of ovulation: 50 mg once daily for 5 days starting from 5th day of cycle. Treatment is given monthly. Conception occurs in many women who previously were amenorrhoeic or had anovular cycles. If 1–2 months treatment does not result in conception—the daily dose may be doubled for 2–3 cycles.

No more than 6 treatment cycles should be tried. The antiestrogenic effect of clomiphene on developing follicle, endometrium or cervical mucus can be counterproductive. Luteal phase dysfunction has also been blamed for therapeutic failures. Addition of menotropins or chorionic gonadotropin on the last 2 days of the course improves the success rate.

Clomiphene is well absorbed orally, gets deposited in adipose tissue and has long $t_{1/2}$ of ~6 days. It is largely metabolized and excreted in bile.

Adverse effects Clomiphene can produce polycystic ovaries, multiple pregnancy, hot flashes, gastric upset, vertigo, allergic dermatitis. Risk of ovarian tumour may be increased. Cautious use with lower dose is advised in women with enlarged ovaries.

Other uses To aid in vitro fertilization Clomiphene given with Gn causes synchronous maturation of several ova—improves their harvesting for in vitro fertilization.

Oligozoospermia: Clomiphene increases Gn secretion in men as well. This promotes spermatogenesis and testosterone secretion if the same have been deficient. For male infertility—25 mg daily given for 24 days in a month with 6 days rest for upto 6 months has been recommended. However, success rates are low.

CLOMID, FERTOMID. CLOFERT, CLOME 25, 50, 100 mg tab.

SELECTIVE ESTROGEN RECEPTOR DOWN-REGULATOR

Fulvestrant It is the first member of a distinct class of ER ligands called 'selective estrogen receptor down-regulators' (SERDs) or 'pure estrogen antagonists' that has been introduced for the treatment of locally advanced or metastatic ER positive breast cancer in postmenopausal women which has stopped responding to tamoxifen. In contrast to tamoxifen, it inhibits ER dimerization so that ER interaction with DNA is prevented and receptor degradation is enhanced. The ER is thus down regulated resulting in more complete

suppression of ER responsive gene function. This feature along with its higher affinity for the ER probably accounts for its efficacy in tamoxifen resistant cases.

Fulvestrant is administered as (250 to 500 mg) monthly i.m. injections in the buttock. It is slowly absorbed and has an elimination $t_{1/2}$ of more than a month. FULVENAT 250 mg/vial inj.

SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMs)

These are drugs which exert estrogenic as well as antiestrogenic actions in a tissue selective manner.

That ligand binding could change the configuration of ER in multiple ways allowing interaction with different coactivators and corepressors in a tissue specific manner has paved the way for development of compounds with unique profile of agonistic and antagonistic actions in different tissues. These drugs have been designated 'selective estrogen receptor modulators' (SERMs), and three SERMs *Tamoxifen citrate*, *Raloxifene* and *Toremifene* are in clinical use. It has been demonstrated that the conformation of ER after binding tamoxifen or raloxifene is different from that after binding estradiol.

Tamoxifen citrate Though chemically related to clomiphene, it has complex actions, viz acts as potent estrogen antagonist in breast carcinoma cells, blood vessels and at some peripheral sites, but as partial agonist in uterus, bone, liver and pituitary. Inhibition of human breast cancer cells and hot flashes reflect antiestrogenic action, while the weak estrogen agonistic action manifests as stimulation of endometrial proliferation, lowering of Gn and prolactin levels in postmenopausal women as well as improvement in their bone density.

A decrease in total and LDL cholesterol without any change in HDL and triglyceride level reflects estrogenic action. Similar to estrogen HRT, it increases the risk of deep vein thrombosis by 2–3 times.

Tamoxifen and aromatase inhibitors (AIs), e.g. letrozole, are the established hormonal

treatment options for breast cancer. In early cases tamoxifen is given as postmastectomy adjuvant therapy, while in advanced cases, it is a constituent of palliative treatment. Response rates are high in ER-positive breast carcinomas, but some ER-negative tumours also respond. However, use of tamoxifen for ER negative breast carcinoma (primary as well as metastatic) is usually not recommended. Tamoxifen is the only drug approved for primary as well as metastatic breast carcinoma in premenopausal women. However, two recent trials (SOFT and TEXT) have shown that exemestane (an AI) given along with ovarian suppression reduced chances of relapse of high-risk ER positive breast cancer in premenopausal women, and was a more effective option than tamoxifen plus ovarian suppression. Tamoxifen is also effective in surgically treated cancer of male breast.

Based on large epidemiological studies which have shown 45% reduction in the incidence of ER-positive breast cancer, tamoxifen has been approved for primary prophylaxis of breast cancer in high-risk women. Recurrence rate in ipsilateral as well as contralateral breasts is reduced by tamoxifen. Traditionally, benefit of tamoxifen prophylaxis was considered to be limited to 5 years, but recently the ATLAS trial comparing 5 years vs 10 years of adjuvant tamoxifen, and the 'aTTom' study have shown that disease free survival was higher in women who were treated for 10 years. However, due to greater reduction of risk of contralateral breast cancer by AIs, as well as increased risk of endometrial carcinoma and thromboembolic events, tamoxifen adjuvant therapy of breast carcinoma in postmenopausal women is generally replaced after 2 years by an AI, while in premenopausal women, tamoxifen itself is continued till 5 years postmastectomy.

Improvement in bone mass due to anti-resorptive effect, and in lipid profile are the other benefits of tamoxifen therapy.

Tamoxifen is effective orally; has a biphasic plasma $t_{1/2}$ (10 hours and 7 days) and a long duration of action. Some metabolites of

tamoxifen are more potent antiestrogens. The drug is excreted primarily in the bile.

Dose 20 mg/day in 1 or 2 doses, max. 40 mg/day; TAMOXIFEN, MAMOFEN, TAMODEX 10, 20 mg tabs.

Male infertility: May be used as alternative to clomiphene.

Side effects Hot flashes, vomiting, rashes, vaginal bleeding, vaginal discharge and menstrual irregularities are the side effects. Increased risk of venous thromboembolism is due to estrogenic action on clotting mechanism.

Infrequent side effects are dermatitis, anorexia, depression, mild leucopenia and ocular changes. Tamoxifen is much less toxic than other anticancer drugs.

Toremifene It is a newer congener of tamoxifen with similar actions, but is a weaker ER agonist. Uses and adverse effects are also similar.

Raloxifene This SERM has a different pattern of action than tamoxifen. It is an estrogen partial agonist in bone, on lipid metabolism and cardiovascular system, but an antagonist in endometrium and breast. It has high affinity for both $ER\alpha$ and $ER\beta$, and has a distinct DNA target the 'raloxifene response element' (RRE).

Several long-term multicentric studies have shown that raloxifene prevents bone loss in postmenopausal women; bone mineral density (BMD) may even increase by 0.9–3.4% over years in different bones, particularly the lumbar vertebrae. However, accelerated bone loss occurs when raloxifene is stopped. The risk of vertebral fracture is reduced to half, but not that of long bones. Raloxifene is less efficacious than bisphosphonates in preventing fractures.

In postmenopausal women raloxifene reduces LDL cholesterol, probably by upregulating hepatic LDL receptors. In contrast to estrogen HRT there is no increase in HDL and triglyceride levels. Follow up studies have shown that raloxifene reduces the risk of breast cancer by 65%, though the protection was confined to ER-positive breast cancer.

Raloxifene does not stimulate endometrial proliferation and there is no increase in the risk of endometrial carcinoma. No relief of

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menopausal vasomotor symptoms occurs; rather hot flashes may be induced in some women.

Raloxifene is absorbed orally but has low bioavailability due to extensive first pass glucuronidation. The $t_{1/2}$ is 28 hours and major route of excretion is faeces.

Side effects Hot flashes, leg cramps are generally mild; vaginal bleeding is occasional. The only serious concern is 3-fold increase in risk of deep vein thrombosis and pulmonary embolism. However, similar risk attends estrogen HRT.

Use Raloxifene is a second line drug for prevention and treatment of osteoporosis in postmenopausal women; Ca^{2+} and vit D supplements enhance the benefit. According to British guidelines, raloxifene is not recommended for primary prophylaxis of osteoporotic fractures in postmenopausal women, but is an alternative option for secondary prevention and treatment of vertebral fractures, i.e. in those who have already suffered a fracture. It is also approved for prevention of breast cancer in women with risk factors.

Dose: 60 mg/day;

BONMAX, RALOTAB, ESSERM 60 mg tab.

AROMATASE INHIBITORS

Aromatization of 'A' ring of testosterone and androstenedione is the final and key step in the production of estrogens (estradiol/estrone) in the body. In addition to the circulating hormone, locally produced estrogens appear to play an important role in the development of breast cancer. Though some aromatase inhibitors (AIs) were produced in the past, three newer 'third generation' AIs *Letrozole*, *Anastrozole* and *Exemestane* have demonstrated clinical superiority and are widely used now in the treatment of breast cancer.

Properties of AIs are compared with that of tamoxifen in Table 22.1.

Letrozole It is an orally active nonsteroidal (type 2) compound that reversibly inhibits aromatization including that within the breast cancer cells, resulting in nearly total estrogen deprivation in postmenopausal women. However

Table 22.1: Comparative properties of tamoxifen (SERM) and letrozole/anastrozole (AIs)

Tamoxifen	Letrozole/Anastrozole
1. Estrogen antagonist in breast and blood vessels, but agonist in uterus, bone, liver and pituitary.	1. Inhibits production of estrogens in all tissues. Nearly total estrogen deprivation.
2. Can be used for breast Ca. in premenopausal women as well.	2. Not to be used in premenopausal women.
3. Less effective in delaying recurrence when used as adjuvant therapy after surgery.	3. More effective in delaying recurrence of early stage breast Ca. (adjuvant therapy).
4. Prophylactic use for breast Ca. recurrence usually limited to 5 years.	4. Continues to exert prophylactic effect beyond 5 years.
5. Less delay in disease progression and lower survival advantage in advanced/metastatic breast Ca. than AIs.	5. Greater delay in disease progression and greater survival advantage in palliative treatment of advanced/ metastatic breast Ca.
6. Not effective in failure cases.	6. Effective in tamoxifen failure cases of advanced breast Ca.
7. Causes endometrial hyperplasia, predisposes to endometrial carcinoma.	7. No endometrial hyperplasia/cancer predisposition.
8. No bone loss, no increase in fractures or arthritic symptoms.	8. Accelerates bone loss, predisposes to fractures, arthritic symptoms.
9. Increases risk of venous thromboembolism.	9. No increase in thromboembolic risk.
10. Improves lipid profile; small lowering of LDL Ch.	10. No effect on lipid profile.

SERM—Selective estrogen receptor modulator; AIs—Aromatase inhibitors; Ca.—Carcinoma; LDL Ch—Low density lipoprotein cholesterol

in those with functioning ovaries, estrogen production is not totally blocked. As such, AIs are not recommended in premenopausal women, unless ovaries are removed, or Gn secretion from pituitary is suppressed. Proliferation of estrogen dependent breast carcinoma cells is suppressed to a greater extent than with tamoxifen. Letrozole is rapidly absorbed with 100% oral bioavailability, large volume of distribution, slow metabolism and a $t_{1/2}$ of ~40 hours. Randomized clinical trials have established its utility in:

(a) *Early breast cancer*: Letrozole is a first line drug for adjuvant therapy after mastectomy in ER+ive postmenopausal women. Extended adjuvant therapy with letrozole beyond the standard 5 year tamoxifen treatment continues to afford protection. Replacement of tamoxifen by an AI is now recommended after 2 years (sequential therapy) because AIs do not predispose to thromboembolism and endometrial cancer. Survival is prolonged in patients who have positive axillary lymph nodes.

(b) *Advanced breast cancer*: Current guidelines recommend letrozole as first line therapy because of longer time to disease progression and higher response rate obtained with it compared to tamoxifen. It is also effective as second line treatment when tamoxifen has failed.

Adverse effects Hot flashes, vaginal dryness, nausea, diarrhoea, dyspepsia and thinning of hair are the side effects. Joint pain and stiffness are common; bone loss may be accelerated. However, there is no endometrial hyperplasia or increased risk of endometrial carcinoma. Risk of venous thromboembolism is also not increased, and there is no deterioration of lipid profile.

Dose: 2.5 mg OD oral.

LETOVAL, LETROZ, FEMARA, ONCOLET 2.5 mg tab.

Though contraindicated in premenopausal women, letrozole was clandestinely promoted and tested as an ovulation inducing fertility drug. Use of letrozole for inducing ovulation in infertile women has been banned in India since Oct. 2011.

Anastrozole Another nonsteroidal and reversible (Type 2) AI, more potent than letrozole and suitable for single daily dosing. It accumulates

in the body to produce peak effect after 7-10 days. Anastrozole is useful as adjuvant therapy in early ER+ive breast cancer as well as for palliation of advanced cases in postmenopausal women. In early cases, tumor recurrence time was found to be longer than with tamoxifen. Risk of new tumor appearing in the contralateral breast was also lower with anastrozole. A longer time to disease progression compared to tamoxifen has been obtained in advanced ER+ive breast cancer. Many tamoxifen resistant cases responded with increased survival. Like letrozole, it is also a first line drug for early as well as advanced breast carcinoma in postmenopausal women. Side effects are similar to those with letrozole.

Dose: 1 mg OD.

ALTRAZ, ARMOTRAZ, ANABREZ 1 mg tab.

Exemestane: This steroidal and irreversible (Type 1) inhibitor of aromatase acts like a suicide substrate by covalent binding to the enzyme. As a result >90% suppression of estradiol production is obtained. However, it has weak androgenic activity similar to androstenedione. Exemestane has been found beneficial in early breast cancer by reducing the risk of disease progression when it was substituted for tamoxifen as adjuvant therapy. In advanced breast cancer, longer survival, increased time to disease progression and fewer treatment failures have been obtained with exemestane. It is administered orally and is well tolerated.

Adverse effects are similar to other AIs.

Dose: 25 mg OD oral after meals; those receiving CYP3A4 inducer 50 mg OD.

EXMASIN, XTANE 25 mg tab.

PROGESTINS

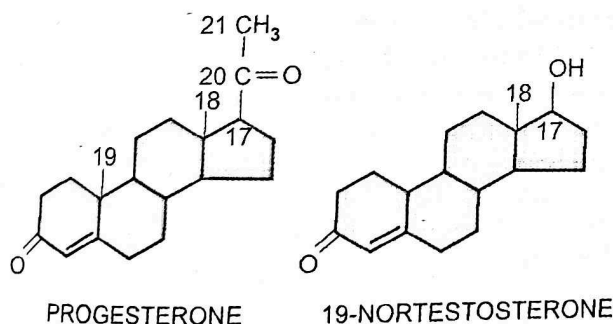
These are substances which convert the estrogen primed proliferative endometrium to secretory and maintain pregnancy in animals spayed after conception (*Progestin* = favouring pregnancy).

At the turn of the last century it became apparent that ovaries secrete two hormones, and that corpus luteum was essential for maintenance of pregnancy. Progesterone was isolated in 1929, but its full therapeutic potential has been

exploited only after the 1950s when a large number of orally active synthetic progestins were developed.

Natural progestin Progesterone, a 21 carbon steroid, is the natural progestin and is derived from cholesterol (see Fig. 20.1). It is secreted by the corpus luteum (10–20 mg/day) in the later half of menstrual cycle under the influence of LH. Its production declines a few days before the next menstrual flow. If the ovum gets fertilized and implants—the blastocyst immediately starts producing chorionic gonadotropin which is absorbed into maternal circulation and sustains the corpus luteum in early pregnancy. Placenta starts secreting lots of estrogens and progesterone from 2nd trimester till term. Men produce 1–5 mg progesterone per day from adrenals and testes; its role if any, in males is not known.

Synthetic progestins A number of synthetic progestins with high oral activity have been produced. These are either progesterone derivatives (21 C) or 19-nortestosterone derivatives, also called 'estrans' (18C).



The progesterone derivatives are almost pure progestins, have weaker antiovarian action and are used primarily as adjuvants to estrogens for HRT in postmenopausal women, threatened abortion, endometriosis, etc. for selective progestational effect. The older 19-nortestosterone derivatives, e.g. *norethindrone* and *lynestrenol* developed in the 1950-60s have additional weak estrogenic, androgenic, anabolic and potent antiovarian action. They are used primarily in combined contraceptive pills. Estrans with a 13-ethyl substitution are called 'gonanes', e.g. *norgestrel*. Gonanes are more potent (especially

the levoisomers, e.g. *levonorgestrel*) and have reduced androgenic activity.

In the 1980-90s a number of other gonane compounds were introduced, of which *desogestrel* has been marketed in India. *Desogestrel* and *norgestimate* are prodrugs. In addition to being very potent progestins they have strong antiovarian action (*gestodene* inhibits ovulation at as low as 40 µg/day dose), and little or no androgenic property. Therefore, they do not antagonise the beneficial action of estrogens on lipid profile and are preferable in women with hyperandrogenemia. High antiovarian potency allows reduction of ethinylestradiol dose when these are combined in oral contraceptives.

The newer 19-norprogesterone derivative *nomegestrol* has weak antiandrogenic property, is less antiovarian, but has strong antiestrogenic effect on endometrium. Adverse effects on lipid profile and glucose tolerance appear to be lacking.

PROGESTERONE DERIVATIVES

Medroxyprogesterone acetate
Megestrol acetate
Dydrogesterone
Hydroxyprogesterone caproate

Newer compound
Nomegestrol acetate

19-NORTESTOSTERONE DERIVATIVES

Estrans	Gonanes
Norethindrone	Levonorgestrel
(Norethisterone)	Desogestrel
Lynestrenol	Norgestimate
(Ethinylestrenol)	Gestodene
Allylestrenol	

Actions

The main function of progesterone is preparation of the uterus for nidation and maintenance of pregnancy. The latter is due to prevention of endometrial shedding, decreased uterine motility and inhibition of immunological rejection of the foetus, since progesterone depresses T-cell function and cell-mediated immunity (CMI).

1. Uterus Progesterone brings about secretory changes in the estrogen primed endometrium:

hyperemia, tortuosity of glands and increased secretion occurs while epithelial proliferation is halted. It is lack of progestational support which causes mucosal shedding during menstruation.

Continued action of progesterone (when pregnancy occurs) brings about decidual changes in endometrium—stroma enlarges and becomes spongy, glands atrophy, and sensitivity of myometrium to oxytocin is decreased.

2. **Cervix** Progesterone converts the watery cervical secretion induced by estrogens to viscid, scanty and cellular secretion which is hostile to sperm penetration.

3. **Vagina** Progesterone induces pregnancy like changes in the vaginal mucosa: leukocyte infiltration of cornified epithelium occurs.

4. **Breast** Progesterone causes proliferation of acini in the mammary glands. Cyclic epithelial proliferation and turnover occurs during luteal phase, but continuous exposure to progesterone during pregnancy halts mitotic activity and stabilizes mammary cells. Acting in concert with estrogens, it prepares the breast for lactation. Withdrawal of these hormones after delivery causes release of prolactin from pituitary and milk secretion starts.

5. **CNS** High circulating concentration of progesterone (during pregnancy) appears to have a sedative effect. It can also affect mood.

6. **Body temperature** A slight (0.5°C) rise in body temperature by resetting the hypothalamic thermostat and increasing heat production is induced. This is responsible for the higher body temperature seen during the luteal phase.

7. **Respiration** Progestins in relatively higher doses stimulate respiration, as occurs during pregnancy.

8. **Metabolism** Prolonged use of oral contraceptives impairs glucose tolerance in some women. This has been ascribed to the progestational component. Progestins, especially those with androgenic activity (19-nortestosterone derivatives) tend to raise LDL and lower HDL cholesterol levels. This may counteract the beneficial effect of estrogen used concurrently

for HRT or in contraceptives. Micronized oral progesterone formulation (referred to as 'natural progesterone') does not affect the beneficial effect of estrogen on LDL and HDL cholesterol.

9. **Pituitary** Progesterone is a weak inhibitor of Gn secretion from pituitary. It exerts negative feedback primarily at the level of hypothalamic pulse generator—reducing the frequency of GnRH pulses. However, the amount of LH at each pulse may increase. Administration of progestin during the follicular phase suppresses the preovulatory LH surge and prevents ovulation. It synergises with estrogen for the antiovaratory action. The gonanes markedly suppress GnRH and are potent antiovaratory drugs.

Mechanism of action

Unlike other steroid receptors, the progesterone receptor (PR) has a limited distribution in the body: confined mostly to the female genital tract, breast, CNS and pituitary. The PR is normally present in the nucleus of target cells. Analogous to ER, upon hormone binding the PR undergoes dimerization, attaches to progesterone response element (PRE) of target genes and regulates transcription through coactivators. The antiprogestins also bind to PR, but the conformation assumed is different from agonist bound receptor and opposite effects are produced by interaction with corepressors.

The PR exists in a short (PR-A) and a longer (PR-B) isoforms. The two have differing activities, but because the ligand binding domain of both is identical, all agonists and antagonists display similar binding properties for them. Tissue selective modulation of PR has not yet been possible, as has been in the case of ER. Progesterone also acts on cell membrane receptors in certain tissues and produces rapid effects, like Ca^{2+} release from spermatozoa and oocyte maturation, but the physiological significance of these receptors is not clear.

Estrogens have been shown to increase PR density, whereas progesterone represses ER and enhances local degradation of estradiol.

Pharmacokinetics

Progesterone, unless specially formulated, is inactive orally because of high first-pass metabolism in liver. It is mostly injected i.m. in oily solution. Even after an i.m. dose it is rapidly

cleared from plasma and has a short $t_{1/2}$ (5–7 min). Nearly complete degradation occurs in the liver—major product is pregnanediol which is excreted in urine as glucuronide and sulfate conjugates. However, effects of progesterone last longer than the hormone itself.

A micronized formulation of progesterone has been developed for oral administration. Microfine particles of the drug are suspended in oil and dispensed in gelatin capsules. Absorption occurs through lymphatics bypassing the liver. Though bioavailability is low, effective concentrations are attained in the body.

Most of the synthetic progestins are orally active and are metabolized slowly; have plasma $t_{1/2}$ ranging from 8–24 hours.

Preparations and dose

1. Progesterone: 10–100 mg i.m. (as oily solution) OD; PROGEST, PROLUTON, GESTONE 50 mg/ml inj., 1 and 2 ml amp; 100–400 mg OD oral: NATUROGEST, DURAGEST, OGEST 100, 200, 400 mg caps containing micronized oily suspension.
2. Hydroxyprogesterone caproate: 250–500 mg i.m. at 2–14 days intervals; PROLUTON DEPOT, MAINTANE INJ, PROCAPRIN 250 mg/ml in 1 and 2 ml amp.
3. Medroxyprogesterone acetate: 5–20 mg OD–BD oral, 50–150 mg i.m. at 1–3 month interval; FARLUTAL 2.5, 5, 10 mg tab., PROVERA, MEPRATE, MODUS 2.5, 10 mg tab, DEPOT-PROVERA 150 mg in 1 ml inj. (as contraceptive). Has weak androgenic and antiestrogenic property.
4. Dydrogesterone: 5–10 mg OD/TDS oral; DUPHASTON 5 mg tab. It has poor antioviulatory action: may be preferred when contraceptive effect is not required.
5. Norethindrone (Norethisterone): 5–10 mg OD–BD oral; PRIMOLUT-N, STYPTIN, REGESTRONE, NORGEST 5 mg tab; REGESTRONE HRT, NORETA HRT 1 mg tab (for HRT); NORISTERAT 200 mg/ml inj (as enanthate) for contraception 1 ml i.m every 2 months; has androgenic, anabolic and antiestrogenic activity.
6. Lynestrenol (Ethinylestrenol): 5–10 mg OD oral; ORGAMETRIL 5 mg tab. Has additional androgenic, anabolic and estrogenic activity.
7. Allylestrenol: 10–40 mg/day; GESTANIN, FETUGARD, MAINTANE 5 mg tab. Has been especially used for threatened/habitual abortion, PROFAR 25 mg tab.
8. Levonorgestrel: 0.1–0.5 mg/day; DUOLUTON-L, OVRAL 0.25 mg+ ethinylestradiol 0.05 mg tab. Has androgenic, anabolic and antiestrogenic property.
9. Desogestrel 150 µg + ethinylestradiol 30 µg (NOVELON) tab, 1 tab OD 3 week on 1 week off cyclic therapy. (Other preparations are given with oral contraceptives).

Adverse effects

- Breast engorgement, headache, rise in body temperature, edema, esophageal reflux, acne and mood swings may occur with higher doses.
- Irregular bleeding or amenorrhoea can occur if a progestin is given continuously.
- The 19-nortestosterone derivatives lower plasma HDL levels—may promote atherogenesis, but progesterone and its derivatives have no such effect.
- Long-term use of progestin in HRT may increase the risk of breast cancer.
- Blood sugar may rise and diabetes may be precipitated by long-term use of potent agents like levonorgestrel.
- Intramuscular injection of progesterone is painful.
- Given in early pregnancy, progestins can cause masculinization of female foetus and other congenital abnormalities.

Use of a progestin for diagnosis of pregnancy is contraindicated.

Uses

1. *As contraceptive* Most common use (see later).

2. *Hormone replacement therapy (HRT)* In nonhysterectomised postmenopausal women estrogen therapy is supplemented with a progestin for 10–12 days each month to counteract the risk of inducing endometrial carcinoma. Micronized oral progesterone lacking androgenic activity is preferred. Progesterone may be omitted if very low dose estrogen is used.

3. *Dysfunctional uterine bleeding* Frequent or heavy irregular menstrual bleeding is often associated with anovular cycles occurring near menopause. Continued estrogenic action on endometrium (causing hyperplasia) without progesterone induction and withdrawal resulting in incomplete sloughing leads to irregular, often profuse bleeding. A progestin in relatively large doses (medroxyprogesterone acetate 10–20 mg/day or norethindrone 5–10 mg/day or equivalent) promptly stops bleeding and keeps it in abeyance as long as given, followed by bleeding on

stoppage. Subsequently cyclic treatment at lower doses regularizes and normalizes menstrual flow. A progestin with inherent estrogenic action is preferred; often supplemental dose of estrogen is combined, or a combination oral contraceptive pill is given cyclically for 3–6 months.

4. Endometriosis This condition results from presence of endometrium at ectopic sites. Manifestations are dysmenorrhoea, painful pelvic swellings and infertility. Continuous administration of progestin induces an anovulatory, hypo-estrogenic state by suppressing Gn release. The direct action on endometrium prevents bleeding in the ectopic sites by suppressing menstruation. Treatment for a few months may cause atrophy and regression of the ectopic masses. Therapy can be withdrawn in many cases after 6 months without reactivation, but return of fertility is not certain. Progestin treatment of endometriosis is inexpensive and generally well tolerated, but not all cases respond and recurrences are frequent. Initial progestin therapy is often replaced by cyclic treatment with an estrogen-progestin contraceptive pill given for 3–6 months. GnRH agonist and danazol are alternatives used in nonresponsive cases. Intrauterine levonorgestrel system has also been used in refractory cases. Aromatase inhibitors have been tried in resistant cases, but their beneficial role is not established.

5. Premenstrual syndrome/tension Some women develop headache, irritability, fluid retention, distention and breast tenderness a few days preceding menstruation. When depression predominates, it has been labelled 'premenstrual dysphoric disorder'. Fluoxetine and other SSRIs given daily on symptom days dampen irritability and mood changes in majority of women. Severe premenstrual syndrome requires suppression of ovulation by combined estrogen-progesterone treatment given cyclically. Relatively higher dose of progestin is generally used. Ovarian suppression with GnRH agonist may be required in nonresponsive cases. Progestins are added to estrogen when it is used for severe dysmenorrhoea.

6. Threatened/habitual abortion In most such patients there is no progesterone deficiency, and administration of excess hormone is of no benefit. Progestin therapy may be considered in those patients who have established deficiency. However, progestins are briskly promoted and almost routinely prescribed in India. There is some evidence of its efficacy in preventing premature delivery in high risk pregnancy. If such use is made—a pure progestin without estrogenic or androgenic activity should be employed.

7. Endometrial carcinoma Progestins are palliative in about 50% cases of advanced/metastatic endometrial carcinoma. High doses are needed.

IMPEDED ANDROGEN / PROGESTIN

Danazol It is an orally active isoxazol derivative of ethisterone which has weak androgenic, anabolic, progestational and glucocorticoid activities. However, the most prominent action is suppression of Gn secretion from pituitary in both men and women → inhibition of testicular/ovarian function. In menstruating women, the midcycle surge of FSH and LH is suppressed, but basal level of these Gns is not much affected. In addition, danazol suppresses gonadal function directly by inhibiting steroidogenic CYP enzymes, but not the aromatase needed for estrogen production. In women, endometrial atrophy occurs over few weeks and amenorrhoea may supervene. Danazol has also been labelled as an impeded/attenuated androgen, because it binds to the androgen receptor and translocates it into the nucleus to induce production of some androgen-specific RNA. Danazol is metabolized with a $t_{1/2}$ of 12–18 hours.

Dose: 200–600 mg/day;

DANAZOL, LADOGAL, DANOGEN, GONABLOK 50, 100, 200 mg cap.

Uses

- 1. Endometriosis** Danazol causes improvement in ~75% cases by inhibiting ovarian function. Relief of dysmenorrhoea is prompt. Pain, dyspareunia and excessive bleeding regress slowly. Estrogen-progestin combination contraceptive is the first line drug. Non-responsive cases are treated by a high dose progestin alone. The Gn RH agonists given by intranasal spray daily or by monthly injection for 6–12 months are another option (see Ch. 17). Danazol is infrequently used now because of androgenic side effects and risk of liver damage.
- 2. Menorrhagia** Danazol reduces menstrual blood loss. Usually complete amenorrhoea does not occur with 200 mg/day. It is a second line drug to an oral progestin.

3. *Fibrocystic breast disease* (chronic cystic mastitis): 3-6 months danazol treatment causes improvement with decrease in pain, nodularity and engorgement in ~75% cases.

4. *Hereditary angioneurotic edema* Danazol is a 17α alkylated steroid. Like other such compounds, it has prophylactic effect in this condition by inducing complement (C1) esterase inhibitor (see p. 324).

Side effects are frequent and dose related. Complete amenorrhoea occurs with higher doses. Androgenic side effects are acne, hirsutism, decreased breast size, deepening of voice, edema and weight gain. Loss of libido in men, hot flashes in women and night sweats, muscle cramps, g.i. upset, elevation of hepatic enzymes are the other problems.

ANTI-PROGESTIN

Mifepristone It is a 19-norsteroid with potent antiprogestational and significant antiglucocorticoid, antiandrogenic activity.

Given during the follicular phase, its anti-progestin action results in attenuation of the midcycle Gn surge from pituitary. This causes slowing of follicular development and delay/failure of ovulation. If given during the luteal phase, it prevents secretory changes by blocking progesterone action on the endometrium. Later in the cycle, it blocks progesterone support to the endometrium, unrestrains PG release from it—this stimulates uterine contractions. Mifepristone also sensitizes the myometrium to PGs and induces menstruation. If implantation has occurred, it blocks decidualization, so that the conceptus is dislodged, HCG production falls, secondary luteolysis occurs—endogenous progesterone secretion decreases and cervix is softened. All these effects lead to abortion.

Mifepristone is a partial agonist and competitive antagonist at both A and B forms of PR. In the absence of progesterone (during anovulatory cycles or after menopause) it exerts weak progestational activity and induces predecidual changes. Therefore, it is now regarded as 'progesterone receptor modulator' rather than 'pure antagonist.' The weak agonistic action is not manifest in the presence of progesterone.

The antiglucocorticoid action of usual doses is also not manifest in normal individuals because blockade of the negative feedback at hypothalamic-pituitary level elicits ACTH release, so that

plasma cortisol rises and overcomes the direct antiglucocorticoid action. Amelioration of Cushing's symptoms has been obtained with large doses (see p. 319).

Pharmacokinetics Mifepristone is active orally, but bioavailability is only 25%. It is largely metabolized in liver by CYP 3A4 and excreted in bile; some enterohepatic circulation occurs; $t_{1/2}$ is 20-36 hr.

Interaction with CYP 3A4 inhibitors (erythromycin, ketoconazole) and inducers (rifampin, anticonvulsants) has been reported.

Uses

1. *Termination of pregnancy* of up to 7 weeks: 600 mg as single oral dose causes complete abortion in 60-85% cases. To improve the success rate, current recommendation is to follow it up 48 hours later by a single 400 μ g oral dose of misoprostol. This achieves >90% success rate and is the accepted nonsurgical method of early first trimester abortion. In place of oral misoprostol, a 1 mg gemeprost pessary can be inserted intravaginally. Mifepristone administered within 10 days of a missed period results in an apparent late heavy period (with dislodged blastocyst) in upto 90% cases.

This procedure is generally safe, but prolonged bleeding and failed abortion are the problems in some cases. Anorexia, nausea, tiredness, abdominal discomfort, uterine cramps, loose motions are the other side effects.

2. *Cervical ripening* 24-30 hours before attempting surgical abortion or induction of labour, mifepristone 600 mg results in softening of cervix; the procedure is facilitated.

3. *Postcoital contraceptive* Mifepristone 600 mg given within 72 hr of intercourse interferes with implantation and is a highly effective method of emergency contraception. The subsequent menstrual cycle, however, is disturbed.

4. *Once-a-month contraceptive* A single 200 mg dose of mifepristone given 2 days after midcycle each month causes luteolysis and prevents conception on most occasions. Administering mifepristone in late luteal phase to

dislodge the embryo (if present) and to ensure menstruation irrespective of conception, has also been tried. These alternative methods of contraception, though attractive, may prolong/disrupt the next menstrual cycle, and thus cannot be used continuously. There is little experience and little justification to use these methods on regular basis.

5. Induction of labour By blocking the relaxant action of progesterone on uterus of late pregnancy, mifepristone can promote labour. It may be tried in cases with intrauterine foetal death and to deliver abnormal foetuses.

6. Cushing's syndrome Mifepristone may have palliative effect due to glucocorticoid receptor blocking property, but efficacy is low. It may be tried in case the causative tumour is nonresectable.

Other proposed uses are—in endometriosis, uterine fibroid, certain breast cancers and in meningioma.

MIFEGEST, MIFEPRIN 200 mg tab.

T-PILL + MISO, ABORTOM: Mifepristone 200 mg (3 tabs) + Misoprostol 200 µg (2 tabs); for medical termination of pregnancy of upto 49 days: take 3 tablets of T-PILL on day 1, followed on day 3 by 2 tablets of MISO.

Ulipristal It is a recently approved 'selective progesterone receptor modulator' (SPRM) for use as emergency contraceptive. It inhibits ovulation by suppressing LH surge as well as by direct effect on follicular rupture. In addition, its action on endometrium can interfere with implantation. In clinical trials the efficacy of ulipristal (30 mg) as emergency contraceptive has been rated equal to that of levonorgestrel (1.5 mg) when taken within 72 hours of unprotected intercourse, and to be more effective when taken between 72–120 hours. Thus, it may have an advantage, if the woman misses to take the drug within 72 hours.

Headache, nausea, vomiting, abdominal pain and menstrual delay are the side effects, as they are with levonorgestrel. Few cases of ovarian cysts are reported.

The antiglucocorticoid activity of ulipristal is weaker than that of mifepristone.

Onapristone (a pure progesterone antagonist) and Gestinone (more efficacious in endometriosis) are the other antiprogestins.

HORMONAL CONTRACEPTIVES

These are hormonal preparations used for reversible suppression of fertility. Because of

our alarming population trends, antifertility drugs are a growing need. In developing countries particularly, the mortality rate has declined and birth rate has increased due to urbanization. In the earlier part of the 20th century, methods of contraception used (condoms, diaphragms, spermicidal creams, foam tablets, etc.) were intimately related to sexual intercourse, therefore, despised by most couples. These devices have a higher failure rate as well. Rock and Pincus (1955) announced the successful use of an oral progestin for contraception, separating fertility control from coitus.

It was soon discovered that addition of a small quantity of an estrogen enhanced their efficacy; combined pills have become the most popular method of contraception, particularly because the hormone content of the pills has been reduced, minimizing the potential harm and affording other health benefits.

FEMALE CONTRACEPTION

Over 100 million women worldwide are currently using hormonal contraceptives. With these drugs, fertility can be suppressed at will, for as long as desired, with almost 100% confidence and complete return of fertility on discontinuation. The efficacy, convenience, low cost and overall safety of oral contraceptives (OCs) has allowed women to decide whether and when they want to become pregnant and to plan their activities. A variety of oral and parenteral preparations are now available offering individual choices.

TYPES OF METHODS

Oral

1. Combined pill It contains an estrogen and a progestin in fixed dose for all the days of a treatment cycle (monophasic). With accumulated experience, it has been possible to reduce the amount of estrogen and progestin in the 'second generation' OC pills without compromising efficacy, but reducing side effects and complications. 'Third generation' pills containing newer progestins like desogestrel with

Table 22.2: Oral contraceptive preparations

PROGESTIN		ESTROGEN		TRADE NAME
COMBINED PILLS				
1. Norgestrel	0.3 mg	Ethinylestradiol	30 µg	MALA-D (21 tabs + 7 ferrous sulfate 60 mg tabs.)
2. Norgestrel	0.5 mg	Ethinylestradiol	50 µg	OVRAL-G 20 tabs.
3. Levonorgestrel	0.25 mg	Ethinylestradiol	50 µg	OVRAL, DUOLUTON-L 21 tabs.
4. Levonorgestrel	0.15 mg	Ethinylestradiol	30 µg	OVRAL-L, OVIPAUS 21 tabs.
5. Levonorgestrel	0.1 mg	Ethinylestradiol	20 µg	LOETTE, OVILOW, COMBEE 21 tabs
6. Desogestrel	0.15 mg	Ethinylestradiol	30 µg	NOVELON 21 tabs.
7. Desogestrel	0.15 mg	Ethinylestradiol	20 µg	FEMILON 21 tabs.
PHASED PILL				
1. Levonorgestrel	50-75 -125 µg	Ethinylestradiol	30-40 -30 µg	TRIQUILAR (6 + 5 + 10 tablets)
2. Norethindrone	0.5-0.75 -1.0 mg	Ethinylestradiol	35-35 -35 µg	ORTHONOVUM 7/7/7 (7+7+7 tabs)
POSTCOITAL PILL				
1. Levonorgestrel	0.25 mg	Ethinylestradiol	50 µg	OVRAL, DUOLUTON-L (2+2 tabs)
2. Levonorgestrel	0.75 mg 1.5 mg	-Nil -Nil-	—	NORLEVO, ECEE2 (1+1 tab)— IPILL, NOFEAR-72, OH GOD (1 tab)
MINI PILLS				
1. Norethindrone	0.35 mg	-Nil-	—	MICRONOR*, NOR-QD*
2. Norgestrel	75 µg	-Nil-	—	OVRETTE*

*Not marketed in India.

improved profile of action have been introduced in the 1990s. Ethinylestradiol 30 µg daily is considered threshold but can be reduced to 20 µg/day if a progestin with potent antiovaratory action is included. The progestin is a 19-nortestosterone because these compounds have potent antiovaratory action. Used alone the ovulation inhibitory dose (per day) of the currently used progestins is estimated to be—levonorgestrel 60 µg, desogestrel 60 µg, norgestimate 200 µg, gestodene 40 µg, but the amount in the pill is 2–3 times higher to attain 100% certainty. While both estrogens and progestins synergise to inhibit ovulation, the progestin ensures prompt bleeding at the end of a cycle and blocks the risk of developing endometrial carcinoma due to the estrogen. One tablet is taken daily for 21 days, starting on the 5th day of menstruation. The next course is started after a gap of 7 days in which bleeding occurs. Thus, a cycle

of 28 days is maintained. Calendar packs of pills are available (Table 22.2). This is the most popular and most efficacious method.

2. Phased pill Triphasic regimens have been introduced to permit reduction in total steroid dose without compromising efficacy by mimicking the normal hormonal pattern in a menstrual cycle. The estrogen dose is kept constant (or varied slightly between 30–40 µg), while the amount of progestin is low in the first phase and progressively higher in the second and third phases.

Phasic pills are particularly recommended for women over 35 years of age and for those with no withdrawal bleeding or breakthrough bleeding while on monophasic pill, or when other risk factors are present. However, evidence of superiority of triphasic pills over monophasic pills is insufficient.

3. *Progestin-only pill (Minipill)* It has been devised to eliminate the estrogen, because many of the long-term risks have been ascribed to this component. A low-dose progestin-only pill is an alternative for women in whom an estrogen is contraindicated. It is taken daily continuously without any gap. The menstrual cycle tends to become irregular and ovulation occurs in 20–30% women, but other mechanisms (hostile cervical mucus and interference with implantation) contribute to the contraceptive action. The efficacy is lower (96–98%) compared to 98–99.9% with combined pill. Pregnancy should be suspected if amenorrhoea of more than 2 months occurs. This method is not popular.

4. *Emergency (postcoital) pill* These are for use in a woman not taking any contraceptive who had a sexual intercourse risking unwanted pregnancy. The most commonly used and standard regimen is—

- Levonorgestrel 0.75 mg two doses 12 hours apart, or 1.5 mg single dose taken as soon as possible, but before 72 hours of unprotected intercourse.

Trials conducted globally by a WHO task force on postovulatory methods of fertility control have found this regimen to be 2–3 times more effective and better tolerated than the earlier 'Yuzpe method' which used levonorgestrel 0.5 mg + ethinylestradiol 0.1 mg, two doses at 12 hours interval within 72 hours of exposure. Incidence of nausea and vomiting is ~6% in the progestin only regimen compared to 20–50% with the estrogen+progestin regimen. Headache and other side effects are also milder. However, the next period may be delayed or disrupted with either regimens.

Recently (2010) a SPRM ulipristal has been approved for emergency contraception.

- Ulipristal 30 mg single dose as soon as possible, but within 120 hours of intercourse.

It is an equally effective (failure rate 1–3% compared to levonorgestrel 2–4%) and equally well tolerated alternative method now available with an extended window of protective action (see p. 346).

Another antiprogestin that has been used, particularly in Europe and China, with high success rate and few side effects is—

- Mifepristone 600 mg single dose taken within 72 hours of intercourse.

Emergency postcoital contraception should be reserved for unexpected or accidental exposure (rape, condom rupture) only, because all emergency regimens have higher failure rate and side effects than regular low-dose combined pill.

Injectable

These contraceptives have been developed to obviate the need for daily ingestion of pills. They are given i.m. as oily solution; are highly effective; over 50 million women have used them so far. Their major limitations are:

(a) Animal data has indicated carcinogenic potential, but there is no proof from human studies despite >30 years of experience. No increase in overall risk of cervical, ovarian or hepatic cancer has been noted by a WHO sponsored study. Breast cancer risk may be slightly increased in younger women (< 35 yr). The logistics of administration and supervision for mass use are considered inadequate in developing countries and use-effectiveness in field conditions is low. In India approval has been granted for use only under close supervision, but not on mass scale under the National Programme.

(b) Menstrual irregularities, excessive bleeding or amenorrhoea are very common; incidence of amenorrhoea increases with increasing duration of use. Return of fertility may take 6–30 months after discontinuation; permanent sterility may occur in some women. Weight gain and headache occur in >5% subjects. Bone mineral density may decrease after 2–3 years of use (especially with DMPA) due to low estrogen levels caused by Gn suppression. This may also produce menopause-like symptoms (hot flashes, vaginal dryness, reduced libido).

Only the *long-acting progestin alone* injections are in use now. They are injected once in

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2-3 months depending on the steroid and its dose. Two compounds have been marketed:

- (a) Depot medroxyprogesterone acetate (DMPA) 150 mg at 3-month intervals. After i.m. injection peak blood levels are reached in 3 weeks and decline with a $t_{1/2}$ of ~ 50 days.

DEPOT-PROVERA 150 mg in 1 ml vial for deep i.m. injection during first 5 days of menstrual cycle. Repeat every 3 months.

- (b) Norethindrone (Norethisterone) enanthate (NEE) 200 mg at 2-month intervals.

NORISTERAT 200 mg in 1 ml vial for deep i.m. injection during first 5 days of menstrual cycle. Repeat every 2 months.

The most important drawback is complete disruption of menstrual bleeding pattern or total amenorrhoea (more common with DMPA). It is not suitable for adolescent girls and lactating mothers. Use of DMPA is generally restricted to women who are unlikely to use other contraceptives effectively. NEE is shorter acting and failure rates have been higher than with DMPA. All fixed dose combination injectable preparations of synthetic estrogens and progestins are not allowed in India and discontinued in most countries.

Implants These are drug delivery systems implanted under the skin, from which the steroid is released slowly over a period of 1-5 years. They consist of either—

- (a) Biodegradable polymeric matrices—do not need to be removed on expiry.
(b) Non-biodegradable rubber membranes—have to be removed on expiry.

NORPLANT: A set of 6 capsules each containing 36 mg levonorgestrel (total 216 mg) for subcutaneous implantation is available in some countries, but has been discontinued in the USA. It works for up to 5 years.

A progestin impregnated intrauterine insert (PROGESTASERT) has been introduced in some countries. It contains 52 mg of levonorgestrel which primarily acts locally on endometrium. The device remains effective for 5 years, but efficacy is rated lower.

Transdermal contraceptive A transdermal patch containing a progestin norelgestromin and ethinylestradiol for once weekly application for 3 weeks followed by one week gap is available in some countries.

MECHANISM OF ACTION

Hormonal contraceptives interfere with fertility in many ways; the relative importance depends on the type of method. This is summarized in Table 22.3.

1. Inhibition of Gn release from pituitary by reinforcement of normal feedback inhibition. The progestin reduces frequency of LH secretory pulses (an optimum pulse frequency is required for triggering ovulation) while the estrogen primarily reduces FSH secretion. Both synergise to inhibit midcycle LH surge. When the combined pill is taken both FSH and LH are reduced and the midcycle surge is abolished. As a result, follicles fail to develop and fail to rupture. *Suppression of ovulation* is the primary mode of action of combined oral pill.

The low dose progestin-only pill and progestin-only injectable regimen also attenuate LH surge but less consistently—ovulation may occur irregularly in ~ 1/3 cycles. Postcoital pill when taken before ovulation can dampen LH surge and inhibit ovulation in some cases. However, pregnancy is still prevented by direct actions on the genital tract.

2. Thick *cervical mucus* secretion *hostile to sperm penetration* is evoked by progestin action. As such, this mechanism can operate with all methods except postcoital pill.
3. Even if ovulation and fertilization occur, the blastocyst may fail to implant because *endometrium* is either hyperproliferative or hypersecretory or atrophic and in any case *out of phase* with fertilization—not suitable for nidation. This action appears to be the most important in case of minipills and postcoital pill.
4. *Uterine and tubal contractions* may be modified to disfavour fertilization. This action is uncertain but probably contributes to the efficacy of minipills and postcoital pill.
5. The postcoital pill may *dislodge* a just implanted blastocyst or may interfere with fertilization/implantation.

Practical considerations

1. Discontinuation of all OCs results in full return of fertility within 1–2 months. There may even be a rebound increase in fertility—chances of multiple pregnancy are more if conception occurs within 2–3 cycles. With injectable preparations, return of fertility is delayed. The cycles take several months to normalize or may not do so at all. They are to be used only if the risk of permanent infertility is acceptable.
2. If a woman on combined pills misses to take a tablet, she should be advised to take two tablets the next day and continue as usual. If more than 2 tablets are missed, then the course should be interrupted, an alternative method of contraception used and next course started on the 5th day of bleeding.
3. If pregnancy occurs during use of hormonal contraceptives—it should be terminated by suction-aspiration, because the risk of malformations, genital carcinoma in female offspring and undescended testes in male offspring is increased.
4. While for most women a pill containing 30 µg ethinylestradiol is sufficient, the obese may require a pill containing 50 µg, and only 20 µg may be appropriate/sufficient for those with cardiovascular risk factor, as well as for those above 40 years age.

5. If breakthrough bleeding occurs—switch over to a pill containing higher estrogen dose.
6. In women with contraindications for estrogen (see below), a progestin only contraceptive may be used.

ADVERSE EFFECTS

Since contraceptives are used in otherwise healthy and young women, adverse effects, especially long-term consequences, assume great significance. The adverse effects are dose dependent; most of the early data with high-dose preparations cannot be directly extrapolated to the present-day low-dose preparations which carry relatively minor risk. The following applies primarily to combined oral pill which has been most extensively used.

A. Nonserious side effects These are frequent, especially in the first 1–3 cycles, and then disappear gradually.

1. Nausea and vomiting: similar to morning sickness of pregnancy.
2. Headache is generally mild; migraine may be precipitated or worsened.
3. Breakthrough bleeding or spotting: especially with progestin-only preparations. Shift to triphasic pill may overcome the breakthrough bleeding. Rarely bleeding fails to occur during the gap period. Prolonged amenorrhoea or cycle disruption occurs in few women taking injectables or minipill.
4. Breast discomfort.

B. Side effects that appear later

1. Weight gain, acne and increased body hair may be noted due to androgenic action of older 19-nortestosterone progestins. The newer ones like desogestrel are relatively free of this effect.
2. Chloasma: pigmentation of cheeks, nose and forehead, similar to that occurring in pregnancy.
3. Pruritus vulvae is infrequent.
4. Carbohydrate intolerance and precipitation of diabetes in few subjects taking high dose preparations; but this is unlikely with the present pills. Many large studies have found no link between OC use and development of diabetes.

5. Mood swings and mental depression can occur in some women. Abdominal distention is occasional, especially reported with progesterone-only contraceptives.

C. Serious complications

1. *Leg vein thrombosis and pulmonary embolism:* The older preparations increased the incidence of venous thromboembolism, but this is found to be less marked (only 2–3 patients per 1000 women years) with the newer reduced steroid content pills. However, even low-dose pills pose significant risk in women >35 years of age, diabetics, hypertensives and in those who smoke. The excess risk is due to the estrogen component of the OC, and normalizes shortly after stopping the OC.

2. *Coronary and cerebral thrombosis resulting in myocardial infarction or stroke:* A 2 to 6-fold increase in risk was estimated earlier, but recent studies have demonstrated only small increase in incidence with the low dose pills in the absence of other risk factors. Women above 35-year age are particularly at risk.

The estrogen component of OC has been mainly held responsible for venous thromboembolism, while both estrogen and progestin have been blamed for the arterial phenomena. The mechanisms involved may be:

- Increase in blood clotting factors (coagulability is enhanced).
- Decreased antithrombin III.
- Decreased plasminogen activator in endothelium.
- Increased platelet aggregation.

3. *Rise in BP:* Occurred in 5–10% women taking the earlier pills. This again is less frequent and smaller in magnitude with the low-dose pills of today. If the BP rises, best is to stop OCs: the BP normalizes in the next 3–6 months. Both the estrogen and progestin components are responsible for this effect, probably by increasing plasma angiotensinogen level and renin activity which have been found to be raised during OC use. Aldosterone secretion is enhanced resulting in salt and water retention.

4. Estrogen tends to raise plasma HDL/LDL ratio (beneficial), but the progestin nullifies this benefit. Lipid profile is not significantly altered by low dose OCs, except that triglyceride level may rise marginally which poses no excess risk.

5. *Genital carcinoma:* An increased incidence of vaginal, cervical, and breast cancers was feared on the basis of animal data, but extensive epidemiological data over the past 30 years has repeatedly shown that oral as well as injected contraceptives do not increase the occurrence of these cancers in the general population. However, risk is increased in predisposed individuals. Growth of already existing hormone dependent tumour may be hastened.

Epidemiological data has recorded minor increase in breast cancer incidence among current OC users, but not among past users. Since breast cancer is rare in young women, this finding is considered inconsequential.

A protective effect against endometrial carcinoma has been shown for the progestin component. Prolonged suppression of gonadotropic stimulation of ovary may account for the lower incidence of ovarian malignancy noted in contraceptive users.

6. *Benign hepatomas:* which may rupture or turn malignant; incidence of this rare tumour appears to be slightly higher in OC users.

7. *Gallstones:* Estrogens increase biliary cholesterol excretion; incidence of gallstones is slightly higher in women who are taking OCs, or after long-term use.

Contraindications

The combined oral contraceptive pill is absolutely contraindicated in:

1. Thromboembolic, coronary and cerebrovascular disease or a history of it.
2. Moderate-to-severe hypertension; hyperlipidaemia.
3. Active liver disease, hepatoma or h/o jaundice during past pregnancy.
4. Suspected/overt malignancy of genitals/ breast.
5. Porphyria.
6. Impending major surgery—to avoid excess risk of postoperative thromboembolism. Estrogen

containing contraceptive should be stopped 4 weeks before surgery.

Relative contraindications (requiring avoidance/cautious use under supervision)

1. Diabetes: control may be vitiated.
2. Obesity
3. Smoking
4. Undiagnosed vaginal bleeding
5. Uterine leiomyoma: may enlarge with estrogenic preparations; progestin only pills can be used.
6. Mentally ill
7. Age above 35 years
8. Mild hypertension
9. Migraine
10. Gallbladder disease.

Interactions Contraceptive failure may occur if the following drugs are used concurrently:

(a) *Enzyme inducers*: phenytoin, phenobarbitone, primidone, carbamazepine, rifampin, ritonavir. Metabolism of estrogenic as well as progestational component is increased.

(b) *Suppression of intestinal microflora*: tetracyclines, ampicillin, etc. Deconjugation of estrogens excreted in bile fails to occur → their enterohepatic circulation is interrupted → blood levels fall.

With both types of interacting drugs, it is wise to switch over to a preparation containing 50 µg of ethinylestradiol or to use alternative method of contraception. Rifampin is usually taken for a long time and is such a potent enzyme inducer that alternative contraception should be advised.

Other health benefits Apart from benefits due to prevention of unwanted pregnancy and the risks during delivery, use of oral contraceptives affords certain other beneficial effects as a bonus:

- Lower risk of developing endometrial and ovarian carcinoma; probably colorectal cancer as well.
- Reduced menstrual blood loss and associated anaemia; cycles if irregular become regular; premenstrual tension, dysmenorrhoea and menorrhagia are ameliorated.

- Endometriosis and pelvic inflammatory disease tend to subside.
- Reduced incidence as well as symptomatic relief of fibrocystic breast disease and ovarian cysts.

Ormeloxifene (Centchroman) It is a nonsteroidal SERM developed at CDRI India as an oral contraceptive. It has predominant estrogen antagonistic action in uterus and breast with little action on vaginal epithelium and cervical mucus. Endometrial proliferation is suppressed by down regulation of endometrial ER. Contraceptive action is probably due to utero-embryonic asynchrony and failure of implantation. Pituitary, ovarian and other endocrine functions remain practically unaffected. Menstrual cycle is not disrupted, but in some women it may be lengthened irregularly. Excessive bleeding attending anovulatory cycles (that generally occurs near menopause) is diminished; ormeloxifene is also approved for use in dysfunctional uterine bleeding.

The plasma $t_{1/2}$ of ormeloxifene is long (~1 week). It prevents conception as long as taken with return of fertility few months after stoppage. Failure rate is considered acceptable, but it has failed to gain popularity for use as contraceptive. Side effects are nausea, headache, fluid retention, weight gain, rise in BP and prolongation of menstrual cycles.

Dose: For contraception—30 mg twice a week for 12 weeks followed by once a week.

For dysfunctional uterine bleeding—60 mg twice a week for 12 weeks, then once a week for 12 weeks.

CENTRON 30 mg tab, SAHELI 60 mg tab.

MALE CONTRACEPTION

The only way to suppress male fertility by drugs is to inhibit spermatogenesis. Though considerable effort has been made in this direction and effective drugs have been found, no satisfactory/acceptable solution is yet tangible. Reasons are—

1. Complete suppression of spermatogenesis is relatively difficult without affecting other tissues: millions of spermatozoa are released at

each ejaculation vs a single ovum per month in women.

2. Spermatogenesis takes 64 days. A drug which even completely inhibited spermatogenesis will take a long latent period to produce infertility. Accordingly, return of fertility will be slow.
3. Gonadotropin suppression inhibits testosterone secretion as well, resulting in loss of libido and impotence, which is unacceptable to all men and to most spouses.
4. Risk of adverse effects.
5. Most importantly—men don't get pregnant: few would be ready to bear the contingency of regular medication so that their sexual partners do not become pregnant.

Drugs and approaches tried are—

1. *Antiandrogens* Depress spermatogenesis, but raise Gns; cause unacceptable loss of libido.
2. *Estrogens and progestins* Act by suppressing Gns—cause unacceptable feminization.

3. *Androgens* They inhibit Gns but have poor efficacy. Even combination with progestin is not reliable.

4. *Superactive Gn RH analogues* They inhibit Gn release by continuous action; inhibit testosterone secretion as well; produce impotence, loss of libido.

5. *Cytotoxic drugs* Cadmium, nitrofurans and indoles suppress spermatogenesis, but are toxic.

6. *Gossypol* It is a nonsteroidal compound, obtained from cotton seed which has been studied in China. It is effective orally—causes suppression of spermatogenesis and reduces sperm motility—infertility develops after a couple of months. Fertility is restored several months after discontinuation. However, about 10% men remain oligozoospermic. During treatment serum LH and testosterone levels do not change; libido and potency are not affected. The mechanism of action though not clearly known, appears to involve direct toxicity on seminiferous epithelium.

Most important adverse effect of gossypol is hypokalaemia (due to renal loss of K^+) with its attendant muscular weakness (even paralysis). Other side effects are—edema, diarrhoea, breathlessness and neuritis. Its use has now been dropped.

PROBLEM DIRECTED STUDY

22.1 A 55-year-old postmenopausal woman developed a cancerous lump in the left breast for which radical mastectomy was performed. The tumour was ER positive and only one of the excised axillary lymph nodes had metastasis. She was put on adjuvant therapy with tamoxifen 20 mg per day. On her checkup visit one year later, she was found to be asymptomatic with no sign of local recurrence or lymph node enlargement, but ultrasound examination of the uterus revealed thickening of endometrium.

- (a) What could be the cause and implication of the increase in endometrial thickness?
- (b) Should the same adjuvant therapy continue, or should it be stopped altogether, or be replaced by another drug? Give reasons.

22.2 A 28-year-old mother with a 9 month baby wants to space out her next child and consults you for taking oral contraceptive.

- (a) What questions will you ask, what physical examination will you perform and what investigations will you order before advising her whether she should take oral contraceptive or not, as well as for selecting the contraceptive preparation most suitable for her?
- (see Appendix-1 for solutions)