EXHIBIT 1027

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Physiology, Pathophysiology, and
Clinical Management

4th Edition

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The three-dimensional structure of IGF based on x-ray of rhombohedral 2-Zn
insulin crystals and proposed confirmation based on model building for IGF.
(Redrawn from ER Froesch, J Zapf, E Rinderknecht, et al. *Cold Spring Harbor
Conf. Cell Proliferation* 6:62, 1979.)

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CONTRACEPTION

Daniel R. Mishell, Jr.

CHAPTER OUTLINE

KEY POINTS

- The effectiveness and incidence of use in the United States of the various types of contraceptives currently available are discussed.
- Information about spermicidal and barrier contraception is presented.
- The effectiveness, mechanisms of action, pharmacodynamics, and endocrinologic effects of the various types of steroid contraceptives currently available are reviewed.
- Information about the most commonly used steroid contraceptive, the oral combination formulations, is presented.

- Progestins given by injection as well as in subdermal capsules are described.
- For use of these agents, data are summarized regarding their adverse clinical and metabolic effects as well as their neoplastic effects and effects on future reproduction after use is discontinued.
- Information about the various types of postcoital contraceptive agents is presented as well as the data involving use of the progesterone receptor agonist mifepristone as an oral agent to induce abortion in early gestation.
- The types of intrauterine devices and their mechanisms of action as well as the adverse effects of these contraceptive agents are summarized.

Reversible contraception is defined as the temporary prevention of fertility and includes all the currently available contraceptive methods except sterilization. Sterilization should be considered a permanent prevention of fertility even though both vasectomy and tubal interruption can usually be reversed by a meticulous surgical procedure. The reversible methods are also called active methods; sterilization is also called a terminal method. A perfect method of contraception for all individuals is not currently available and probably will never be developed. Each of the various methods of contraception currently available has certain advantages and disadvantages. Therefore, when giving advice about contraception, the clinician should explain to the couple the advantages and disadvantages of each method so that they will be fully informed and can rationally choose the method most suitable for them.

CONTRACEPTIVE USE IN THE UNITED STATES

In 1995, it was estimated that there were 69.5 million women between the ages of 15 and 50 years in the United States, and 53 percent of them were married.[1] Of the nearly 70 million women in the reproductive age group in the United States in 1995, slightly more than half used a reversible method of contraception, about one fourth had one member of the couple sterilized by tubal ligation or vasectomy, and about one fifth used no method. Among the group using no method of contraception, about half had

TABLE 25–1

Contraceptive Methods Used by U.S. Women Aged 15 to 50 Years

	1993 (%)	1994 (%)	1995 (%)
Oral contraceptives	25	24	26
Sterilization	27	26	24
Tubal ligation	15	15	15
Vasectomy	13	12	10
Condom	19	19	19
Withdrawal	6	5	6
Rhythm	3	3	3
Diaphragm	2	2	2
Sponge	2	1	1
Vaginal suppository	2	1	1
Douche	1	1	1
Foam	1	1	1
IUD	1	1	1
Cream/jelly alone	1	1	1
Progestin implant	1	1	1
Progestin injection	*	1	1
Cervical cap	*	*	*
Female condom/pouch	*	*	*
No method	19	19	20
Hysterectomy/menopause	8	9	6
Pregnant	2	2	3
Trying to conceive	2	2	2

*Less than 1 percent.
From 1995 Ortho Birth Control Survey. Raritan, NJ, Ortho Pharmaceutical, 1996.

a prior hysterectomy or were pregnant, infertile, or trying to conceive. The other half either were not sexually active or were having infrequent episodes of coitus or otherwise did not believe there was a need for contraception. Thus, about 56 million women, approximately 80 percent of those in the reproductive age group in the United States, used some method of contraception in 1995[1] (Table 25–1).

Of the nonsurgical, reversible methods of contraception, oral contraceptives (OCs) were most popular, used by 26 percent of all women in this age group. OCs were followed in frequency of use by the condom, withdrawal, progestin injection, periodic abstinence, diaphragm, and spermicides alone. The intrauterine device (IUD) and progestin implants, the two most effective methods of reversible contraception, were each used by less than 1 million women.

Of women who initiated contraception in 1995, about one third selected OCs. Of all women currently in the reproductive age group in the United States, more than three fourths, 77 percent, have taken OCs at some time in their life. The average length of time of OC use by an individual woman is 5.8 years. Condom use has increased in the United States in the past two decades and is the third most popular method of contraception used by about one fifth of reproductive age women.

CONTRACEPTIVE EFFECTIVENESS

It is difficult to determine the actual effectiveness of a contraceptive method because of the many factors that affect contraceptive failure. The terms method effectiveness and use effectiveness (or method failure and patient failure) were previously used to describe conception occurring while the contraceptive method was being used

correctly or incorrectly. These have now been replaced by the terms typical use and perfect use.

The percentage of failure rates with the first year of use for the various methods of contraception available in the United States is shown in Table 25–2. In this table is an estimate of the percentage of women continuing to use the method after 1 year has elapsed since starting to use the method.[2] The actual use failure rates for durations more than 1 year are available for certain methods of long-acting contraceptives. The failure rate for 5 years of use of the six progestin implants, Norplant, in clinical trials is 1.1 percent.[3] The cumulative failure rate of the copper T380 IUD was 1.0, 1.4, and 1.6 per 100 women after 3, 5, and 7 years of use in a large World Health Organization (WHO) study.[4] The failure rate of all types of tubal sterilization is 1.31 after 5 years and 1.85 per 100 women after 10 years, being highest for tubal fulguration and lowest for segmental resection in the 10 years after the procedure.[5] In counseling women about long-term failure rates, they should be in-

TABLE 25–2

Failure Rates of Various Contraceptive Methods

METHOD	PERCENTAGE OF WOMEN EXPERIENCING AN ACCIDENTAL PREGNANCY WITHIN THE FIRST YEAR OF USE		PERCENTAGE OF WOMEN CONTINUING USE AT 1 YEAR
	Typical Use	Perfect Use	
Chance	85	85	
Spermicides	21	6	43
Periodic abstinence	20		67
Calendar		9	
Ovulation method		3	
Symptothermal		2	
Post ovulation		1	
Withdrawal	19	4	
Cap			
Parous women	36	26	45
Nulliparous women	18	9	58
Sponge			
Parous women	36	20	45
Nulliparous women	18	9	58
Diaphragm	18	6	58
Condom			
Female (Reality)	21	5	56
Male	12	3	63
Pill	3		72
Progestin-only		0.5	
Combined		0.1	
IUD			
Progesterone T	2.0	1.5	81
Copper T380A	0.8	0.6	78
LNg20	0.1	0.1	81
Depo-Provera	0.3	0.3	70
Norplant (six capsules)	0.09	0.09	85
Female sterilization	0.4	0.4	100
Male sterilization	0.15	0.10	100

Emergency contraceptive pills treatment initiated within 72 hours after unprotected intercourse reduces the risk of pregnancy by at least 75%.
Lactational amonorrhea methods a highly effective, *temporary* method of contraception.

From Contraceptive Technology update. Monthly newsletter from Health Professionals, American Health Consultants. Don't neglect perfect-use failure rates when talking to patients. Contraceptive Technology, Feb. 1996, Vol. 17, No. 1, pp 13–24.

formed about the high incidence of ectopic pregnancies that occur in women who conceive using progestin-only methods, the IUD, and female sterilization. Ectopic pregnancy rates for women conceiving while they are using these methods range from about 30 percent with tubal sterilization failure, 25 percent with implant failure, and 5 percent with copper IUD failure.[5, 6]

SPERMICIDES: FOAMS, CREAMS, AND SUPPOSITORIES

All spermicidal agents contain a surfactant, usually nonoxynol 9, that immobilizes or kills sperm on contact. They also provide a mechanical barrier and need to be placed into the vagina before each coital act. The effectiveness of these agents increases with increasing age of the woman and is similar to that of the diaphragm in all age and income groups. Although a few early studies linked the use of a spermicide at the time of conception with an increased risk of some congenital malformations, several well-performed studies have shown no increased risk of congenital malformation in the newborns[7-9] or karyotypic abnormalities in the spontaneous abortuses[10] of women who conceived while using spermicides.

BARRIER TECHNIQUES

Diaphragm

A diaphragm must be carefully fitted by the health care provider. The largest size that does not cause discomfort or undue pressure on the vaginal epithelium should be used. After the fitting, the woman should remove the diaphragm and reinsert it herself. She should then be examined to make sure the diaphragm is covering the cervix. The diaphragm should be used with a spermicide and be left in place for at least 8 hours after the last coital act. If repeated intercourse takes place or coitus occurs more than 8 hours after insertion of the diaphragm, additional spermicide should be used.

Although it is advisable to use a spermicide with the diaphragm, it may not be necessary because it has not been conclusively demonstrated that pregnancy rates are lower when a spermicide is used with a diaphragm than when the diaphragm is used alone.[11] The number of urinary tract infections in women who use diaphragms is significantly higher than in nonusers, probably because of the mechanical obstruction of the outflow of urine by the diaphragm.[12] Diaphragm users should also be cautioned not to leave the device in place for more than 24 hours, because ulceration of the vaginal epithelium may occur with prolonged usage.

Cervical Cap

The cervical cap, a cup-shaped plastic or rubber device that fits around the cervix, has been used as a barrier contraceptive for decades, mainly in Britain and other parts of Europe.

There has been a recent resurgence of interest in the use of this older method because the cervical cap can be left in place longer than the diaphragm and is more comfortable. The various types of caps are manufactured in different sizes and should be fitted to the cervix by a clinician. The Prentif cavity-rim cervical cap was approved for general use in the United States in 1988. The product labeling stipulates that the cap should be left on the cervix for no more than 48 hours and that a spermicide should always be placed inside the cap before use.[13] The cap is manufactured in four sizes and requires more training than the diaphragm, both for the provider to fit it and for the user to place it correctly. Failure rates with the cervical cap are similar to those observed with the diaphragm. Because of concern about a possible adverse effect of the cap on cervical tissue, the cervical cap should be used only by women with normal cervical cytology, and it is recommended that users have another cervical cytologic examination 3 months after starting to use this method.

Male Condom

Use of the male condom by individuals with multiple sex partners should be encouraged. The male condom is the most effective method of contraception to prevent transmission of sexually transmitted diseases. The male condom should not be applied tightly. The tip should extend beyond the end of the penis by about ½ inch to collect the ejaculate. Care must be taken on withdrawal not to spill the ejaculate. When used by strongly motivated couples, the male condom is highly effective.

Female Condom

A female condom was approved for marketing in the United States in 1994. It consists of a soft, loose-fitting sheath and two flexible polyurethane rings. One ring lies inside the vagina at the closed end of the sheath and serves as an insertion mechanism and internal anchor. The outer ring forms the external edge of the device and remains outside the vagina after insertion, thus providing protection to the labia and the base of the penis during intercourse. The condom is prelubricated and is intended for one-time use only. Fitting by a health professional is not required.[14]

In comparison to the male condom, the female condom has the advantage of being able to be inserted before beginning sexual activity and to be left in place for a longer time after ejaculation occurs. Because the female condom also covers the external genitalia, it should offer greater protection against the transfer of certain sexually transmitted organisms, particularly genital herpes. Because polyurethane is stronger than the latex used in male condoms, the female condom is less likely to rupture. In a multicenter clinical trial, the cumulative pregnancy rate in U.S. centers at 6 months was 12.4 percent. The 6-month pregnancy rate with perfect use was 2.6 percent, indicating that the probable 1-year pregnancy rate with perfect use would be slightly more than 5 percent.[15] At the end of 6 months in the U.S. study, about one third of the women had discontinued use of this method. Because clinical trials with use of the female condom have not compared its use with other barrier techniques, an exact comparison with other contraceptive methods cannot be made. Trussel and colleagues,[15] using the data of other studies, concluded that the efficacy rate of the female condom with perfect use would be similar to that of the diaphragm and cervical cap,

but the failure rate of the female condom with typical use would be higher than that of the diaphragm. Because of the lack of prospective clinical trials with the male condom, no statistical comparison of the effectiveness of the two types of condoms can be made. No data exist in which the effectiveness of the female condom for reducing sexual disease transmission is analyzed. Because polyurethane does not allow virus transmission, it should reduce the risk of a woman's acquiring human immunodeficiency virus infection.

ORAL STEROID CONTRACEPTIVES

Oral steroid contraceptives (OCs) were initially marketed in the United States in 1960. Because contraceptive steroid formulations with more than 50 μg of estrogen were associated with a greater incidence of adverse effects without greater efficacy, they are no longer marketed for contraceptive use in the United States, Canada, and Great Britain. Indications for prescribing formulations with 50 μg of estrogen are uncommon. In 1996, only about 2.5 percent of all OC prescriptions in the United States were for formulations with 50 μg of estrogen. OC formulations currently marketed in the United States, excluding generic brands, are listed in Table 25–3.

Pharmacology

There are three major types of OC formulations: fixed-dose combination, combination phasic, and daily progestin. The combination formulations are the most widely used and most effective. They consist of tablets containing both an estrogen and progestin given continuously for 3 weeks. No steroids are given for the next 7 days, after which time the active combination is given for an additional 3 weeks. Uterine bleeding usually occurs in the week when no steroid is ingested. Without estrogenic stimulation, the endometrium usually begins to slough 1 to 3 days after steroid ingestion is stopped. Withdrawal bleeding usually lasts 3 to 4 days and uterine blood loss averages about 25 ml, less than the mean of about 35 ml that occurs during menses in a normal ovulatory cycle.

All currently marketed formulations are made from synthetic steroids and contain no natural estrogens or progestins. There are two major types of synthetic progestins: derivatives of 19-nortestosterone and derivatives of 17α-acetoxyprogesterone. The latter group are C_{21} progestins, called pregnanes, and are structurally related to progesterone. Medroxyprogesterone acetate and megestrol acetate are C_{21} progestins marketed as tablets for noncontraceptive usage. In contrast to the 19-nortestosterone derivatives, when high dosages of the C_{21} progestins were given to female beagle dogs (an animal previously used for OC toxicology testing), the animals developed an increased incidence of mammary cancer. Because of this carcinogenic effect, oral contraceptives containing these progestins are no longer marketed despite the fact that the beagle, unlike the human, metabolizes C_{21} progestins to estrogen, which then stimulates mammary nodules that can become carcinogenic in this animal.

The steroid structure of the 19-nortestosterone progestins more closely resembles testosterone than the C_{21} acetoxy-
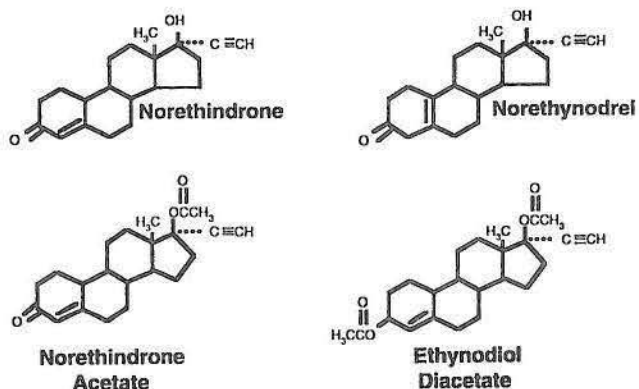

Figure 25–1 ≡ Chemical structures of the estrane progestins used in oral contraceptives.

progestins. Therefore, all progestational agents currently used in OCs have some degree of androgenic activity. The 19-nortestosterone progestins used in OCs are of two major types, called estranes and gonanes. Although the original estrane, norethynodrel, is no longer used in currently marketed OCs, other estranes, norethindrone and its derivatives with one or two acetates, norethindrone acetate and ethynodiol diacetate, are used in several marketed formulations (Fig. 25–1). Gonanes have greater progestational activity per unit weight than estranes do, and thus a smaller amount of the gonane type of progestin is used in OC formulations. The parent compound of the gonanes is dl-norgestrel, which consists of two isomers, dextro and levo. Only the levo form is biologically active. Both dl-norgestrel and its active isomer levonorgestrel are present in several OC formulations. Three less androgenic derivatives of levonorgestrel, namely, desogestrel, norgestimate, and gestodene, have also been synthesized (Fig. 25–2). Formulations with each of these three progestins have been marketed in Europe for many years, and formulations with desogestrel and norgestimate, but not gestodene, have been marketed in the United States since 1992.

With the exception of two daily progestin-only formulations, the progestins are combined with varying dosages of two estrogens, ethinyl estradiol and ethinyl estradiol 3-methyl ether, also known as mestranol (Fig. 25–3). All the older, higher dosage OC formulations contained mestranol, and this steroid is still present in some 50-μg formulations. All formulations with less than 50 μg of estrogen contain only the parent compound ethinyl estradiol. In common
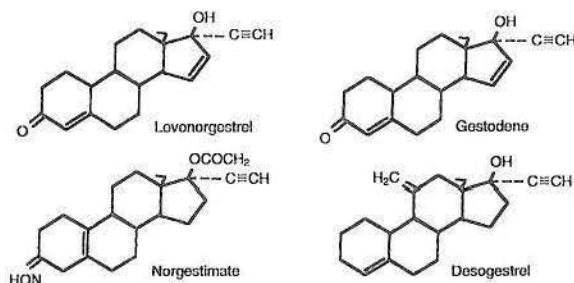

Figure 25–2 ≡ Chemical structure of the gonane progestins used in oral contraceptives.

▪ TABLE 25-3

Estrogen and Progestin Components of Oral Contraceptives

MANUFACTURER	PRODUCT TYPE	PROGESTIN	ESTROGEN*
Berlex			
Levlen	Combination	0.15 mg levonorgestrel	30 µg
Tri-Levlen 6/	Combination, triphasic	0.05 mg levonorgestrel	30 µg
5/		0.075 mg levonorgestrel	40 µg
10/		0.125 mg levonorgestrel	30 µg
Bristol-Myers Squibb			
Ovcon 35	Combination	0.4 mg norethindrone	35 µg
Ovcon 50	Combination	1.0 mg norethindrone	50 µg
Organon			
Desogen	Combination	0.15 mg desogestrel	35 µg
Ortho-MacNeil Pharmaceutical			
Micronor	Progestin-only	0.35 mg norethindrone	
Modicon	Combination	0.5 mg norethindrone	35 µg
Ortho-Cept	Combination	0.15 mg desogestrel	30 µg
Ortho-Cyclen	Combination	0.25 mg norgestimate	35 µg
Ortho-Novum 1/35	Combination	1.0 mg norethindrone	35 µg
Ortho-Novum 1/50	Combination	1.0 mg norethindrone	50 µg†
Ortho-Novum 7/	Combination, triphasic	0.5 mg norethindrone	35 µg
7/		0.75 mg norethindrone	35 µg
7/		1.0 mg norethindrone	35 µg
Ortho-Novum 10/	Combination, biphasic	0.5 mg norethindrone	35 µg
11/		1.0 mg norethindrone .	35 µg
Ortho-Tricyclin	Combination, triphasic	0.18 mg norgestimate	35 µg
		0.215 mg norgestimate	35 µg
		0.25 mg norgestimate	35 µg
Parke-Davis			
Estrostep	Combination	1.0 mg norethindrone acetate	20 µg
		1.0 mg norethindrone acetate	30 µg
		1.0 mg norethindrone acetate	35 U
Loestrin 1/20	Combination	1.0 mg norethindrone acetate	20 µg
Loestrin 1.5/30	Combination	1.5 mg norethindrone acetate	30 µg
Norlestrin 1/50	Combination	1.0 mg norethindrone acetate	50 µg†
Norlestrin 2.5/50	Combination	2.5 mg norethindrone acetate	50 µg†
Roche Laboratories			
Brevicon	Combination	0.5 mg norethindrone	35 µg
Norinyl 1 + 35	Combination	1.0 mg norethindrone	35 µg
Norinyl 1 + 50	Combination	1.0 mg norethindrone	50 µg
Nor-QD	Progestin-only	0.35 mg norethindrone	
Tri-Norinyl 7/	Combination, triphasic	0.5 mg norethindrone	35 µg
9/		1 mg norethindrone	35 µg
5/		0.5 mg norethindrone	35 µg
Searle			
Demulen 1/35	Combination	1.0 mg ethynodiol diacetate	35 µg
Demulen 1/50	Combination	1.0 mg ethynodiol diacetate	50 µg
Wyeth-Ayerst			
Alesse	Combination	0.1 mg levonorgestrel	20 µg
Lo/Ovral	Combination	3.0 mg norethindrone	30 µg
Nordette	Combination	0.15 mg norethindrone	30 µg
Ovral	Combination	0.5 mg norgestrel	50 µg
Ovrette	Progestin-only	0.075 µg norgestrel	30 µg
Triphasil 6/	Combination, triphasic	0.05 µg levonorgestrel	30 µg
5/		0.75 µg levonorgestrel	40 µg
10/		1.25 µg levonorgestrel	30 µg

*Ethinyl estradiol unless noted.
†Mestranol.

usage, formulations with 50 µg or more of estrogen (ethinyl estradiol or mestranol) have been termed first-generation OCs. Those with less than 50 µg of estrogen, 20 to 35 µg of ethinyl estradiol, are called second-generation products if they contain any progestin except the three newest levonorgestrel derivatives. Those formulations with desogestrel, norgestimate, and gestodene are called third-generation formulations. All the synthetic estrogens and progestins in OCs have an ethinyl group at position 17. The presence of this ethinyl group enhances the oral activity of these agents, because their essential functional groups are not as rapidly metabolized as they pass through the intestinal mucosa and the liver through the portal system, in contrast to what occurs when natural sex steroids are ingested orally. The synthetic steroids thus have greater oral potency per unit of weight than the natural steroids. It has been estimated that ethinyl estradiol has about 100 times the potency of an equivalent weight of conjugated equine
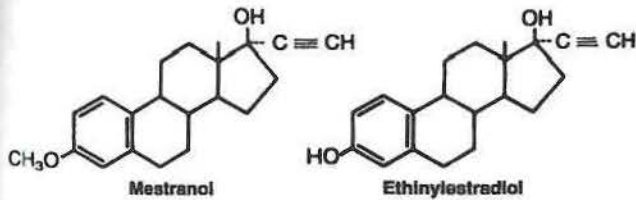
Figure 25-3 ■ Structures of the two estrogens used in combination oral contraceptives.

estrogen or estrone sulfate for stimulating synthesis of various hepatic globulins.

The various modifications in chemical structure of the different synthetic progestins and estrogens also affect their biologic activity. Thus, one cannot define the pharmacologic activity of the progestin or estrogen in a particular contraceptive steroid formulation on the basis of only the amount of steroid present. The biologic activity of each steroid also has to be considered. By use of established tests for progestational activity in animals, it has been found that a given weight of norgestrel is several times more potent than the same weight of norethindrone. Studies in humans, using delay of menses[16] or endometrial histologic alterations such as subnuclear vacuolization[17, 18] as endpoints, also determined that norgestrel is about 10 times more potent than the same weight of norethindrone. Norethindrone acetate and ethynodiol diacetate are metabolized in the body to norethindrone. Studies in humans, measuring progestational activity as described before, as well as other studies comparing the effects of serum lipids in humans indicate that each of these three progestins has approximately equal potency per unit of weight, whereas levonorgestrel is 10 to 20 times as potent.[19] Each of the three most recently developed levonorgestrel derivatives has been shown in animal but not human studies to have similar or greater progestogenic potency than an equivalent weight of levonorgestrel, with less androgenic activity.[20] The magnitude of difference in androgenic and progestational effects produced by each progestin is called selectivity.

The two estrogenic compounds used in OCs, ethinyl estradiol and its 3-methyl ether, mestranol, also have different biologic activity in women. To become biologically effective, mestranol must be demethylated to ethinyl estradiol, because mestranol does not bind to the estrogen cytosol receptor. The degree of conversion of mestranol to ethinyl estradiol varies among individuals; some are able to convert it completely, whereas others convert only a portion of it. Thus, in some women, a given weight of mestranol is as potent as the same weight of ethinyl estradiol; in other women, it is only about half as potent. Overall, it has been estimated, by use of human endometrial response and effect on liver corticosteroid-binding globulin production as endpoints, that ethinyl estradiol is about 1.7 times as potent as the same weight of mestranol.[21] The biologic activity as well as the quantity of both steroid components needs to be evaluated in comparing potency of the various formulations.

Radioimmunoassay methods have been developed to measure blood levels of these synthetic estrogens and progestins. Peak plasma levels of ethinyl estradiol are lower and occur about 2 to 4 hours later after ingestion of mestra-

nol than after ingestion of ethinyl estradiol.[22] The delay is due to the time necessary for mestranol to be demethylated to ethinyl estradiol in the liver.

When different doses of dl-norgestrel were administered to women, it was found that the serum levels of levonorgestrel were related to the dosage.[23] Peak serum levels were found 0.5 to 3 hours after oral administration, followed by a rapid, sharp decline (Fig. 25–4). However, 24 hours after ingestion, 20 to 25 percent of the peak level of levonorgestrel was still present in the serum. After 5 days of norgestrel administration, measurable amounts of levonorgestrel were present for at least the following 5 days.

Brenner and coworkers[24] measured serum levels of levonorgestrel, follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, and progesterone 3 hours after ingestion of a combination OC containing 0.5 mg of dl-norgestrel and 50 μg of ethinyl estradiol in three women during two consecutive cycles as well as during the intervening pill-free interval. Daily levels of levonorgestrel rose during the first few days of ingestion, reached a plateau thereafter, and declined after ingestion of the last pill (Fig. 25–5). Nevertheless, substantial amounts of levonorgestrel remained in the serum for at least the first 3 to 4 days after the last pill was ingested. These steroid levels were sufficient to suppress gonadotropin release during the 1-week interval when no steroid was administered. Thus, follicle maturation, as evidenced by rising estradiol levels,
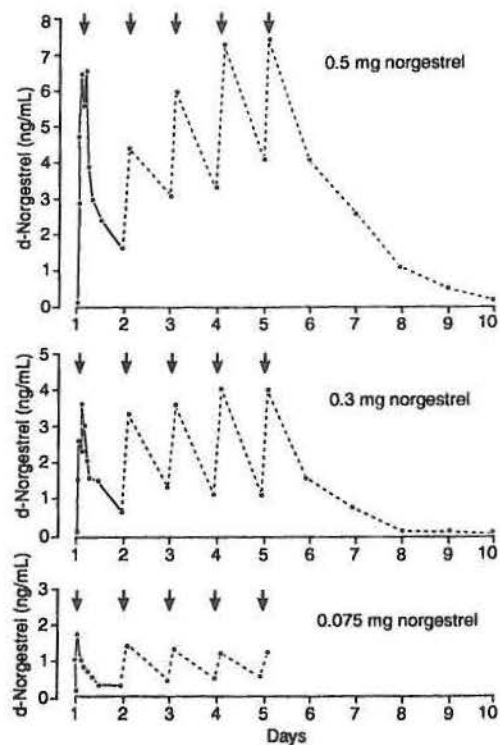
Figure 25–4 ■ Serum d-norgestrel levels in three subjects receiving 500 μg of dl-norgestrel and 50 μg of ethinyl estradiol (Ovral). Arrows indicate time of ingestion. (From Brenner PF, Mishell DR Jr, Stanczyk FZ, Goebelsmann U. Serum levels of d-norgestrel, luteinizing hormone, follicle-stimulating hormone, estradiol, and progesterone in women during and following ingestion of combination oral contraceptives containing dl-norgestrel. Am J Obstet Gynecol 129:133–140, 1977.)
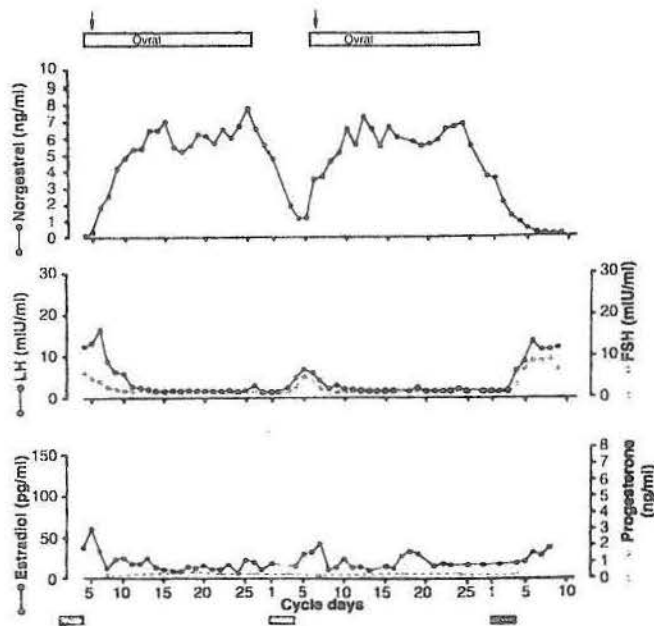
Figure 25-5 ■ Serum d-norgestrel, FSH, LH, estradiol, and progesterone levels in patients during and after oral administration of 500 μg of dl-norgestrel and 50 μg of ethinyl estradiol (Ovral) for two subsequent 21-day periods interrupted by a pill-free interval of 6 days. (From Brenner PF, Mishell DR Jr, Stanczyk FZ, Goebelsmann U. Serum levels of d-norgestrel, luteinizing hormone, follicle-stimulating hormone, estradiol, and progesterone in women during and following ingestion of combination oral contraceptives containing dl-norgestrel. Am J Obstet Gynecol 129:133–140, 1977.)

did not occur during the 1 week when no steroid was being ingested. When lower doses of steroids are administered, follicular growth but not ovulation may occur because of initiation of growth of the dominant follicle during the time that no steroid is being ingested.

From these data, it seems reasonable to conclude that accidental pregnancies during OC use probably occur not because of failure to ingest one or two pills more than a few days after a treatment cycle is initiated but rather because initiation of the next cycle of medication is delayed for a few days. Therefore, it is important that the pill-free interval is not extended more than 7 days. This is best accomplished by ingesting either a placebo or iron tablet daily during the steroid-free interval (the so-called 28-day package). If a 3-week pill package is used, treatment is best started on the first Sunday after menses begins instead of the first or fifth day of the cycle. It is easier to remember to start the new package on a Sunday. Women should be advised that the most important pill to remember to take is the first one of each cycle.

Mechanisms of Action

The estrogen-progestin combination is the most effective type of OC formulation, because these preparations consistently inhibit the midcycle gonadotropin surge and thus prevent ovulation. The progestin-only formulations have a lower dose of progestin than the combined agents and do not consistently inhibit ovulation. Both types of formulations also act on other aspects of the reproductive process:

(1) they alter the cervical mucus, making it thick, viscid, and scanty, which retards sperm penetration; (2) they alter motility of the uterus and oviduct, thus impairing transport of both ova and sperm; (3) they alter the endometrium so that its glandular production of glycogen is diminished and less energy is available for the blastocyst to survive in the uterine cavity; and (4) they may alter ovarian responsiveness to gonadotropin stimulation. With both types of formulations, neither gonadotropin production nor ovarian steroidogenesis is completely abolished. Levels of endogenous estradiol in the peripheral blood during ingestion of high-dose combination OCs are similar to those found in the early follicular phase of the normal cycle.[25]

Contraceptive steroids prevent ovulation both by interfering with release of gonadotropin-releasing hormone (GnRH) from the hypothalamus and by suppressing pituitary release of LH and FSH. Several studies in humans showed most women who had been ingesting combination OCs had suppression of the release of LH and FSH after infusion of GnRH, indicating that the steroids had a direct inhibitory effect on the pituitary as well as on the hypothalamus.[26]

Direct pituitary inhibition occurs in about 80 percent of women ingesting high-dose combination OCs. Pituitary suppression is unrelated to the age of the woman or the duration of steroid use but is related to the potency of the formulation. The effect is more pronounced with formulations containing a more potent progestin[27] and with those containing 50 μg or more of estrogen than with 30- to 35-μg estrogen-containing formulations.[28] It has not been demonstrated that the degree of pituitary suppression is related to the occurrence of amenorrhea after OC use is stopped. There are data showing that the mean time to conception after discontinuation of OC use is shorter in women ingesting preparations with less than 50 μg of estrogen (4.01 cycles) than in those ingesting formulations with 50 μg of estrogen or more (4.79 cycles).[29]

The daily progestin-only preparations do not consistently inhibit ovulation. They exert their contraceptive action by the other mechanisms listed before, but because of the inconsistent ovulation inhibition, their effectiveness is significantly less than that of the combination types of OCs. Because a lower dose of progestin is used in these formulations than in the combination tablets, it is important that these preparations be consistently taken at the same time of day to ensure that blood levels do not fall below the effective contraceptive level.

No significant difference in clinical effectiveness has been demonstrated among the various combination formulations currently available in the United States. As long as no tablets are omitted (perfect use), the pregnancy rate is less than 0.2 percent at the end of 1 year with all marketed combination formulations.

Metabolic Effects

The synthetic steroids in OC formulations have many metabolic effects in addition to their contraceptive actions (Table 25-4). These metabolic effects can produce both the more common, less serious side effects as well as the rare, potentially serious complications. The magnitude of these effects is directly related to the dosage and potency of the

TABLE 25–4

Metabolic Effect of Contraceptive Steroids

	CHEMICAL EFFECTS	CLINICAL EFFECTS
Estrogen: Ethinyl estradiol		
Proteins		
Albumin	↓	None
Amino acids	↓	None
Globulins	↑	
Angiotensinogen		↑ Blood pressure
Clotting factors		Hypercoagulability
Carrier proteins (CBG, TBG, transferrin, ceruloplasmin)		None
Carbohydrate		
Plasma insulin	None	None
Glucose tolerance	None	None
Lipids		
Cholesterol	↑	None
Triglyceride	↑	None
HDL cholesterol	↑	? ↓ Cardiovascular disease
LDL cholesterol	↓	? ↓ Cardiovascular disease
Electrolytes		
Sodium excretion	↓	Fluid retention Edema
Vitamins		
B-complex	↓	None
Ascorbic acid	↓	None
Vitamin A	↑	None
Other		
Breast	↑	Breast tenderness
Endometrial steroid receptors	↑	Endometrial hyperplasia
Skin	↓	↓ Sebum production ↑ Facial pigmentation
Progestins: 19-Nortestosterone derivatives		
Proteins	None	None
Carbohydrate		
Plasma insulin	↑	None
Glucose tolerance	↓	None
Lipids		
Cholesterol	↓	None
Triglyceride	↓	None
HDL cholesterol	↓	? ↑ Cardiovascular disease
LDL cholesterol	↑	? ↑ Cardiovascular disease
Other		
Nitrogen retention	↑	↑ Body weight
Skin—sebum production	↑	↑ Acne
CNS effects	↑	Nervousness, fatigue, depression
Endometrial steroid receptors	↓	No withdrawal bleeding

CBG, corticosteroid-binding globulin; TBG, thyroid-binding globulin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CNS, central nervous system.

steroids in the formulations. Fortunately, in most instances, the more common adverse effects are relatively mild.

The most frequent symptoms produced by the estrogen component include nausea (a central nervous system effect), breast tenderness, and fluid retention (which usually does not exceed 3 to 4 pounds of body weight) because of decreased sodium excretion. Minor, clinically insignificant changes in circulating vitamin levels also occurred after ingestion of the higher dosage OCs. These changes included a decrease in levels of the B-complex vitamins and ascorbic acid and increases in levels of vitamin A. Even with use of the agents containing a high steroid dose, dietary vitamin supplementation was not necessary, because the changes in circulating vitamin levels were small and clinically insignificant. Estrogen can also cause melasma, pigmentation of the malar eminences, to develop. Melasma is accentuated by sunlight and usually takes a long time to disappear after OCs are discontinued. The incidence of all these estrogenic side effects is much less with use of formulations of lower estrogen dose than with those of high estrogen dose.

With high doses of estrogen, OC usage was found to accelerate the development of the symptoms of gallbladder disease in young women but did not increase the overall incidence of cholelithiasis. The results of the large British Family Planning Association study[30] and a case-control study[31] indicate that the use of high-dose OCs does not increase the incidence of gallbladder disease in women. When the data were stratified among women of different body weight or different age, no increased risk of gallbladder disease was found in any subgroup. These results indicate that development of gallbladder disease is not a risk factor associated with OC use, even if these agents contain high doses of steroids and are used for more than 8 years.[32]

Mood and Depression

It was previously postulated that high dosages of the synthetic estrogens could also produce changes in mood and depression brought about by diversion of tryptophan metabolism from its minor pathway in the brain to its major pathway in the liver. The end product of tryptophan metabolism, serotonin, is thus decreased in the central nervous system, and it was postulated that the resultant lowering of serotonin could produce depression in some women and sleepiness and mood changes in others.

Analysis of the data from the Royal College of General Practitioners (RCGP) cohort study indicated that OC use was positively correlated with the incidence of depression, which in turn was directly related to the dose of estrogen in the formulation.[33] In this study, an increased incidence of depression was not found to occur among users of OCs containing less than 50 μg of estrogen. Data from postmenopausal women receiving estrogen therapy alone as well as estrogen-progestin sequential therapy indicate that administration of physiologic doses of estrogen alone, which is less potent than the pharmacologic dose used in OCs, improves the mood of women, whereas the addition of a progestin increases the amount of depression, irritability, tension, and fatigue.[34] These studies indicate that the progestin component of the agents may be the major cause of the adverse mood changes and tiredness observed in some women after ingestion of OCs, but it has not been definitely established which of the steroid components is the major factor in producing adverse mood changes. Possibly, both are involved.

Androgenic Effects

The progestins, because they are structurally related to testosterone, also produce certain adverse androgenic effects. These include weight gain, acne, and a symptom perceived by some women as nervousness. Some women gain a considerable amount of weight when they take OCs, and this weight gain is believed to be produced by the anabolic effect of the progestin component. Although estrogens decrease sebum production, progestins increase it and can cause acne to develop or worsen. Thus, women who have acne should be given a formulation with a low progestin–estrogen ratio.

The final symptom produced by the progestin component is failure of withdrawal bleeding or amenorrhea. Because the progestins decrease the synthesis of estrogen receptors in the endometrium, endometrial growth is decreased, and some women have failure of withdrawal bleeding. This symptom is not important medically, but because bleeding serves as a signal that the woman is not pregnant, it is desirable to have some amount of periodic withdrawal bleeding during the days she is not taking these steroids. The two steroid components can act together to produce irregular bleeding. Unscheduled (breakthrough) bleeding (which is usually produced by insufficient estrogen, too much progestin, or a combination of both) as well as failure of withdrawal bleeding can be alleviated by increasing the amount of estrogen in the formulation or by switching to a more estrogenic formulation.

Hepatic Proteins

The synthetic estrogens used in OCs cause an increase in the hepatic production of several globulins. Progesterone and androgenic progestins do not affect the synthesis of globulins except that of sex hormone–binding globulin (SHBG). Synthesis of SHBG is reduced by androgens, including the androgenic progestins. Some of the globulins that are increased by ethinyl estradiol ingestion, such as factors V, VIII, and X and fibrinogen, enhance thrombosis,[35] whereas another globulin, angiotensinogen, may be converted to angiotensin and increase blood pressure in some users.[36] The circulating levels of each of these globulins are directly correlated with the amount of estrogen in the OC formulation. Epidemiologic studies have shown that the incidence of both venous and arterial thrombosis is also directly related to the dose of estrogen.[35, 37, 38]

Although angiotensinogen levels are lower in women who ingest formulations with 30 to 35 μg of ethinyl estradiol than in those who ingest formulations of higher estrogen dosage, a slight but significant increase in mean blood pressure still occurs in women who ingest the lower dosage formulations.[36, 39] Thus, blood pressure should be monitored in all users of OCs. There is some indirect evidence that the progestin component may also raise blood pressure. However, women who receive progestins without estrogen do not have an increase in blood pressure over time,[36] indicating that the estrogen component is the major cause of elevated blood pressure in a few users of OCs.

Another globulin, SHBG, binds circulating levels of estrogens and androgens. Progesterone is bound to corticosteroid-binding globulin, but because the progestins used in oral contraceptives are 19-nortestosterone derivatives, they are bound to SHBG. Estrogens increase SHBG levels, whereas androgens, including 19-nortestosterone derivatives, decrease SHBG levels. Thus, measurement of SHBG is one way to determine the relative estrogenic/androgenic balance of different OC formulations. Van der Vange and associates[40] measured SHBG levels before and 6 months after ingestion of several OC formulations containing about the same amount of ethinyl estradiol. The greatest increase occurred with formulations containing cyproterone acetate (not used in OC formulations in the United States), desogestrel, and gestodene. SHBG increases of lesser magnitude occurred after ingestion of formulations containing low doses of norethindrone and levonorgestrel. Because SHBG binds endogenous testosterone and prevents it from acting on the target tissue, formulations causing the greatest increase in SHBG should be associated with the least amount of androgenic effects. These formulations are particularly useful for treating women with symptoms of hyperandrogenism such as polycystic ovary syndrome.

Carbohydrate Metabolism

The effect of OCs on glucose metabolism is mainly related to the dose, potency, and chemical structure of the progestin. Conflicting data exist as to whether the estrogen component affects carbohydrate metabolism. The estrogen may act synergistically with the progestin to impair glucose tolerance. In general, the higher the dose and potency of the progestin, the greater the magnitude of impaired glucose metabolism. The degree of alteration appears to be greater with gonanes than with estranes. Several studies have shown that formulations with a low dose of progestin, including one containing levonorgestrel, do not significantly alter levels of glucose, insulin, or glucagon after a glucose load in healthy women[41, 42] or in those with a history of gestational diabetes.[43] However, other studies indicate that the multiphasic formulations with norgestrel, but not those with norethindrone, produce some deterioration of glucose tolerance in normal women[44] as well as in those with a history of gestational diabetes.[45] Some studies have shown increased levels of both glucose and insulin when glucose tolerance tests were administered to women ingesting desogestrel-containing OCs.[46–48]

Data from 20 years of experience using mainly high-dose formulations in the large RCGP cohort study indicated that there was no increased risk for development of diabetes mellitus among current OC users (relative risk [RR], 0.80) or former OC users (RR, 0.82) even among women who had used OCs for 10 years or more.[49] More than 1 million person-years of follow-up of OC users in the large Nurses' Health Study cohort were analyzed in 1992. Although type II diabetes mellitus developed in more than 2000 women, the risk was not increased among current OC users (RR, 0.71) and only marginally increased in past OC users (RR, 1.11),[50] only among women who had used high-dose formulations many years previously, not for those who had used lower dose formulations.

Kjos and colleagues[51] observed a group of women with a history of gestational diabetes mellitus for several years after the end of the pregnancy. In the first year, women ingesting a low-dose levonorgestrel formulation had a greater risk of developing diabetes mellitus than did a

control group not taking OCs. On the other hand, women ingesting a low-dose norethindrone formulation did not have a greater risk of developing diabetes mellitus than control subjects did. After the first year following delivery, women ingesting both types of OCs had no greater risks of developing diabetes mellitus than did the control group. When OCs are prescribed for women with a history of glucose intolerance, formulations with a low dose of a norethindrone-type progestin are probably preferable to levonorgestrel preparations. In addition, glucose tolerance should be monitored periodically.

Lipids

The estrogen component of OCs causes an increase in high-density lipoprotein (HDL) cholesterol, a decrease in low-density lipoprotein (LDL) cholesterol, and an increase in total cholesterol and triglyceride levels. The progestin component causes a decrease in HDL, an increase in LDL, and a decrease in total cholesterol and triglyceride levels.

The older formulations with high doses of progestin had adverse effects on the lipid profile although they also contained high doses of the synthetic estrogen. These progestin-dominant formulations produced a decrease in HDL cholesterol levels and an increase in LDL cholesterol levels.[52] They also caused an increase in serum triglyceride levels because the estrogen has a greater effect on triglyceride synthesis than does the progestin. Short-term longitudinal studies of several phasic formulations containing levonorgestrel and norethindrone found that a significant increase in triglyceride levels still occurred but there was little change in either HDL cholesterol or LDL cholesterol levels as well as in total cholesterol levels because the effects of each steroid on lipid synthesis were offset by the other.[53, 54]

In a cross-sectional study in which lipid levels were measured in a large number of women ingesting several OC formulations and compared with those of nonusers, Godsland and colleagues[47] reported that there were insignificant differences in HDL and LDL cholesterol levels compared with those of nonusers when low-dose monophasic and triphasic levonorgestrel and norethindrone formulations were ingested. The women ingesting formulations with only 0.5 mg of norethindrone or 150 μg of desogestrel had a significant increase in HDL cholesterol levels and a significant decrease in LDL cholesterol levels.[46] The three most recently developed progestins have less androgenic activity than the older progestins and as such, when com-

bined with an estrogen, would be expected to have less adverse effect on lipid metabolism than the older formulations. Speroff and associates,[20] in 1993, reviewed data from the published studies in which lipid levels were measured in women ingesting formulations with the three less androgenic progestins. They reported that with use of these formulations, there was a significant increase in HDL cholesterol levels, a significant decrease in LDL cholesterol levels, little change in total cholesterol levels, and a substantial increase in triglyceride levels (Table 25-5). The long-term effect, if any, of these changes in lipid parameters remains to be determined.

Coagulation Parameters

As previously mentioned, the estrogen component of OCs increases the synthesis of several coagulation factors, including fibrinogen, which enhances thrombosis in a dose-dependent manner. The effect of OCs on parameters that inhibit coagulation, such as protein C, protein S, and antithrombin III, is less clear because of the diversity of techniques used to measure these parameters in different laboratories. A similar lack of consistency occurs when parameters that enhance fibrinolysis (such as plasminogen) or inhibit fibrinolysis (such as plasminogen activator inhibitor 1) are measured in OC users.

Changes in most of these coagulation parameters in OC users are small, if they occur at all, and there is no evidence that these minor alterations in levels of coagulation parameters measured in the laboratory have any effect on the clinical risk of developing venous or arterial thrombosis. Nevertheless, if the woman has an inherited coagulation disorder that increases her risk of developing thrombosis, such as protein C, protein S, or antithrombin III deficiency or the more common activated protein C resistance, her risk of developing thrombosis is increased several-fold if she ingests estrogen-containing OCs.[55] Vandenbroucke and coworkers[56] reported that the relative risk of developing deep venous thrombosis among women with activated protein C resistance with OC use was increased 30-fold compared with that of nonusers without the mutation. They estimated that the annual incidence of deep venous thrombosis in a woman of reproductive age with this genetic mutation was about 6 per 10,000 women if she did not take OCs and about 30 per 10,000 women if she took them. At present, it is not recommended that screening for these coagulation deficiencies be undertaken before OC use

■ TABLE 25-5

Lipid Changes With Oral Contraceptives Containing New Progestins

PROGESTIN	N	PERCENTAGE CHANGE FROM BASELINE					
		TG	C	LDL-C	HDL-C	Apo B	Apo A-I
Desogestrel	608	29.3	2.8	−2.1	12.9	10.5	11.3
Gestodene	296	38.3	3.8	−2.5	8.1	16.0	7.1
Norgestimate	>2550	14.8	4.3	−0.2	9.9	5.3	7.3

TG, triglyceride; C, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; apo, apoprotein.
From Speroff L, DeCherney A, and the Advisory Board for the New Progestins.
Evaluation of a new generation of oral contraceptives. Obstet Gynecol 81:1034–1047, 1993.

is started unless the woman has a personal or family history of thrombotic events.

Cardiovascular Events

The cause of the increased incidence of both venous and arterial cardiovascular disease, including myocardial infarction (MI), in users of OCs appears to be thrombosis and not atherosclerosis.

Venous Thromboembolism

Gerstman and colleagues[38] analyzed the effect of OCs with different doses of estrogen on the incidence of venous thromboembolism (VTE) in a historical cohort study of more than 230,000 women aged 15 to 44 years. Among users of OC formulations with less than 50 μg of estrogen, the rate of VTE per 10,000 woman-years was 4.2; with use of the 50-μg estrogen formulation, the rate was 7.0; and in users of formulations with more than 50 μg of estrogen, the rate increased to 10.0 per 10,000 woman-years (Table 25–6). These data confirm earlier findings indicating that the risk of VTE is directly related to the dose of estrogen in the formulation. The background rate of VTE in women of reproductive age is about 0.8 per 10,000 woman-years. A large observational study found that the incidence of venous thromboembolic events among users of OCs with 20 to 50 μg of ethinyl estradiol was 3 per 10,000 woman-years, about four times the background rate of women of reproductive age but half the rate of 6 per 10,000 woman-years associated with pregnancy.[57]

Three population-based studies have been performed to determine the risk of VTE in users of OCs containing mainly less than 50 μg of estrogen.[58–60] These studies were consistent and showed that the risk of deep venous thrombosis was increased approximately fourfold among women using OCs compared with women not using OCs. Thus, use of OCs with less than 50 μg of estrogen is associated with about a threefold to fourfold increased risk of VTE compared with a nonpregnant population not taking OCs but about a 50 percent reduction in risk of VTE compared with a pregnant or recently postpartum population.

In late 1995 and early 1996, results of four observational studies showed that the risk of VTE among women ingesting low-estrogen formulations containing desogestrel or gestodene was increased about 1.5 to 2.5 times that of women ingesting formulations containing less than 50 μg of estrogen and levonorgestrel.[58, 60–62] Because these studies were not prospective comparative trials, controversy exists as to whether the increased risk of VTE was causally related to formulations containing these progestins or whether the increased risk was due to certain types of bias. Selection bias, diagnostic bias, and referral bias could have accounted for the differences, but a causal relation cannot be disproved.[63] Few data have been published to date regarding the risk of VTE with norgestimate-containing compounds, so it remains uncertain whether formulations containing this progestin are associated with an increased risk of VTE compared with use of low-estrogen levonorgestrel compounds.

Myocardial Infarction

Neither epidemiologic studies of humans nor experimental studies with subhuman primates have observed an acceleration of atherosclerosis with the ingestion of OCs. Nearly all the published epidemiologic studies indicate that there is no increased risk of MI among former users of OCs.[64–66] The incidence of cardiovascular disease is also not correlated with the duration of OC use.[67] Further data indicating that the increased risk of MI in OC users is due to thrombosis, not atherosclerosis, are provided by an angiographic study of young women who had an MI performed in 1983 by Engel and associates.[68] In this study, only 36 percent of users of OCs containing 50 μg of ethinyl estradiol had evidence of coronary atherosclerosis compared with 79 percent of nonusers.

A study with cynomolgus macaque monkeys found that the ingestion of an OC containing high doses of norgestrel and ethinyl estradiol lowered HDL cholesterol levels significantly.[69] However, after 2 years of ingesting this formulation and being fed an atherogenic diet, these animals had a significantly smaller area of coronary artery atherosclerosis than did a control group of female monkeys not ingesting OCs but fed the same diet. Another group of monkeys that received levonorgestrel without estrogen also had lowered HDL cholesterol levels. In this group, the extent of coronary atherosclerosis was significantly increased compared with that of the control group. The results of this study have since been confirmed in a larger study with two high-dose estrogen-progestin formulations.[70] Both of these compounds lowered the HDL cholesterol levels by half and tripled the ratio of cholesterol to HDL cholesterol. In this study, the mean extent of coronary artery plaque formation in the high-risk control group of female animals was more than 3 times greater than that found in animals ingesting a high-dose norgestrel compound and more than 10 times greater than that found in animals ingesting a high-dose ethynodiol diacetate compound. These studies suggest that the estrogen component of OCs has a direct protective effect on the coronary arteries, reducing the extent of atherosclerosis that would otherwise be accelerated by decreased levels of HDL cholesterol.

The epidemiologic studies that reported an increased incidence of MI in older users of OCs were published in the late 1970s and thus used as a database women who ingested only formulations with 50 μg or more of estrogen.

■ TABLE 25–6

Rates of Deep Venous Thromboembolic Disease in Oral Contraceptive Estrogen Dose–Refined Cohorts

ESTROGEN-DEFINED COHORTS (μg)	NUMBER OF CASES	PERSON-YEARS (× 10,000)	RATES/10,000 PERSON-YEARS
<50	53	12.7	4.2
50	69	9.8	7.0
>50	20	2.0	10.0
All	142	24.5	5.8

From Gerstman BB, Piper JM, Tomita DK, et al. Oral contraceptive estrogen dose and the risk of deep venous thromboembolic disease. Am J Epidemiol 133:32–37, 1991.

In these case-control and cohort studies, a significantly increased incidence of MI was found mainly among older users who had risk factors that caused arterial narrowing, such as pre-existing hypercholesterolemia, hypertension, diabetes mellitus, or smoking more than 15 cigarettes a day.[71]

Data accumulated during the first 10 years of the RCGP study (1968 to 1978), in which the majority of users ingested formulations with more than 50 μg of estrogen and high doses of progestin, showed that a significantly increased relative risk of death from circulatory disease occurred only among women older than 35 years who also smoked.[67] A more recent analysis of data obtained during the first 20 years of this study (1968 through 1987) revealed that there was no significant increased relative risk of acute MI among current or former users of OCs who did not smoke any cigarettes[72] (Table 25–7). Women who smoked and did not use OCs had a greater risk of MI than did nonsmokers whether or not they used OCs. Even though most of the women in this study used high-dose formulations, a significantly increased risk of MI with OC use compared with that of smokers not using OCs occurred only among both light (fewer than 15 cigarettes per day) and heavy cigarette smokers. OC users who were heavy smokers had a greater relative risk than did light smokers. A case-control study analyzed the relation between OC use and the risk of MI among women admitted to a group of New England hospitals between 1985 and 1988. The relative risk of MI among current OC users was not significantly increased (RR, 1.1; confidence interval [CI], 0.4 to 3.1).[66] Among women who smoked at least 25 cigarettes a day, current OC use increased the risk of MI 30-fold. Smoking alone, without use of OCs, increased the risk of MI about ninefold. These data indicate that cigarette smoking is an independent risk factor for MI, but the use of high-dose OCs by cigarette smokers significantly enhances their risk of experiencing an MI, the two factors acting synergistically. Current or prior OC use is not associated with an increased risk of MI in nonsmokers.

Stroke

Although epidemiologic data from studies performed in the 1970s indicated that there was possibly a causal relation between ingestion of high-dose OC formulations and stroke, the data were conflicting; some studies showed a significantly increased risk of thrombotic stroke, others an increased risk of hemorrhagic stroke, and still others no significantly increased risk of either entity.[73] Furthermore,

as occurred with MI, the studies that did show a significantly increased risk of stroke in OC users indicated that the increased risk was mainly limited to older women who also smoked or were hypertensive.[74]

Data from the epidemiologic studies of OC use and cardiovascular disease performed in the 1960s and 1970s are not relevant to their current use, because the dose of both steroid components in the formulations now being marketed is markedly less, and women with cardiovascular risk factors such as uncontrolled hypertension are no longer receiving these agents. Furthermore, it is strongly recommended not to prescribe OCs to women older than 35 years who also smoke.

A nested case-control analysis by Hannaford and colleagues[75] examined the data obtained between 1968 and 1990 during the RCGP's Oral Contraception Study to determine the relationship between OC use and the risk of first-ever stroke including the diagnosis of subarachnoid hemorrhage, cerebral hemorrhage, or thromboembolic stroke. Women using OCs containing a high estrogen dose, more than 50 μg, had nearly a sixfold increase in the risk of stroke; women ingesting OC formulations containing 30 to 35 μg of estrogen did not have an increased risk. An analysis of strokes occurring in a large health maintenance organization in California during the years 1991 to 1994 indicated that the users had no significant increase of either thromboembolic or hemorrhagic stroke with OC use. In this study, the relative risk of thromboembolic stroke was 0.65 and of hemorrhagic stroke 1.01 for OC users compared with women who never used OCs and 1.18 and 1.13 compared with never users and past users.[76]

The results of these recent epidemiologic studies indicate that use of low-dose estrogen-progestin OC formulations by nonsmoking women without risk factors for cardiovascular disease is not associated with an increased incidence of either MI or stroke. Smoking is a risk factor for arterial but not venous thrombosis. Combination OCs should not be prescribed to women older than 35 years who smoke cigarettes or use alternative forms of nicotine.

Reproductive Effects

In an attempt to determine whether the reproductive endocrine system recovers normally after cessation of OC therapy, Klein and Mishell[77] measured serum levels of FSH, LH, estradiol, progesterone, and prolactin in six women every day for 2 months after they discontinued use of high-dose OCs. Except for a variable prolongation of the follicular phase of the first postcontraceptive cycle, the

■ TABLE 25–7

Relative Risk of Myocardial Infarction in Relation to Smoking and Oral Contraceptive Use*

SMOKING	ORAL CONTRACEPTIVE USE		
	Never (CL)	Previously (CL)	Current (CL)
Never	1.0	1.1 (0.6–2.2)	0.9 (0.3–2.7)
<15 cig/day	2.0 (1.0–3.9)	1.3 (0.6–2.8)	3.5 (1.3–9.5)
≥15 cig/day	3.3 (1.6–6.7)	4.3 (2.3–8.0)	20.8 (5.2–83.1)

*Royal College of General Practitioners study, 1968–1987. N = 158. CL, confidence limits.
Modified from Croft P, Hannaford PC. Risk factors for acute myocardial infarction in women. Br Med J 298:1245, 1991.

patterns and levels of all of these hormones were indistinguishable from those found in normal ovulating subjects. In these six women, the initial LH peak occurred from 21 to 28 days after ingestion of the last tablet. These results indicate that after a variable but usually short interval after the cessation of oral steroids, their suppressive effect on the hypothalamic-pituitary-ovarian axis disappears. After the initial recovery, completely normal endocrine function occurs.

As previously mentioned, the delay in the return of fertility is greater for women discontinuing use of OCs with 50 µg of estrogen or more than with those containing lower doses of estrogen.[29] However, use of the low-dose formulations still causes a significant reduction in time to conception rates, with a mean of 5.88 cycles for OC users compared with 3.18 cycles for women discontinuing other contraceptive methods. Among women stopping use of OCs to conceive, the reduced probability of conception compared with that of women stopping use of other methods is greatest in the first month after their use is stopped and decreases steadily thereafter. There is little if any effect of duration of OC use on the length of delay of subsequent conception, but the magnitude of the delay to return of conception after OC use is greater among older primiparous women than among others.

Thus, for about 2 years after the discontinuation of contraceptives to conceive, the rate of return of fertility is lower for users of OCs than for women who have used barrier methods, but eventually the percentage of women who conceive after ceasing to use each of these contraceptive methods becomes the same.[78] Thus, the use of OCs does not cause permanent infertility.

Neither the rate of spontaneous abortion nor the incidence of chromosome abnormalities[79] in abortuses is increased in women who conceive in the first or subsequent months after they cease to use OCs. Several cohort and case-control studies of large numbers of babies born to women who stopped using OCs have been undertaken. These studies indicate that these infants have no greater chance of being born with any type of birth defect than do infants born to women in the general population, even if conception occurred in the first month after the medication was discontinued.[80-82] If OCs are accidentally ingested during the first few months of pregnancy, a large cohort study reported that there is no significantly increased risk of congenital malformations among the offspring of users overall or among those of nonsmoking users.[82]

Neoplastic Effects

OCs have been extensively used for more than 35 years, and numerous epidemiologic studies of both cohort and case-control design have been performed to determine the relation between use of these agents and the development of various types of neoplasms. Because as yet no elderly women have used OCs during their early reproductive years, the studies thus far published usually restrict the analysis to women younger than 60 years. Because hormones are mainly considered to be promoters, not initiators, of cancers, any adverse oncologic effects of these steroids should show a dose response, as demonstrated by an increased risk occurring with increased duration of use.

In 1995, Schlesselman[83] addressed this issue by performing a meta-analysis of the epidemiologic studies reported between 1980 and 1994 that analyzed the effect of OCs according to their duration of use on cancer of the breast, organs of the female reproductive tract, and liver.[83]
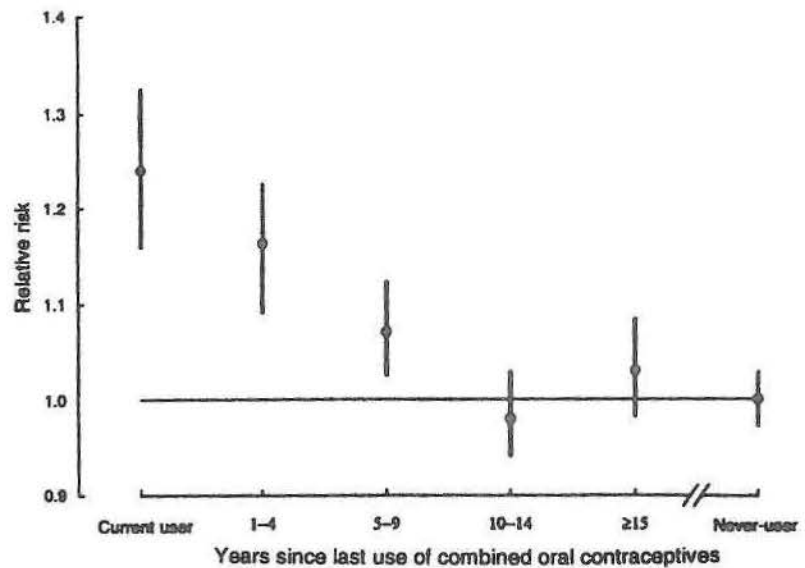
Breast Cancer

Because estrogen stimulates the growth of breast tissue, there have been concerns that the high dose of exogenous estrogen in OCs could either initiate or promote breast cancer in humans. Accordingly, numerous epidemiologic studies have been published in which breast cancer risk among OC users has been determined. In 1991, Thomas[84] published a comprehensive review of the results of all previously published epidemiologic studies of breast cancer risk in relation to use of combined OCs. Both case-control and cohort studies were analyzed, and the summary relative risk was determined by meta-analysis. There were 15 case-control studies conducted in developed countries that included women of all ages at risk for having used OCs. These papers were published between 1974 and 1990, and the relative risk of breast cancer with OC use ranged from 0.7 to 1.6 in the individual studies. Only one of these studies reported a significant increase in breast cancer risk, and the summary relative risk obtained by combining data for all the studies was 1.0 (CI, 1.0 to 1.1).[84]

Eight case-control and one cohort study investigated the relative risk of breast cancer in OC users who did and did not have a family history of breast cancer. None of the studies showed a significant difference in risk of breast cancer among OC users who did and did not have a family history of breast cancer.

In 1996, a large international collaborative group reanalyzed the entire worldwide epidemiologic data that had investigated the relation between risk of breast cancer and use of OCs. Analysis was done of data from 54 studies performed in 25 countries, involving more than 53,000 women with breast cancer and more than 100,000 control subjects. The analysis indicated that while women took OCs, they had a slightly increased risk of having breast cancer diagnosed (RR, 1.24; CI, 1.15 to 1.30)[85] (Fig. 25–6). The magnitude of risk of having breast cancer diagnosed declined steadily after stopping OCs, so there was no longer a significantly increased risk 10 years or more after stopping their use (RR, 1.01; CI, 0.96 to 1.05).[85] It is of interest that the cancers diagnosed in women taking OCs were less advanced clinically than those that occurred in the nonusers. The risk of having breast cancer that had spread beyond the breast compared with a localized tumor was significantly reduced (RR, 0.88; CI, 0.81 to 0.95) in OC users compared with nonusers. The group concluded that these results could be explained by the fact that breast cancer is diagnosed earlier in OC users than in nonusers or could be due to biologic effects of the OCs.[86]

The clinical meaning of this vast amount of epidemiologic data with small changes in relative risk is difficult to interpret. It appears that the dose or type of either steroid as well as duration of OC use is not related to breast cancer risk. Because there is no relation between dose or duration of use of estrogen, it is unlikely that OCs initiate breast cancer. Furthermore, the collaborative analysis found that

Figure 25-6 Relative risk of breast cancer by time since last use of combined oral contraceptives. Dots are point estimates. Vertical line indicates 95 percent confidence intervals. (From Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: Collaborative reanalysis of individual data on 53,297 women with breast cancer and 100,239 women without breast cancer from 54 epidemiological studies. Lancet 347:1713–1727, 1996. © by The Lancet Ltd.)

there was no significant increase in risk of breast cancer with OC use at very young ages, use before a first birth, or use by women with a family history of breast cancer. Two findings are important. One is that with current OC use or use within 5 years, the risk of breast cancer diagnosis is increased by about 25 percent. The second is that the increased risk of breast cancer in current OC users is limited to localized disease, and OC users have a significantly reduced incidence of disease that has spread beyond the breast. A decreased risk of advanced disease is also found in more older former OC users than nonusers who have breast cancer. Because the increased risk of breast cancer with OC use is confined to current and recent users, if there is an excess in incidence, the magnitude of increased incidence is small because breast cancer is uncommon before the age of 45 years. Furthermore, the contraceptive steroids probably act to promote the growth or increase the chance of diagnosis of existing cancers because breast cancer has been thought to usually take many years to become clinically evident after the cancer is initiated. Overall, the large body of data regarding OC use and breast cancer risk is reassuring.

Cervical Cancer

The epidemiologic data regarding the risk of invasive cervical cancer as well as cervical intraepithelial neoplasia and OC use are conflicting. Confounding factors such as the woman's age at first sexual intercourse, number of sexual partners, exposure to human papillomavirus (possibly greater among OC users), cytologic screening (probably more frequent among OC users), and use of barrier contraceptives or spermicides (primarily by women in the control group) as well as cigarette smoking (an independent risk factor for this disease) could account for the different results in different studies. In most of these studies, statistical corrections were made for these confounding factors, and the control group did not use barrier methods of contraception in many of them.

As reported by Schlesselman's review of 14 studies of

more than 3800 women with invasive cervical cancer, there is a significant trend of increased risk of this disease with increased duration of OC use. The relative risk of disease with 4, 8, and 12 years of OC use increased from 1.37 to 1.60 to 1.77, respectively.[83]

Two of three case-control studies also reported that the risk of invasive cervical cancer was significantly increased with long-term OC use, with a relative risk between 1.5 and 2.5.[87-89] Three case-control studies have reported that the risk of adenocarcinoma of the cervix was significantly increased about twofold among OC users compared with nonusers.[87, 90, 91] In two of these studies, the risk of this type of tumor increased with increasing duration of use; in one study, a fourfold increased risk was reached with more than 12 years of OC use. Adenocarcinoma of the cervix is uncommon before the age of 55 years, with an incidence of about 1 per 1000 women. In contrast to these findings, the majority of well-controlled studies indicate that there is no significant change in risk of cervical intraepithelial neoplasia with OC use.[88] Because invasive epithelial cervical cancer is usually preceded by dysplasia, the relation between OC use and increased risk of epithelial cervical cancer is unlikely to be causal. However, it is possible that a causal relation exists between OC use and an increased risk of cervical adenocarcinoma.

Endometrial Cancer

Twelve case-control studies and three cohort studies have examined the relation between OCs and endometrial cancer, and all but two of these studies have indicated that the use of these agents has a protective effect against endometrial cancer, the third most common cancer among United States women.[83, 92] Women who use OCs for at least 1 year have an age-adjusted relative risk of 0.5 for diagnosis of endometrial cancer between the ages of 40 and 55 years compared with nonusers. This protective effect is related to duration of use, increasing from a 20 percent reduction risk with 1 year of use to a 40 percent reduction with 2 years of use to about a 60 percent reduction with 4 years

of use. Voigt and colleagues[93] reported that the protective effect of OCs on endometrial cancer occurred with use of combination formulations with both high and low doses of progestin.

Ovarian Cancer

As summarized by Hankinson and coworkers[94] in 1992, there were 20 published reports examining the use of OCs with subsequent development of ovarian cancer, and 18 of these found a reduction in risk specifically of the most common type—epithelial ovarian cancers (Fig. 25–7). The summary relative risk of ovarian cancer among ever-users of OCs was 0.64, a 36 percent reduction. OCs reduce the risk of the four main histologic types of epithelial ovarian cancer (serous, mucinous, endometrioid, and clear cell), and the risk of invasive ovarian cancers as well as of those with low malignant potential is reduced. The magnitude of the decrease in risk is directly related to the duration of OC use, increasing from about a 40 percent reduction with 4 years of use to a 53 percent reduction with 8 years of use and a 60 percent reduction with 12 years of use. Beyond 1 year, there is about an 11 percent reduction in ovarian cancer risk for each of the first 5 years of use. The protective effect begins within 10 years of first use and continues for at least 20 years after the use of OCs ends. A study by Rosenberg and associates[95] found a similar level of protection with low-dose monophasic formulations as well as with higher dose agents. Insufficient data on ovarian cancer risk with use of phasic formulations are currently available. As with endometrial cancer, the protective effect occurs only in women of low parity (≤4), who are at greatest risk for this type of cancer.

Liver Adenoma and Cancer

The development of a benign hepatocellular adenoma is a rare occurrence in long-term users of OCs, and the increased risk of th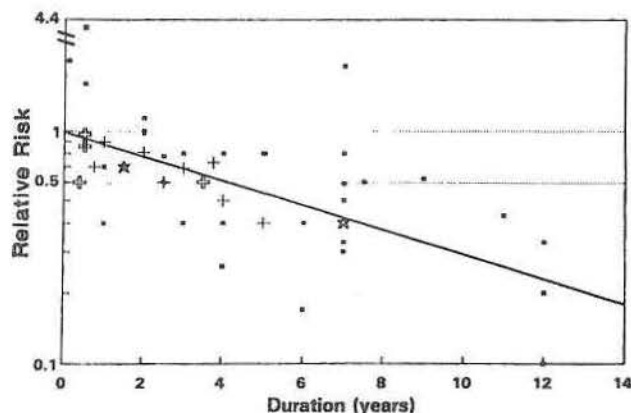is tumor was associated with prolonged use of high-dose formulations, particularly those containing mestranol. Although two British studies reported an increased risk of liver cancer among users of OCs, the number of patients was small and the results could have been influenced by confounding factors.[96, 97] The rate of death from the disease has remained unchanged in the United States during the past 25 years, a period when millions of women have used these agents. Data from a large multicenter epidemiologic study coordinated by the WHO found no increased risk of liver cancer associated with OC users in countries with a high prevalence rate of this neoplasm.[98] This study found no change in risk with increasing duration of use or time since first or last use.

Pituitary Adenoma

OCs mask the predominant symptoms produced by prolactinoma—amenorrhea and galactorrhea. When OC use is discontinued, these symptoms occur, suggesting a causal relation. However, data from three studies indicate that the incidence of pituitary adenoma among users of OCs is not higher than that among matched control subjects.[99]

Malignant Melanoma

Several epidemiologic studies have been undertaken to assess the relation of OC use and malignant melanoma. The results are ambiguous, because an increased risk, a decreased risk, and no effect have all been reported. In a review by Prentice and Thomas[73] in 1987, the summary relative risk for eight case-control studies was 1.0 and for three cohort studies 1.4, an insignificant increase. A more recent analysis of the two large British cohort studies that were initiated in 1968, involving more than 40,000 women, reported that the adjusted relative risk of malignant melanoma in OC users was 0.92 and 0.85.[100] The results of these large studies of long duration indicate that OC use does not increase the risk of malignant melanoma.

Contraindications to Use

OCs can be prescribed for the majority of women of reproductive age, because these women are young and generally healthy. However, there are certain absolute contraindications: a history of vascular disease (including thromboembolism, thrombophlebitis, atherosclerosis, and stroke) and systemic disease that has altered the vascular system, such as lupus erythematosus or diabetes with retinopathy or nephropathy. Cigarette smoking by OC users older than 35 and uncontrolled hypertension are also contraindications. One of the contraindications listed in the product labeling is cancer of the breast or endometrium, although there are no data indicating that OCs are harmful to women with these diseases. Pregnant women should not take OCs, because it has been theorized that there may be masculinizing effect of the 19-nonprogestins on the external genitalia of female fetuses.

Women with functional heart diseases should not use OCs, because the fluid retention they produce could result in congestive heart failure. There is no evidence, however, that individuals with asymptomatic mitral valve prolapse should not use OCs. Women with active liver disease

Figure 25–7 ▪ Relative risk of ovarian cancer associated with different durations of oral contraceptive use: findings of 15 studies. Study categories, indicating category weights ranging from smallest (weight in bottom 25 percent of range) to largest (weight in top 25 percent of range): squares = 1 (smallest); pluses = 2; open crosses = 3; stars = 4 (largest). (From Hankinson SE, Colditz GA, Hunter DJ, et al. A quantitative assessment of oral contraceptive use and risk of ovarian cancer. Obstet Gynecol 80:708–714, 1992.)

should not take OCs. However, women who have recovered from liver disease, such as viral hepatitis, and whose liver function test results have returned to normal can safely take OCs.

Relative contraindications to OC use include heavy cigarette smoking by women younger than age 35, migraine headaches, undiagnosed causes of amenorrhea, and depression. About 20 percent of women have migraine headaches, and their frequency and severity can be worsened by OC use. There is currently no evidence that the risk of stroke is significantly increased in women with migraine headaches who use OCs compared with nonusers. Unless the women have peripheral neurologic symptoms with the migraine headaches, OCs can be used. If fainting, temporary loss of vision or speech, or paresthesias develop in an OC user, the use of OCs should be stopped because of their thrombophilic effect.

Because OC use may mask the symptoms produced by a prolactin-secreting adenoma (amenorrhea and galactorrhea), amenorrheic women should not receive OCs until the diagnosis for this symptom is established. If galactorrhea develops during OC use, OCs should be discontinued, and after 2 weeks a serum prolactin level should be measured. If it is elevated, further diagnostic evaluations are indicated. The presence of a prolactin-secreting macroadenoma but not a microadenoma is a contraindication for OC use. Use of OCs does not cause enlargement of prolactin-secreting pituitary microadenomas or worsen functional prolactinoma as was previously believed. Women with gestational diabetes can take low-dose OC formulations, because these agents do not affect glucose tolerance or accelerate the development of diabetes mellitus.[101] Insulin-dependent diabetes without vascular disease is also not a contraindication for low-dose OC use.

Contraceptive Use

Initiation

ADOLESCENTS

In deciding whether a sexually active pubertal girl should use OCs for contraception, the clinician should be more concerned about compliance with the regimen than about possible physiologic harm. As long as she has demonstrated maturity of the hypothalamic-pituitary-ovarian axis with at least three regular, presumably ovulatory, menstrual cycles, it is safe to prescribe OCs without concern that their use will permanently alter future reproductive endocrinologic function. It is not necessary to be concerned about accelerating epiphyseal closure in the postmenarcheal female. Endogenous estrogens have already initiated the process a few years before menarche, and use of contraceptive steroids will not hasten it.

AFTER PREGNANCY

There is a difference in the relationship of the return of ovulation and bleeding between the postabortal woman and one who has had a term delivery. The first episode of menstrual bleeding in the postabortal woman is usually preceded by ovulation. After a term delivery, the first episode of bleeding is usually but not always anovulatory. Ovulation occurs sooner after an abortion, usually between 2 and 4 weeks, than after a term delivery, when ovulation is usually delayed beyond 6 weeks but may occur as early as 4 weeks in a woman who is not breast feeding.

Thus, after spontaneous or induced abortion of a fetus of less than 12 weeks' gestation, OCs should be started immediately to prevent conception after the first ovulation. For women who deliver after 28 weeks and are not nursing, the combination pills should be initiated 2 to 3 weeks after delivery. If the termination of pregnancy occurs between 21 and 28 weeks, contraceptive steroids should be started 1 week later; the reason for delay in this instance is that the normally increased risk of thromboembolism occurring post partum may be further enhanced by the thrombophilic effects of combination OCs. Because the first ovulation is delayed for at least 4 weeks after a term delivery, there is no need to expose the woman to this increased risk.

Estrogen inhibits the action of prolactin in breast tissue receptors; therefore, the use of combination OCs (those containing both estrogen and progestin) diminishes the amount of milk produced by OC users who breast feed their babies. Although the diminution of milk production is directly related to the amount of estrogen in the contraceptive formulation, only one study has been published in which the amount of breast milk was measured by breast pump in women using formulations with less than 50 μg of estrogen. In this study, the use of this low dose of estrogen reduced the amount of breast milk.[102] Thus, it is probably best for women who are nursing not to use combination OCs unless supplemental feeding is given to the infant.

Women who are breast feeding every 4 hours, including during the night, will not ovulate until at least 10 weeks after delivery and thus do not need contraception before that time. Because only a small percentage of breast feeding women will ovulate as long as they continue full nursing and remain amenorrheic, either a barrier method or a progestin-only OC can be used until menses resume. Progestins do not diminish the amount of breast milk, and progestin-only OCs are effective in this group of women. Once supplemental feeding is introduced, ovulation can resume promptly, and more effective contraception is then needed. Combination OCs should be used once supplemental feeding is initiated.

CYCLING WOMEN

At the initial visit, after a history and physical examination have determined that there are no medical contraindications for OCs, the woman should be informed about the benefits and risks. For medicolegal reasons, it is best to note on the patient's medical record that the benefits and risks have been explained to her.

Type of Formulation

In determining which formulation to use, it is best initially to prescribe a formulation with less than 50 μg of ethinyl estradiol, because these agents are associated with less cardiovascular risk as well as fewer estrogenic side effects than formulations with 50 μg of estrogen. It would also appear reasonable to use formulations with the lowest androgenic potency of progestin, because there would be

less androgenic, metabolic, and clinical adverse effects associated with their use. The development of multiphasic formulations has allowed the total dose of progestin to be reduced compared with some monophasic formulations, without increasing the incidence of breakthrough bleeding. However, several monophasic formulations have a lower total dose of progestin per cycle than the multiphasic formulations, and the incidence of follicular enlargement is more frequent with multiphasic than with monophasic formulations.[103]

The U.S. Food and Drug Administration (FDA) has stated that the product prescribed should be one that contains the least amount of estrogen and progestin that is compatible with a low failure rate and the needs of the individual woman. Because few randomized studies have been performed comparing the different marketed formulations, until large-scale comparative studies are performed, the clinician must decide on the formulation to use on the basis of which have the least adverse effects among women in his or her practice. If estrogenic or progestogenic side effects occur with one formulation, a different agent with less estrogenic or progestogenic activity can be given.

The contraceptive formulations containing progestins and no estrogen have a lower incidence of adverse metabolic effects than do the combination formulations. Because the factors that predispose to thromboembolism are caused by the estrogen component, the incidence of thromboembolism in women ingesting these compounds is not increased. Furthermore, blood pressure is not affected, nausea and breast tenderness are eliminated, and milk production and quality are unchanged. Despite these advantages, these agents have the disadvantages of a high frequency of intermenstrual and other abnormal bleeding patterns (including amenorrhea) and a lower rate of effectiveness than the combined formulations. The failure rate of these preparations is higher than with the combined formulations, and a relatively high percentage of the pregnancies that do occur are ectopic. Because nursing mothers have reduced fertility and are amenorrheic, the major disadvantages of these preparations are minimized for these individuals. Furthermore, because milk production and quality are unaffected in contrast to the changes produced by combination pills, the formulations with only a progestin may be offered to these women while they are nursing. However, a small portion of these synthetic steroids have been detected in breast milk. The long-term effects (if any) of these progestins on the infant are not known, but none has been detected to date. A long-term follow-up study of breast fed children whose mothers ingested combined OCs containing 50 μg of estrogen while they were lactating revealed no difference in mean body weight or height up to 8 years of age compared with breast fed children whose mothers did not ingest OCs.[104] There was also no difference of occurrence of disease or in intellectual or psychologic behavior between the two groups.

Follow-up

If a healthy woman has no contraindications to OC use, it is unnecessary to perform any laboratory tests including cervical cytology unless these are necessary for routine health maintenance. At the end of 3 months, the woman should be seen again; at this time, a nondirected history should be obtained and the blood pressure measured. After this visit, the woman should be seen annually, at which time a nondirected history should again be taken, blood pressure and body weight measured, and a physical examination (including breast, abdominal, and pelvic examination with cervical cytology) performed. It is important to perform annual cervical cytologic screening of OC users, because they are a group at relatively high risk for development of cervical neoplasia. The routine use of other laboratory tests is not indicated unless the woman has a family history of diabetes or vascular disease at a young age. Routine use of these tests in women is not indicated, because the incidence of positive results is extremely low. However, if the woman has a family history of vascular disease, such as MI occurring in family members younger than 50, it would be advisable to obtain a lipid panel before OC use is started; hypertriglyceridemia may be present, and OC use will further raise triglyceride levels. Because the low-dose formulations do not adversely alter the lipid profile except for triglycerides, it is not necessary to measure lipids, other than the routine cholesterol screening every 5 years, in women with no cardiovascular risk factors, even if they are older than 35. If the woman has a family history of diabetes or evidence of diabetes during pregnancy, a 2-hour postprandial blood glucose test should be performed before OCs are started, and if the blood glucose level is elevated, a glucose tolerance test should be performed. If the woman has history of liver disease, a liver panel should be obtained to make certain that liver function is normal before OCs are started.

Drug Interactions

Although synthetic sex steroids can retard the biotransformation of certain drugs (e.g., phenazone and meperidone) as a result of substrate competition, such interference is not important clinically. OC use has not been shown to inhibit the action of other drugs. However, some drugs can interfere clinically with the action of OCs by inducing liver enzymes that convert the steroids to more polar and less biologically active metabolites.

Certain drugs have been shown to accelerate the biotransformation of steroids in humans. These include barbiturates, sulfonamides, cyclophosphamide, and rifampin. Several investigators have reported a relatively high incidence of OC failure in women ingesting rifampin, and these two agents should not be given concurrently.[105] The clinical data concerning OC failure in users of other antibiotics (e.g., penicillin, ampicillin, and sulfonamides), analgesics (e.g., phenytoin), and barbiturates are less clear. A few anecdotal studies have appeared in the literature, but reliable evidence for a clinical inhibitory effect of these drugs on OC effectiveness, such as occurs with rifampin, is not available. One study by Murphy and colleagues[106] showed that when 2 gm of tetracycline was given daily in divided doses, the levels of both ethinyl estradiol and norethindrone in OC users were similar to those before antibiotic use. Women with epilepsy requiring medication should probably be treated with formulations containing 50 μg of estrogen; a higher incidence of abnormal bleeding has been reported in these women with the use of lower

dose estrogen formulations owing to lower circulating levels of ethinyl estradiol brought about by the action of most antiepileptic medications.[107]

Noncontraceptive Health Benefits

In addition to being the most effective method of contraception, OCs provide many other health benefits.[108] Some are due to the fact that the combination OCs contain a potent, orally active progestin as well as an orally active estrogen, and there is no time when the estrogenic target tissues are stimulated by estrogens without a progestin (unopposed estrogen).

Both natural progesterone and the synthetic progestins inhibit the proliferative effect of estrogen, the so-called antiestrogenic effect. Estrogens increase the synthesis of both estrogen and progesterone receptors, whereas progesterone decreases their synthesis. Thus, one mechanism whereby progesterone exerts its antiestrogenic effects is by decreasing the synthesis of estrogen receptors. Relatively little progestin is needed to exert this action, and the amount present in OCs is sufficient. Another way progesterone produces its antiestrogenic action is by stimulating the activity of the enzyme estradiol-17β-dehydrogenase within the endometrial cell. This enzyme converts the more potent estradiol to the less potent estrone, reducing estrogenic action within the cell.

As a result of the antiestrogenic action of the progestins in OCs, the height of the endometrium is less than in an ovulatory cycle, and there is less proliferation of the endometrial glands. These changes produce several substantial benefits for the OC user. One is a reduction in the amount of blood loss at the time of endometrial shedding. In an ovulatory cycle, the mean blood loss during menstruation is about 35 ml, compared with 20 ml for women ingesting OCs. This decreased blood loss makes the development of iron deficiency anemia less likely in OC users than in nonusers.

Because OCs produce regular withdrawal bleeding, it would be expected that OC users would have fewer menstrual disorders than do control subjects. The results of the RCGP study confirmed the fact that OC users were significantly less likely to have menorrhagia, irregular menstruation, or intermenstrual bleeding develop.[109] Because these disorders are frequently treated by curettage or hysterectomy, OC users require these procedures less frequently than do nonusers.

Estrogen exerts a proliferative effect on breast tissue, which also contains estrogen receptors. Progestins may also inhibit the synthesis of estrogen receptors in this organ. Several studies have shown that OCs reduce the incidence of benign breast disease, and two prospective studies have indicated that this reduction is directly related to the amount of progestin in the compounds.[110, 111]

Benefits from Inhibition of Ovulation

Other noncontraceptive medical benefits of OCs result from their main action—inhibition of ovulation. Some disorders, such as dysmenorrhea and premenstrual tension, occur much more frequently in ovulatory than in anovulatory cycles.

Lanes and coworkers[103] studied the rate of functional cysts more than 2 cm in diameter, which required either hospitalization or outpatient surgery, by ultrasonography. They found that low-dose monophasic formulations resulted in about a 50 percent reduction in functional cysts, lower than the 75 percent reduction with high-dose formulations, whereas use of multiphasic formulations had only a slight reduction of ovarian cyst development.

Other Benefits

Several European studies, including the RCGP study, showed that the risk of development of rheumatoid arthritis in OC users was only about half that in control subjects.[112, 113] Another benefit is protection against salpingitis, commonly referred to as pelvic inflammatory disease (PID). The relative risk of PID developing among OC users in most studies is about 0.5, a 50 percent reduction.[114] OCs reduce the clinical development of salpingitis in women infected with gonorrhea. OCs reduce the risk of ectopic pregnancy by more than 90 percent in current users and may reduce the incidence in former users by decreasing their chance of development of salpingitis.

Limited epidemiologic data indicate that OCs may reduce bone loss in perimenopausal women, particularly those with oligomenorrhea.[115] There are noncontraceptive health benefits associated with continuing OC use beyond the age of 40 years into the perimenopausal years. Because the estrogen given for hormone replacement is not as thrombophilic as the estrogen dose currently used in OCs, it is best to switch from OCs to estrogen replacement at about the age of 50 years. To avoid discontinuing OC use when the woman is still ovulating, measurement of the FSH and estradiol levels on the last day of the pill-free interval provides information about ovarian follicular activity. When the FSH level is elevated and the estradiol level is low, OCs should be discontinued and estrogen hormonal replacement begun.[116]

LONG-ACTING CONTRACEPTIVE STEROIDS

To avoid contraceptive failure associated with the need to remember to take OC daily, methods of administering contraceptive steroid formulations at infrequent intervals have been developed. To date, two types of long-acting steroids, injectable suspensions and subdermal implant formulations, have been developed and are being used by women in the United States and elsewhere. Because most of the long-acting steroid formulations contain only a progestin, without an estrogen, endometrial integrity is not maintained and uterine bleeding occurs at irregular and unpredictable intervals. Therefore, women wishing to use these methods need to be counseled about the development of irregular bleeding before their use to enhance continuity of use.

Injectable Suspensions

Three types of injectable steroid formulations are currently in use for contraception throughout the world. These include depot medroxyprogesterone acetate (DMPA), given

in a dose of 150 mg every 3 months; norethindrone enanthate, given in a dose of 200 mg every 2 months; and several once-a-month injections of combinations of different progestins and estrogens. Only the first of these three types is currently available in the United States. Injectable contraceptives are a popular method of contraception worldwide. In the United States, they are used by about 3 percent of women of reproductive age.

Medroxyprogesterone acetate (MPA) is a 17-acetoxy-progesterone compound and is the only progestin used for contraception that is not a 19-nortestosterone derivative. In all currently marketed oral contraceptives, the progestins are all 19-nortestosterone compounds, either estranes or gonanes, and as such have varying degrees of androgenic activity.

The 17-acetoxyprogestins, which do not have androgenic activity and are structurally related to progesterone instead of testosterone, were used in OC formulations about 30 years ago. Although they were approved for contraception in many Western countries in the 1960s, regulatory approval for these agents in the United States was stopped when tests on beagle dogs showed that ingestion of OCs with 17-acetoxyprogestins was associated with an increased risk of mammary cancer. It was discovered later that, unlike humans and other animals, the beagle uniquely metabolizes 17-acetoxyprogestins to estrogen, which causes mammary hyperplasia. Thus, when MPA is ingested by the beagle, this substance behaves differently than it does in the human, in whom it is not metabolized to estrogen. After epidemiologic studies showed that DMPA does not increase the risk of breast cancer in humans, regulatory approval for marketing this agent as a contraceptive was obtained in the United States in 1992.

Depot Formulation of Medroxyprogesterone Acetate

MPA is a 17-acetoxy-6-methyl progestin that has progestogenic activity in the human[117] (Fig. 25–8). Because MPA is not metabolized as rapidly as the parent compound, progesterone, it can be given in smaller amounts than progesterone, with an equivalent amount of progestational activity. DMPA, the long-acting injectable formulation of MPA, consists of a crystalline suspension of this progestational hormone. The effective contraceptive dosage is 150 mg DMPA, which is given by injection deep into the
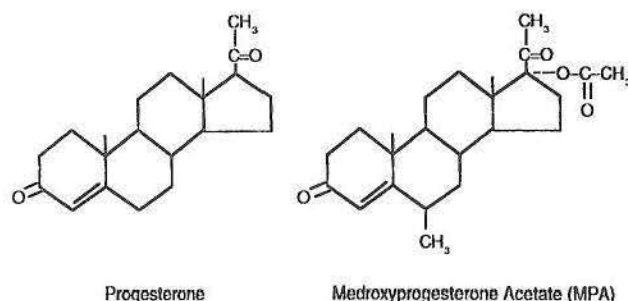

Progesterone   Medroxyprogesterone Acetate (MPA)

Figure 25–8 ▪ Comparative structures of progesterone and MPA. (From Mishell DR Jr. Pharmacokinetics of depot medroxyprogesterone acetate contraception. J Reprod Med 41[suppl]:381–390, 1996.)

gluteal or deltoid muscle, after which the progestin is released slowly into the systemic circulation. The area should not be massaged, so that the drug is released slowly into the circulation and maintains its contraceptive effectiveness for at least 4 months.

DMPA is an extremely effective contraceptive. In a large WHO clinical trial studying use of DMPA, the pregnancy rate at 1 year was only 0.1 percent; at 2 years, the cumulative rate was 0.4 percent.[118] Three mechanisms of action are involved. The major effect is inhibition of ovulation. Second, the endometrium becomes thin and does not secrete sufficient glycogen to provide nutrition for a blastocyst entering the endometrial cavity. Third, DMPA keeps the cervical mucus thick and viscous, so sperm are unlikely to reach the oviduct and fertilize an egg. With these multiple mechanisms of action, DMPA is one of the most effective reversible methods of contraception currently available.

PHARMACOKINETICS

MPA can be detected in the systemic circulation within 30 minutes after its intramuscular injection.[119] Although serum MPA levels vary among individuals, they rise steadily to contraceptively effective blood levels (>0.5 ng/ml) within 24 hours after the injection.

The pattern of MPA clearance from the circulation varies among different studies according to the type of assay used. After DMPA was administered to three subjects, Ortiz and coworkers[119] assayed blood MPA levels daily for 2 weeks, then three times a week for the next 3 months, and then weekly until MPA was undetectable. In two subjects, MPA levels initially plateaued at 1.0 to 1.5 ng/ml for about 3 months, after which they declined slowly to about 0.2 ng/ml during the fifth month (Fig. 25–9). In a third subject, the blood levels were higher during the first month, then ranged between 1.0 and 1.5 ng/ml for the next 2 months, after which there was a further decline. MPA levels remained detectable in the circulation (>0.2 ng/ml) for 7 to 9 months in all three subjects, after which it was not detectable. Estradiol levels were found to be in the range of the early follicular to midfollicular phase, but consistently below 100 pg/ml during the first 4 months after injection. After 4 to 6 months, when MPA levels decreased to less than 0.5 ng/ml, estradiol concentrations rose to preovulatory levels, indicating follicular activity, but ovulation did not occur, as evidenced by persistently low progesterone levels. Return of follicular activity preceded the return of luteal activity by 2 to 3 months. This delay in resumption of luteal activity is probably due to the fact that the circulating MPA levels inhibit the positive feedback effect of the rise of estradiol on the hypothalamic-pituitary axis, which in the absence of MPA would stimulate the midcycle release of LH. The return of luteal activity in this study, indicated by a rise in serum progesterone levels, did not occur until 7 to 9 months after the injection, when the MPA levels were below 0.1 ng/ml.

In another study, performed by Kirton and Cornette[120] using a different assay, MPA levels were much higher, although the pattern was similar to that found in the study by Ortiz,[119] and luteal activity also did not occur until about 7 months after the injection.

A third study of DMPA pharmacokinetics was reported

Figure 25-9 ■ Serum MPA (dots), estradiol (open bars), and progesterone (solid bars) concentrations in three women (subjects A, B, and C) after intramuscular injection of 150 mg of DMPA. Uterine bleeding and spotting are indicated by hatched horizontal bars of full and half thickness, respectively. Undetectable levels of MPA are indicated by V. (From Ortiz A, Hirol M, Stanczyk FZ, et al. Serum medroxyprogesterone acetate [MPA] concentrations and ovarian function following intramuscular injection of depo-MPA. J Clin Endocrinol Metab 445:32–38, 1977. © The Endocrine Society.)
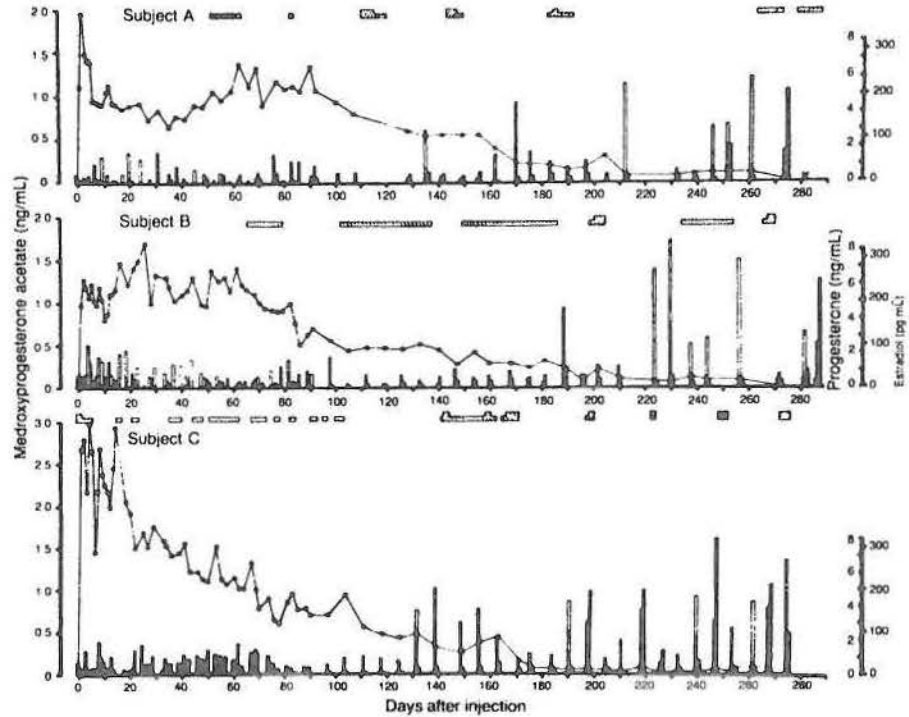
by Fotherby and colleagues[121] and showed an entirely different pattern of MPA clearance after the injection. In this study, the MPA levels fell more rapidly than in the other two studies, and the progesterone levels initially rose about 3.5 months after the injection. On the basis of this study, the product labeling states that if the time interval after the last injection is more than 13 weeks, the provider should determine that the woman is not pregnant before administering the drug. Additional studies are needed to determine more precisely the pharmacodynamics of MPA clearance and time of initial resumption of ovulation because of the differences observed in previous studies.

OVULATORY SUPPRESSION

To determine the effect of DMPA on the hypothalamic-pituitary axis, Mishell and colleagues[122] measured serum LH and FSH levels daily during a control cycle and then for 2 months after a single injection was given. Although the midcycle LH peak was suppressed after the injection, tonic LH was still being secreted in a pulsatile manner, and serum tonic levels were about the same as those found in the follicular phase of the control cycle. The normally occurring peak level of FSH at midcycle was also suppressed after the injection, but tonic FSH levels were in the range of those found in the luteal phase of the control cycle, indicating a lack of complete suppression of the hypothalamic-pituitary axis.

Mishell and colleagues[122] reported that daily progesterone levels were consistently in the follicular-phase range during the first 2 months after the initial injection of DMPA. To obtain suppression of ovulation in the initial injection cycle, DMPA has to be administered within several days after the onset of menses. Siriwongse and associates[123] reported that when the drug was initially given on day 5 or 7 of the cycle, none of the women ovulated, but

when it was given on day 9, 2 of 13 subjects had presumptive evidence of ovulation. The results of this study indicated that DMPA should be given no later than 7 days after the onset of menses to be effective in the first ovulatory cycle. The product labeling states that to ensure the woman is not pregnant at the time of the first injection, it must be given during the first 5 days of the cycle.

Mishell and colleagues[122] reported that circulating estradiol levels during the first 2 months after the initial 150-mg injection of DMPA were similar to the levels found in the follicular phase of the control cycle. Therefore, there is incomplete suppression of follicular activity in the first two cycles after an injection of DMPA.

A cross-sectional study was performed by Mishell and colleagues[122] of 121 women who received 150 mg of DMPA every 3 months for more than 1 year. An assay performed on a serum sample obtained on the day of the next scheduled injection showed marked differences in the estradiol levels, which varied from approximately 15 pg/ml to nearly 100 pg/ml (mean, approximately 42 pg/ml). A similar range and mean value were also found among women who had been receiving DMPA for 1 to 2 years and those who had used it for 4 to 5 years. All these women had moist, well-rugated vaginas, and none stated that her breast size had decreased. None of the women complained of hot flashes. This use of contraceptive doses of DMPA does not decrease endogenous estradiol levels to the postmenopausal range and does not cause symptoms of estrogen deficiency.

RETURN OF FERTILITY

Because of the lag time in clearing DMPA from the circulation, resumption of ovulation is delayed for a variable time, which may last as long as 1 year after the last injection. Women who wish to become pregnant and stop using

DMPA should be informed that there will be a delay in the resumption of fertility until the drug is cleared from the circulation. After this initial delay, fecundability resumes at a rate similar to that found after discontinuation of a barrier contraceptive[124] (Fig. 25–10). Thus, use of DMPA does not prevent return of fertility; it only delays the time at which conception will occur. Because of its long and unpredictable duration of release from the injection site, the time until resumption of fertility may be delayed for 1 year or more after the last injection. Information about the possibility of a long duration of DMPA action needs to be given to women who are considering this method of contraception.

ENDOMETRIAL CHANGES

The histology of the endometrium at various intervals after starting DMPA was examined by Mishell and associates.[125] Histologic examination of endometrial biopsy specimens revealed three types of patterns: proliferative, quiescent, and atrophic. Secretory endometrium was not seen. Most of the women had a quiescent pattern, characterized by narrow, widely spaced glands and decidualization of the stroma.

ADVERSE EFFECTS

Clinical Effects

Bleeding Irregularities. The major side effect of DMPA is complete disruption of the menstrual cycle. In the first 3 months after the first injection, about 30 percent of women are amenorrheic and another 30 percent have irregular bleeding and spotting occurring more than 11 days per
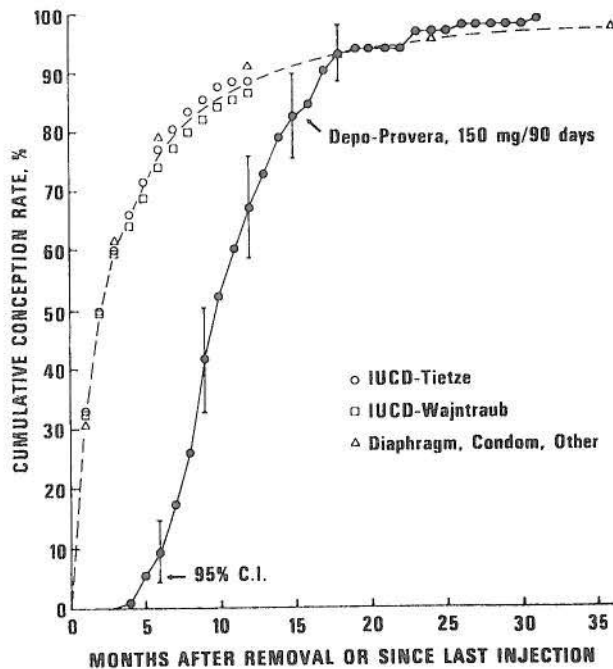

Figure 25–10 ■ Cumulative conception rates of women who discontinued a contraceptive method to become pregnant. (From Schwallie PC, Assenzo JR. The effect of depo-medroxyprogesterone acetate on pituitary and ovarian function, and the return of fertility following its discontinuation: A review. Contraception 10:181–202, 1974.)

month.[126] The bleeding is usually small in amount and does not cause anemia to occur. As duration of therapy increases, the incidence of frequent bleeding steadily declines and the incidence of amenorrhea steadily increases, so that at the end of 2 years about 70 percent of the women treated with DMPA are amenorrheic[126] (Fig. 25–11). Women who use this method of contraception should be counseled that, with time, the irregular bleeding episodes will cease and amenorrhea will most likely occur.

Weight Changes. In five cross-sectional studies, users of DMPA weighed more than a comparison group not using hormonal contraceptives.[127] Several longitudinal studies have indicated that DMPA users gain between 1.5 and 4 kg in their first year of use and continue to gain weight thereafter. None of these studies included a control group, so the weight could be due to factors other than DMPA use. In one retrospective comparative longitudinal study, Moore and coworkers[128] found no significant change in mean weight of DMPA, progestin implant, and OC users. Thus, the effect among DMPA on body weight remains unclear. If DMPA users gain weight, they should be counseled to decrease calorie intake and increase their expenditure of energy.

Mood Changes. The product labeling lists depression and mood changes as side effects of DMPA. Several studies, however, indicate that the incidence of depression and mood change in women using this method of contraception is less than 5 percent.[127] No clinical trials with a comparison group not using DMPA have been performed to determine whether a causal relation between use of DMPA and development of depression exists.

Headache. Although development of headaches is the most frequent medical event reported by DMPA users[129] and a common reason for discontinuation of its use, there are no comparative studies to indicate that use of DMPA increases the incidence or severity of tension or migraine headaches. Therefore, the presence of migraine headaches is not an absolute contraindication for use of DMPA. However, women should be counseled that if the frequency or severity of headaches increases after the injection is given, it may be several months before the drug is cleared from the circulation. For this reason, the presence of migraine headaches may be considered to be a relative contraindication for use of DMPA.

Metabolic Effects

Protein. Because DMPA does not increase liver globulin production as does the estrogen component of OC (ethinyl estradiol), no alteration in blood clotting factors or angiotensinogen levels is associated with its use. Thus, unlike OCs, DMPA has not been associated with an increased incidence of hypertension or thromboembolism.[36] A WHO study reported that mean blood pressure measurements were unchanged in DMPA users after 2 years of injections.[118]

Carbohydrate. There have been two studies in which oral glucose tolerance tests have been performed on longterm DMPA users and matched control subjects not using hormonal contraceptives.[130, 131] The mean glucose levels were slightly greater among the DMPA users than among the control subjects in one but not the other study. Mean insulin levels were also higher. The slight deterioration

Figure 25–11 ▪ Percentage of patients with stated number of days of bleeding and/or spotting per 30-day month. (From Schwallie PC, Assenzo R. Contraceptive use-efficacy study utilizing medroxyprogesterone acetate administered as an intramuscular injection once every 90 days. Fertil Steril 24:331–339, 1973. Reproduced with permission of the American Society for Reproductive Medicine.)
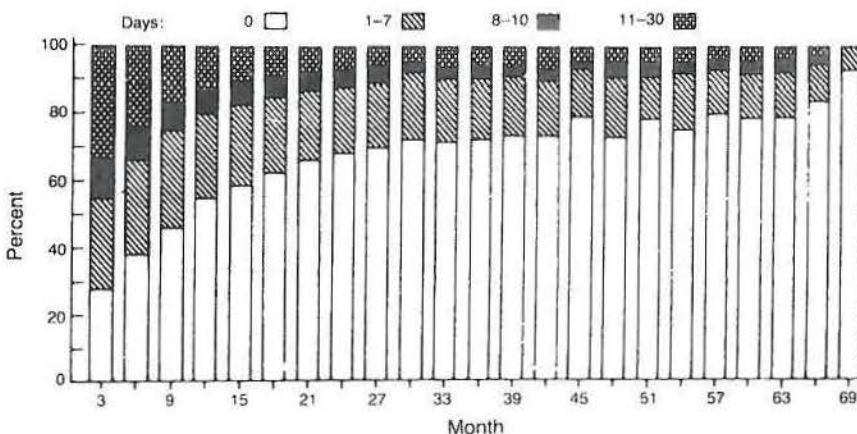
in glucose tolerance among DMPA users is probably not clinically significant and returns to normal after use of DMPA is stopped.

Lipids. Westhoff[127] reviewed the findings of 11 studies that evaluated plasma lipids among groups of women using DMPA. Most of the studies were cross-sectional and compared lipid levels among DMPA users with those of women not using hormonal methods of contraception. There was little or no change in mean triglyceride and total cholesterol levels; however, in all seven studies in which mean HDL cholesterol levels were measured, the levels were lower among the DMPA users. Of the five studies in which LDL cholesterol was measured, three noted an increase among the DMPA users. There are no studies in which the incidence of cardiovascular events among current or former long-term DMPA users was compared with that among control subjects. Therefore, although the lipid changes with DMPA use are not beneficial, there is no evidence to date that they are associated with an acceleration of atherosclerosis.

Bone Loss. One cross-sectional study of 30 long-term DMPA users indicated that they had a reduction in lumbar spine and femoral bone density compared with 30 premenopausal control subjects that was of lesser magnitude than occurred in 30 postmenopausal women whose bone density was also measured concurrently with dual-energy x-ray absorption.[132] A subsequent report by the same group of investigators indicated that after use of DMPA was stopped, there was an increase in bone mineral density of the lumbar spine.[133] Other longitudinal studies have not shown a decrease in bone density in DMPA users.[134–136] The reported effect of DMPA on bone density remains to be clarified with ongoing long-term longitudinal studies. To date, no studies have reported a change in incidence of fractures in current or former long-term DMPA users.

NEOPLASTIC EFFECTS

Breast Cancer. Two large case-control studies, the WHO study[137] and a New Zealand study,[138] indicated that the relative risk of diagnosis of breast cancer among all DMPA users was not significantly changed (RR of 1.2 and CI of 0.96 to 1.15,[137] and RR of 1.0 and CI of 0.8 to 1.3,[138] respectively). When the data from these studies were pooled, the overall breast cancer diagnosis risk among DMPA users was 1.1 (CI, 0.97 to 1.4).[139] In long-term

users, those who had used the drug more than 5 years and those who had started use more than 14 years earlier, the risk of diagnosis of breast cancer was also not increased (RR of 1.0 and CI of 0.70 to 1.5, and RR of 0.89 and CI of 0.6 to 1.3, respectively). However, among those women who had started use within the past 5 years and were mainly younger than 35, there was a significant increased risk of diagnosis of breast cancer (RR, 2.0; CI, 1.5 to 2.8), similar to that found with use of OCs and women with first term pregnancy at an early age. Thus, like other contraceptive steroids, DMPA does not appear to change the overall incidence of diagnosis of breast cancer, and women should be counseled accordingly.

Endometrial Cancer. A WHO case-control study found the risk of endometrial cancer to be significantly reduced among DMPA users (RR, 0.21; CI, 0.06 to 0.79).[140] This reduction in risk persisted for at least 8 years after use was stopped and was similar in magnitude to the protective effect observed with combination OCs.

Ovarian Cancer. In a WHO case-control study, the risk of ovarian cancer among DMPA users was unchanged (RR, 1.07; CI, 0.6 to 1.8).[141] These findings do not demonstrate a protective effect similar to that observed with OCs despite inhibition of ovulation with both agents. The lack of a protective effect observed with DMPA was probably due to the fact that in the countries studied, DMPA was given only to multiparous women, women at low risk of developing epithelial ovarian cancer, who differ from the higher risk women taking OCs.

Cervical Cancer. In a large WHO case-control study, the risk of invasive cancer of the cervix was not increased (RR, 1.1; CI, 0.96 to 1.29),[142] similar to findings observed in a large case-control study in Costa Rica.[143] Long-term use and long time since first use were also not associated with a significant increase in risk of cervical cancer in these studies. The risk of cancer in situ was slightly increased in the WHO study (RR, 1.4; CI, 1.2 to 1.7) but not in the Costa Rica study (RR, 1.1; CI, 0.6 to 1.8) or two New Zealand studies investigating the risk of cancer dysplasia.[144, 145] Thus, the reports in which the neoplastic effects of DMPA on breast and reproductive tract have been investigated are reassuring.

NONCONTRACEPTIVE HEALTH BENEFITS

In a summarization by Cullins,[146] there is good epidemiologic evidence that use of DMPA reduces the risk of iron

deficiency anemia, PID, and endometrial cancer and has a beneficial effect on hematologic parameters in women with sickle cell disease as well as reducing their incidence of clinical problems. DMPA also reduces seizure frequency in women with epilepsy[147] and probably should reduce the incidence of primary dysmenorrhea, ovulation pain, and functional ovarian cyst because it inhibits ovulation. DMPA also reduces the symptoms of endometriosis and in two small studies reduced the incidence of vaginal candidiasis.[148, 149]

CLINICAL RECOMMENDATIONS

Women should be thoroughly counseled about the occurrence of abnormal bleeding and development of amenorrhea with use of DMPA before receiving the first injection. It has been shown that pretreatment counseling improves continuation rates.[150] In addition, women should be counseled that the duration of action may last as long as 1 year after the last injection if they decide to discontinue use to become pregnant or if they experience side effects.

In cycling women, the initial injection should be given no later than day 5 of the cycle to be certain to inhibit ovulation in the initial treatment cycle.[151] Because of an absence of thrombophilic effects, the first injection should be given within 5 days post partum in nonlactating women; but, in women who exclusively breast feed their infants, the product labeling states that the first injection should not be given until at least 6 weeks post partum.[151] DMPA does not affect the quantity or quality of breast milk or the health of children who breast feed during its use.[152] If a woman with lactational amenorrhea wishes to institute DMPA use, it is unlikely that she is pregnant if a qualitative test response for human chorionic gonadotropin (hCG) is negative; therefore, she can receive the injection at that time. If concern about pregnancy exists, use of a barrier contraceptive should be advised for an additional 2 weeks, at which time the assay for hCG should be repeated. If the response is still negative, the injection can be given. A similar protocol can be used for the woman who has received DMPA in the past but is delayed beyond 13 weeks in returning for her next injection and is still amenorrheic. If accidental pregnancy does occur in a DMPA user, there is no evidence that the agent is teratogenic or has an adverse effect on the outcome of the pregnancy.[153]

Subdermal Implants

Subdermal implants of capsules made of polydimethylsiloxane (Silastic) containing levonorgestrel for use as contraceptives have been developed and patented by The Population Council as Norplant. It was approved by the U.S. FDA in 1990, and marketing in this country began in 1991. As with all steroid-containing Silastic devices, the rate of steroid delivery is directly proportional to the surface area of the capsules, whereas duration of action depends on the amount of steroid within the capsules. To produce effective blood levels of norgestrel, it was found necessary to use six capsules filled with crystalline levonorgestrel. The cylindrical capsules are 3.4 cm long and 2.4 mm in outer diameter, with the ends sealed with Silastic medical adhesive. Each capsule contains 36 mg of crystalline levonorgestrel for a total amount of 215 mg in each six-capsule set.

Insertion is performed in an outpatient setting, and the entire procedure takes about 5 minutes. After infiltration of the skin with local anesthetic, a small (3-mm) incision is made with a scalpel, usually in the upper arm, although the lower arm and the inguinal, scapular, and gluteal regions have also been used. When the capsules are inserted in any area of subcutaneous tissue, the steroid diffuses into the circulation at a relatively constant rate. The capsules are implanted into the subcutaneous tissue in a radial pattern through a large (10- to 12-gauge) trocar, and the incision is closed with adhesive. Sutures are not necessary. Because polydimethylsiloxane is not biodegradable, the capsules have to be removed through another incision when desired by the user or at the end of 5 years, which is the duration of maximal contraceptive effectiveness.

After insertion, blood levels of levonorgestrel rise rapidly to reach levels between 1000 and 2000 pg/ml in 24 hours.[154] These levels fall markedly in the first week and then gradually in the first month and then remain relatively constant during the first year of use with the mean level ranging between 250 and 600 pg/ml, which is usually sufficient to inhibit ovulation[155] (Fig. 25–12). At the end of 5 years, mean levonorgestrel· levels range between 170 and 350 pg/ml.[156] Blood levels vary considerably among women, mainly because of differences in body weight. Heavier women have lower circulating levonorgestrel levels than thin women do. When the amount of steroid was measured in capsules removed from women after various times, it was found that the rate of release was fairly constant during the first year of use, averaging about 50 μg of levonorgestrel per day from the six-capsule set. From about the end of the first year of use until 8 years of use, daily release rates declined to about 30 μg/day but remained constant during each day.[154]

With this low level of levonorgestrel, gonadotropin levels are not completely suppressed, and ovarian follicular activity results in periodic peaks of estradiol. Because the level of circulating levonorgestrel is usually sufficient to inhibit the positive feedback effect of these estradiol peaks on LH release, LH levels are lower than normal, even in Norplant users with regular cycles, and ovulation during the first 2 years of use occurs infrequently.[157]

Thus, inhibition of ovulation is one of the major mechanisms of action of this method of contraception. The consistently elevated circulating levels of norgestrel also prevent the normal midcycle thinning of the cervical mucus from occurring. The cervical mucus remains scanty and viscid, and normal sperm penetration does not take place, as demonstrated by both in vivo and in vitro studies.[158, 159] These two mechanisms of action result in a high level of contraceptive effectiveness.

With the less dense tubing currently used, annual pregnancy rates for the first 5 years of use are about 0.2 per 100 women of all body weights, yielding a cumulative 5-year pregnancy rate of 1.1 percent.[154] As with all progestin-only methods of contraception, when pregnancies occur with Norplant, a high percentage, about 20 percent, are ectopic. However, because of its high rate of effectiveness, the overall rate of ectopic pregnancies in Norplant users, 0.28 per 1000 woman-years of use, is reduced compared with ectopic pregnancy rates in the entire United States
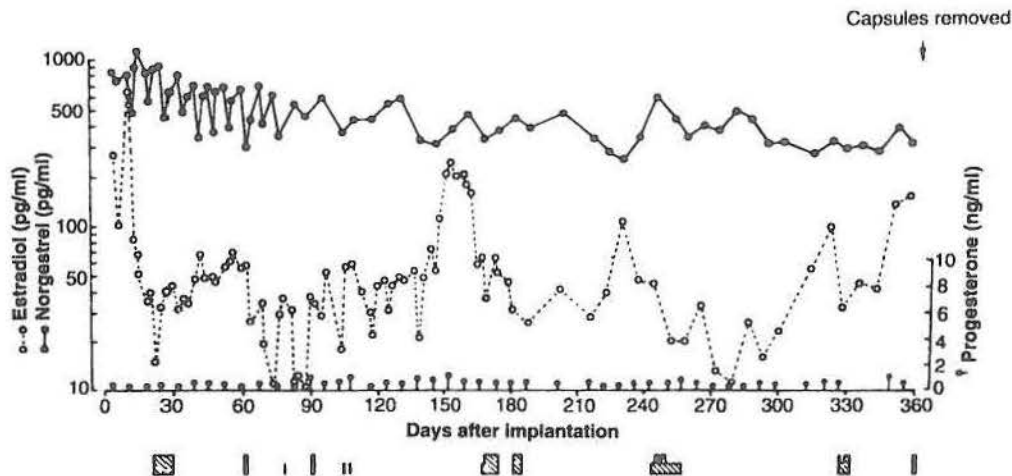
Capsules removed

Figure 25–12 ▪ Serum levels of estradiol, progesterone, and d-norgestrel in a subject with six polysiloxane capsules, each containing 33.9 mg of d-norgestrel, implanted on day 0. Hatched bars represent uterine bleeding. (From Moore LL, Valuck R, McDougall C, et al. A comparative study of one-year weight gain among users of medroxyprogesterone acetate, levonorgestrel implants, and oral contraceptives. Contraception 52:215–220, 1995.)

population of women of reproductive age, 1.5 per 1000 women annually.[160]

Mean estradiol levels in Norplant users, whether they are ovulatory or anovulatory, are about the same as in women with regular ovulatory cycles who used IUDs,[161] and three patterns of estradiol activity have been observed. About half of Norplant users have periodic, irregular peaks of estradiol within the normal range (up to 400 pg/ml), 30 percent have fluctuating estradiol levels with high broad peaks above 400 pg/ml, and about 10 percent have consistently low estradiol levels below 75 pg/ml.[161] After a fall in estradiol level, endometrial sloughing and uterine bleeding or spotting usually occur. Because the peaks and declines in estradiol levels occur at irregular intervals, uterine bleeding also occurs at irregular intervals in the majority of Norplant users.

The major side effect of Norplant use is the irregular pattern of uterine bleeding. Other alterations in uterine blood flow involve changes in duration and volume, with most bleeding episodes being scanty in amount. About half the bleeding episodes can be characterized as fairly regular, with the interval between bleeding episodes ranging between 21 and 35 days; about 40 percent as irregular, with intervals outside this range; and about 10 percent as amenorrheic, with no bleeding for more than a 13-month interval.[162] Bleeding episodes tend to be more prolonged and irregular during the first year of use, after which there is greater frequency of a more regular pattern. Shoupe and colleagues[163] reported that during the first year of use, about one fourth of the cycles were regular, two thirds irregular, and 7 percent amenorrheic. By the fifth year, about two thirds of the cycles were regular and one third irregular, and none was amenorrheic (Fig. 25–13). The mean number of days of bleeding also declines steadily with use.[160] Mean total blood loss in Norplant users is about 25 ml per month.[164] Several clinical studies have shown that the mean hemoglobin concentration in the first 3 years of Norplant use tends to rise slightly. When pregnancies occur in Norplant users, they almost always occur

in women with a recent history of regular cyclic uterine bleeding.

Other problems associated with this method of contraception include infection, local irritation, and painful reaction at the insertion site. Expulsion of a capsule, usually in association with infection, occurs occasionally. The incidence of insertion site infection is less than 1 percent. Headache is the single most frequent medical problem causing removal of the implants, accounting for about 30 percent of the medical reasons for removal.[160] Weight gain was a common reason for medical removal in U.S. studies, whereas weight loss was more common in the Dominican Republic. Other medical problems among Norplant users include acne, mastalgia, and mood changes, including anxiety, depression, and nervousness. Because ovarian follicular
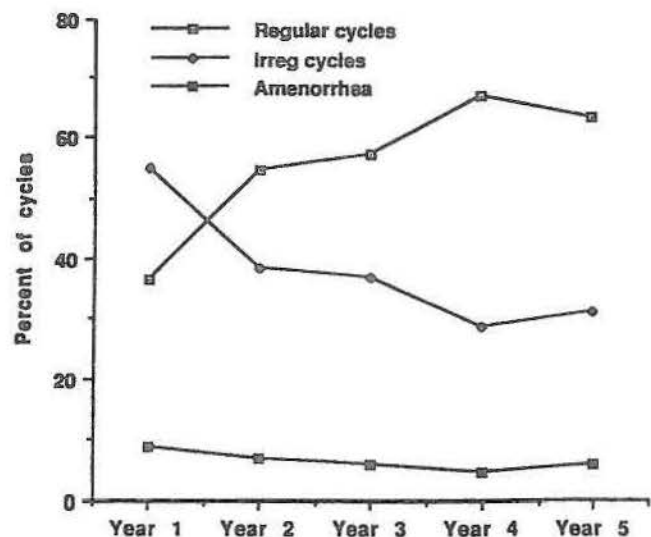

Figure 25–13 ▪ Bleeding patterns calculated on a monthly basis in implant users during 5 years of use. (From Shoupe D, Mishell DR Jr, Bopp BL, Fielding M. The significance of bleeding patterns in Norplant implant users. Obstet Gynecol 77:256–260, 1991.)

development without subsequent ovulation is common among Norplant users, adnexal enlargement due to persistent unruptured follicles has been noted during routine bimanual pelvic examination in many Norplant users. These enlarged follicles, which may reach 5 to 7 cm in diameter, usually spontaneously regress in 1 to 2 months without therapy.

A great number of metabolic studies have been performed among Norplant users in various population groups. Studies of carbohydrate metabolism, serum chemistries, liver function, serum cortisol levels, thyroid function, and blood coagulation have revealed only minimal changes, which remain within the normal range.[162] Several studies have been performed in different countries in which lipoproteins were measured before and after Norplant insertion. In most of these studies, levels of triglycerides, total cholesterol, and LDL cholesterol declined, whereas HDL cholesterol declined slightly or increased.[162] There was little change in the ratio of cholesterol to HDL cholesterol, indicating that Norplant should not enhance the development of atherosclerosis.

The removal process, like the insertion procedure, is performed in the clinic area with use of local anesthesia and a small skin incision. Removal of Norplant is a more difficult process than insertion, because fibrous tissue develops around the capsule and must be cut before removal of the capsules. It is important to insert the capsules superficially to enhance the ease of removal; deeply implanted capsules are more difficult to remove.

After removal, the incision is closed without sutures, and a pressure dressing is applied for about 24 hours. If the woman wishes to continue use, another set can be inserted through the same incision or in the opposite arm. If another set of Norplant is not inserted after removal, the steroid is rapidly cleared from the circulation and serum levels of norgestrel fall rapidly, reaching nearly undetectable levels in 96 hours.[165] If pregnancy is desired, return to ovulation is prompt and is similar to that in women discontinuing nonhormonal methods of reversible contraception, reaching 50 percent at 3 months and 86 percent at 1 year.[160] Continuation rates with Norplant method of contraception are high, ranging from 76 to 99 percent at 1 year in different countries and from 33 to 78 percent at 4 years.[160]

Manufacture of the capsules is complicated, and placing or removing six capsules creates some difficulties; therefore, norgestrel has been fabricated into solid rods that are a homologous mixture of Silastic and crystalline levonorgestrel covered with Silastic tubing. The rods are easier to manufacture, insert, and remove than the capsules. Because of different properties of diffusion, higher blood levels of norgestrel are achieved with a smaller total surface area of the rods. Thus, with two 4-cm covered rods with the same diameter as the capsules, the same release rate for norgestrel, about 50 μg/day, can be achieved as with placement of six 3-cm capsules. During a 3-year clinical study comparing rods and capsules, the serum norgestrel levels, bleeding patterns, and incidence of elevated progesterone levels were similar.[166] A multicenter clinical study has confirmed these findings, and use of the two covered rods has recently been approved by the U.S. FDA for clinical use. Single implants with other progestins such as desoges-

trel have been manufactured and studied in clinical trials. These implants have a probable duration of action of 2 years and are much easier to insert and remove than the multiple levonorgestrel-releasing implants.

EMERGENCY CONTRACEPTION

Various estrogenic compounds have been used for emergency contraception. The estrogen compounds that have been used for this purpose include diethylstilbestrol, 25 to 50 mg/day; ethinyl estradiol, 5 mg/day; and conjugated estrogen, 30 mg/day. Treatment is continued for 5 days. If treatment is begun within 72 hours after an isolated midcycle act of coitus, its effectiveness is good. If more than one episode of coitus has occurred, or if treatment is initiated later than 72 hours after coitus, the method is less effective.

Pregnancy rates among women treated with ethinyl estradiol were 0.6 percent; with diethylstilbestrol, 0.7 percent; and with conjugated estrogen, 1.6 percent.[167] It has been estimated that the clinical pregnancy rate for a single act of midcycle coitus without use of a contraceptive is about 7 percent. Thus, high-dose estrogen is an effective method of postcoital contraception. Side effects associated with this high-dose estrogen therapy are common and severe. They include nausea, vomiting, breast soreness, and menstrual irregularities, which tend to reduce compliance.

Because the side effects of high-dose estrogens cause many women to fail to complete the 5-day treatment course, a regimen of four tablets of an ethinyl estradiol, 0.05 mg, and dl-norgestrel, 0.5 mg, combination OC (Ovral), given in doses of two tablets 12 hours apart, was initially tested in Canada. This regimen was found to have a similar degree of effectiveness with a shorter duration of adverse symptoms than with 5 days of estrogen.

Fasoli and colleagues[167] summarized the results of 11 studies with this treatment regimen involving 3802 women. Failure rates varied widely, from a low of 0.2 percent in a Canadian study to a high of 7.4 percent in an Italian study. The total pregnancy rate in the 11 studies was 1.8 percent, similar to the individual failure rate in the largest studies in this review. Trussell and associates[168] pooled the data from studies that were published between 1977 and 1993 involving 5226 women treated with this regimen. They calculated that the failure rate was 1.5 percent and use of this regimen prevented about 75 percent of the expected pregnancies. Trussell and colleagues also analyzed results of nine published studies in which the effectiveness of this regimen was determined when treatment was initiated 1, 2, or 3 days after midcycle unprotected intercourse. Using logistic regimen analysis, they found that there was no significant difference in failure rates when the first pill was taken on the first, second, or third day after unprotected intercourse.

Ho and Kwan[169] reported results of a randomized trial comparing the use of four tablets of ethinyl estradiol and levonorgestrel taken in divided doses 12 hours apart with a single tablet of 0.75 mg levonorgestrel taken initially and another one 12 hours later. Both regimens were ingested within 48 hours of unprotected intercourse. Failure rates of both regimens, about 2 percent, were similar, but there was significantly less nausea and vomiting with the progestin

alone than with the one combined with estrogen. A strip of four tablets of the combination steroid pills is marketed in several countries under a variety of brand names.

Several authors have advocated that intrauterine insertion of a copper IUD within 5 to 10 days of midcycle coitus is an effective method to prevent continuation of the pregnancy. Fasoli and coworkers[167] summarized the results of four published studies in nine countries involving 875 women. Only one pregnancy occurred after a copper IUD was inserted in these women. Insertion of a copper IUD and ingestion of high-dose estrogens are the most effective methods of emergency contraception, but side effects limit acceptance of the latter, and cost and concern about introducing pathogens into the upper genital tract with IUD insertion limit its widespread use. Because no manufacturer has applied for U.S. FDA approval to market an emergency method of contraception, it is infrequently prescribed by clinicians, and few women in the United States are aware that it is effective, accessible, and safe.

PROGESTERONE ANTAGONISTS

A few years ago Healy and colleagues[170] synthesized a progestogenic steroid compound that had weak progestational activity but marked affinity for progesterone receptors in the endometrium. This compound, called RU 486 or mifepristone (Fig. 25–14), because of its high receptor affinity prevents progesterone from binding to its receptors and thus inhibits the action of circulating progesterone on its target tissue. In clinical trials, it was found that if a single 600-mg dose of RU 486 was administered orally in early pregnancy, before 7 weeks after the onset of the last menses, about 85 percent of the pregnancies spontaneously terminated.[171] When this treatment was combined with administration of a prostaglandin 36 to 48 hours later, the efficacy increased to 96 percent.[172] However, side effects include nausea, vomiting, and abdominal pain. Two prostaglandin analogues, intramuscular sulprostone and vaginal gemeprost, were the agents initially used after mifepristone. Sulprostone is no longer marketed for this purpose, because three women who received this agent with mifepristone suffered an MI. Gemeprost is much more expensive than misoprostol, a prostaglandin analogue widely used to prevent peptic ulcer disease. Therefore, oral administration of misoprostol is now being used more extensively than gemeprost after mifepristone.
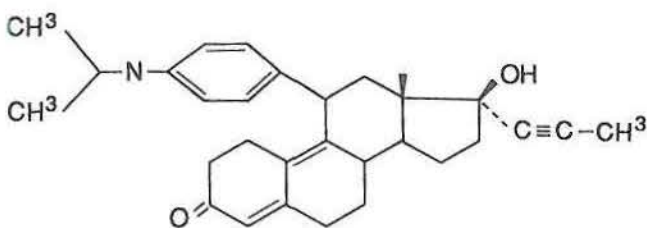
The results of a randomized trial with misoprostol given vaginally or orally suggest that when misoprostol is given vaginally instead of orally, it is more effective and has fewer side effects.[173] A large, multicenter clinical trial with mifepristone followed by oral misoprostol was recently performed in the United States. Therefore, when this drug combination does become available for use in this country, the oral administration of misoprostol will most likely be recommended, even though vaginal administration is probably preferable. The main disadvantage of this medical abortifacient method is prolonged and sometimes heavy uterine bleeding that on occasion can cause anemia, necessitating a blood transfusion and possibly curettage. The mean duration of bleeding after administration of this drug is about 12 days when it is administered alone and 9 days when it is used with a prostaglandin. Distribution of mifepristone is currently limited to a few European countries and China, but compounds with similar activity or steroid enzymatic inhibitors that prevent progesterone synthesis are also being studied.[174]

INTRAUTERINE DEVICES

The main benefits of IUDs are (1) a high level of effectiveness, (2) a lack of associated systemic metabolic effects, and (3) the need for only a single act of motivation for long-term use. Despite these advantages, less than 1 percent of married women of reproductive age use the IUD for contraception in the United States compared with 15 to 30 percent in most European countries and Canada.

Types

In the past 35 years, many types of IUDs have been designed and used clinically. The devices developed and initially used in the 1960s were made of a plastic, polyethylene, impregnated with barium sulfate to make them radiographic. In the 1970s, to diminish the frequency of the side effects of increased uterine bleeding and pain, smaller plastic devices covered with copper were developed and widely used. In the 1980s, devices were developed bearing a larger amount of copper, including sleeves on the horizontal arm, such as the copper T380A and the copper T220C, as well as the Multiload Cu250 and Cu375. These devices have a longer duration of high effectiveness and thus need to be reinserted at less frequent intervals than the devices bearing a smaller amount of copper. The copper T380A IUD is the only copper-bearing IUD currently marketed in the United States, but the Multiload Cu375 is widely used in Europe (Fig. 25–15).

Because of the constant dissolution of copper, which amounts daily to less than that ingested in the normal diet, all copper IUDs have to be replaced periodically. The copper T380A is currently approved for use in the United States for 10 years and may maintain its effectiveness for a longer time. At the scheduled time of removal, the device can be removed and another inserted during the same office visit.

Adding a reservoir of progesterone to the vertical arm also increases the effectiveness of the T-shaped devices. The currently marketed progesterone-releasing IUD allows 65 mg of progesterone to diffuse into the endometrial
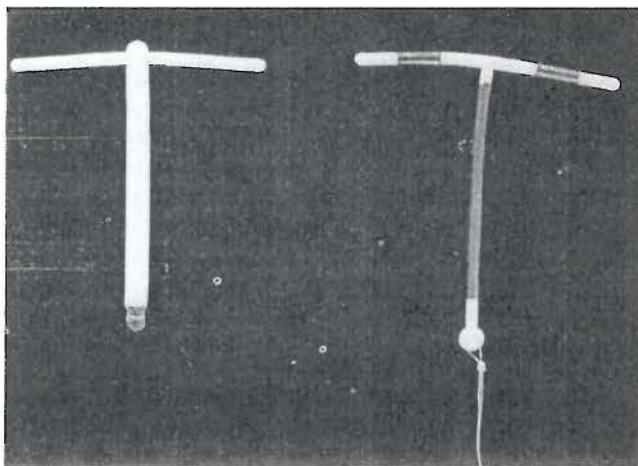
Figure 25-15 ▪ Intrauterine devices currently being marketed in the United States: *left*, progesterone-releasing IUD; *right*, copper T380A.

cavity each day. This amount is sufficient to prevent pregnancy by local action within the endometrial cavity but is not enough to cause a measurable increase in peripheral serum progesterone levels. Because of the progestational effect on the endometrium, the amount of uterine bleeding is reduced with use of this device, and it has been used therapeutically to treat menorrhagia. The currently approved progesterone-releasing IUD needs to be replaced annually, because the reservoir of progesterone becomes depleted after about 18 months of use and the surface area of plastic in this small device is insufficient to produce a sufficiently large leukocytic response to yield a high level of contraceptive effectiveness.

A T-shaped device containing a reservoir of levonorgestrel on the vertical arm has been developed and undergone extensive clinical testing. A large comparative trial of the copper T380A and the levonorgestrel-releasing IUD found that the effectiveness and continuation rates of both devices were similar.[175] Because of the slower rate of release of levonorgestrel than progesterone, the levonorgestrel-releasing IUD has an estimated duration of use of at least 5 years. The levonorgestrel-releasing IUD also reduces menstrual blood loss and has been used therapeutically to treat abnormal uterine bleeding. This device is currently marketed in only a few European countries.

Mechanisms of Action

The main mechanism of contraceptive action of copper-bearing IUDs in the human is a spermicidal effect. This effect is caused by a local sterile inflammatory reaction produced by the presence of the foreign body in the uterine cavity. There is about 1000 percent increase in the number of leukocytes in washings of the human endometrial cavity 18 weeks after the insertion of an IUD, compared with washings obtained before insertion. In addition to causing phagocytosis of spermatozoa, tissue breakdown products of these leukocytes are toxic to all cells, including spermatozoa and the blastocyst. The amount of inflammatory reaction, and thus contraceptive effectiveness, is directly related to the size of the intrauterine foreign body. Copper

markedly increases the extent of the inflammatory reaction, so this metal has been added to the small-sized frame of T-shaped devices.[176] In addition, copper impedes sperm transport and viability in the cervical mucus.[177] Because the copper T380 has about twice as much copper surface area as the previously marketed copper 7 IUD, the former has a lower failure rate than the latter IUD. Sperm transport from the cervix to the oviduct in the first 24 hours after coitus is markedly impaired in women wearing IUDs.[178] Because of the spermicidal action of IUDs, few if any sperm reach the oviducts, and the ovum usually does not become fertilized.[179] Thus, the principal mechanism of action of the copper T380A IUD is as a spermicide, preventing fertilization of the ovum. The progesterone-releasing IUD has a much higher ectopic pregnancy rate than the copper IUD[180] and probably acts mainly by slowing tubal transport of the embryo as well as by preventing implantation of the blastocyst owing to the presence of a high level of progesterone in the uterine cavity.

On removal of the IUD, the inflammatory reaction rapidly disappears. Resumption of fertility after IUD removal is prompt and occurs at the same rate as resumption of fertility after discontinuation of the barrier methods of contraception.[181] The incidence of term deliveries, spontaneous abortion, and ectopic pregnancies in conceptions occurring after IUD removal is the same as in the general noncontracepting population.

Time of Insertion

Although it is widely believed that the optimal time for insertion of an IUD is during the menses, there are data indicating that the IUD can be safely inserted on any day of the cycle provided that the woman is not pregnant.

Adverse Effects

Incidence

In general, in the first year of use, copper IUDs have less than a 1 percent pregnancy rate, a 10 percent expulsion rate, and a 15 percent rate of removal for medical reasons, mainly bleeding and pain. The incidence of each of these events, especially expulsion, diminishes steadily in subsequent years.

In an ongoing WHO study of the copper T380A, termination rates for adverse effects continued to decline annually after the first year following insertion for each of the 7 years in which sufficient data had been accumulated.[4] In this study, the cumulative percentage discontinuation rate for pregnancy, bleeding and pain, and expulsion at the end of 7 years was 1.6, 22.7, and 8.6, respectively.

Uterine Bleeding

The majority of women discontinuing this method of contraception do so for medical reasons. Nearly all the medical reasons accounting for removal of copper-bearing or inert IUDs involve one or more types of abnormal bleeding: heavy or prolonged menses or intermenstrual bleeding.

The copper T380A IUD is associated with about a 55 percent increase in menstrual blood loss.[182] In contrast,

with the progesterone-releasing IUD, the amount of blood loss is significantly reduced to about 25 ml per cycle.[183] There is also reduced blood loss with the levonorgestrel-releasing IUD.

Excessive bleeding in the first few months after IUD insertion should be treated with reassurance and supplemental oral iron as well as systemic administration of one of the prostaglandin synthetase inhibitors during menses. The bleeding usually diminishes with time, as the uterus adjusts to the presence of the foreign body.

Mefenamic acid ingested in a dosage of 500 mg three times a day during the days of menstruation has been shown to reduce menstrual blood loss significantly in IUD users.[184] If excessive bleeding continues despite this treatment, the device should be removed. After a 1-month interval, another type of device may be inserted if the woman still wishes to use an IUD for contraception. Consideration should be given to using a progestin-releasing IUD, because this device is associated with less blood loss than the copper-bearing IUDs.

Perforation

Although uncommon, one of the potentially serious complications associated with use of the IUD is perforation of the uterine fundus. Perforation always occurs at the time of insertion.

In large multiclinic studies, perforation rates for the copper 7 were about 1 per 1000 insertions, but in contrast, perforation rates for the copper T380A were only about 1 in 3000 insertions.[185] Any type of IUD found to be outside the uterus, even if it is asymptomatic, should be removed from the peritoneal cavity because complications such as severe adhesions and bowel obstruction have been reported with intraperitoneal IUDs. Therefore, it is best to remove intraperitoneal IUDs shortly after the diagnosis of perforation is made. Unless severe adhesions have developed, most intraperitoneal IUDs can be removed by means of laparoscopy.

Complications Related to Pregnancy

CONGENITAL ANOMALIES

There is no evidence of an increased incidence of congenital anomalies in infants born with a plastic, copper-bearing, or progesterone-releasing IUD in utero.

SPONTANEOUS ABORTION

In all reported series of pregnancies with any type of IUD in situ, the incidence of fetal death was not significantly increased; however, a significant increase in spontaneous abortion has been consistently observed. If a woman conceives while wearing an IUD that is not subsequently removed, the incidence of spontaneous abortion is about 55 percent, approximately three times greater than would occur in pregnancies without an IUD.[186, 187]

After conception, if the IUD is spontaneously expelled, or if the appendage is visible and the IUD is removed by traction, the incidence of spontaneous abortion is significantly reduced. In one study of women who conceived with copper T devices in place, the incidence of spontaneous abortion was only 20 percent if the device was removed or spontaneously expelled.[186] This figure is similar to the normal incidence of spontaneous abortion and significantly less than the 54 percent incidence of abortion reported in the same study among women retaining the devices in utero. Thus, if a woman conceived with an IUD in place and wishes to continue the pregnancy, the IUD should be removed if the appendage is visible to significantly reduce the chance of spontaneous abortion. If the appendage is not visible, blind probing of the uterine cavity may increase the chance of abortion as well as sepsis. However, several reports indicate that with sonographic guidance, it is possible during early gestation to remove intrauterine IUDs in the lower uterine cavity without a visible appendage and not adversely affect the outcome of the pregnancy.[188, 189]

There was an increased risk of septic abortion if a patient conceived with a shield IUD in place, because of the structure of the multifilament appendage of the shield. However, there is no conclusive evidence that IUDs with monofilament tail strings cause sepsis during pregnancy.

ECTOPIC PREGNANCY

There is about a threefold increase in the risk of the pregnancy's being ectopic if a woman becomes pregnant with a copper IUD in place than if she is using no contraception method. However, because the copper T380 IUD so effectively prevents all pregnancies, with a total pregnancy rate of about 3.4 per 1000 women per year, the estimated ectopic pregnancy rate is only 0.2 to 0.4 per 1000 women per year in women using the IUD.[180] The estimated ectopic pregnancy rate among sexually active U.S. women using no method of contraception has been estimated to be between 3.25 and 4.5 per 1000 woman-years. Thus, the relative risk of ectopic pregnancy with the copper T380A is 0.1.[180]

The total number of pregnancies in women using the progesterone-releasing IUD is approximately 230, and about one in four pregnancies occurring in women using the device will be ectopic. The rate of ectopic pregnancies of 6.8 per 1000 woman-years in women using this device is higher than the 3.25 to 4.5 rate of ectopic pregnancy per 1000 noncontracepting women per year.[180]

The action of progesterone on oviductal motility increases the relative risk of having an ectopic pregnancy with this IUD 1.5 to 1.8 times compared with women using no method of contraception. Thus, the two types of IUDs currently marketed in the United States have differing effects on the risk of ectopic pregnancy. The copper T380 IUD lowers the risk and the progesterone IUD increases the risk compared with use of no contraception. Because a woman's risk of ectopic pregnancy is increased if she becomes pregnant with either IUD in place compared with the overall population of pregnant women, appropriate diagnostic studies should take place early in gestation to establish the diagnosis before tubal rupture occurs.

The increased risk of ectopic pregnancy for a woman who conceives while wearing an IUD is temporary and does not persist after removal of the IUD.[190]

PREMATURITY

In the previously cited study of conceptions occurring in the presence of copper T devices, the rate of prematurity

among livebirths was four times greater when the copper T was left in place than when it was removed.[186]

INFECTION IN THE NONPREGNANT IUD USER

In 1966, a study was performed in which aerobic and anaerobic cultures were made of homogenates of endometrial tissue obtained transfundally from uteri removed by vaginal hysterectomy at various intervals after insertion of the loop IUD.[191] During the first 24 hours after IUD insertion, the normally sterile endometrial cavity was consistently infected with bacteria. Nevertheless, in 80 percent of uteri removed during the following 24 hours, the women's natural defenses had destroyed these bacteria and the endometrial cavities were sterile. In this study, when transfundal cultures were obtained more than 30 days after IUD insertion, the endometrial cavity, the IUD, and the portion of the thread within the cavity were always found to be sterile (Fig. 25–16). These findings indicate that development of PID more than a month after insertion of the IUD is due to infection with a sexually transmitted pathogen and is unrelated to the presence of the device.

Results of a large multicenter study coordinated by the WHO revealed similar findings. In this study of 22,908 women inserted with IUDs, the PID rate was highest in the first 3 weeks after insertion but remained lower and constant during the 8 years thereafter at 0.5 per 1000 woman-years (Fig. 25–17).[192] The results of both of these studies indicate that an IUD should not be inserted into a woman who may have been recently infected with gonococci or chlamydiae. Insertion of the device will transport these pathogens from the cervix into the upper genital tract where the large number of organisms may overcome the host defense and cause salpingitis. If there is clinical suspicion of infectious endocervicitis, cultures should be obtained and the IUD insertion delayed until the results reveal that no pathogenic organisms are present. It does not appear to be cost-effective to administer systemic antibiotics routinely with every IUD insertion, but the insertion procedure should be as aseptic as possible.

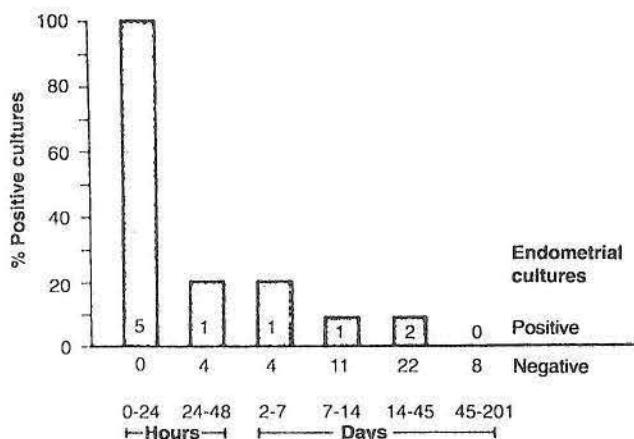There is evidence that IUD users may have an increased

PID incidence rate
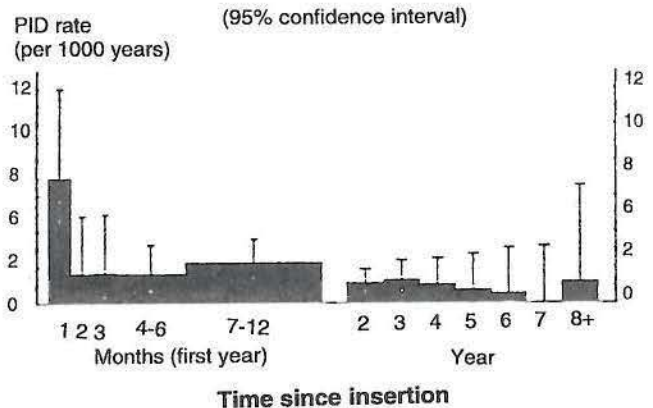(95% confidence interval)

Figure 25–17 ■ Pelvic inflammatory disease (PID) incidence by time since insertion. Incidence rate estimated by the number of PID cases and years of exposure in each time interval; 95 percent confidence intervals were calculated from the Poisson distribution. (From Farley TM, Rosenberg MJ, Rowe PJ, et al. Intrauterine devices and pelvic inflammatory disease: An international perspective. Lancet 339:785–788, 1992. © by The Lancet Ltd.)

risk for colonizing actinomycosis organisms in the upper genital tract. The relationship of actinomycosis to PID is unclear because many women without IUDs have actinomycosis in their vagina and are asymptomatic.[193] If actinomycosis organisms are identified on the routine examination of cervical cytology and the woman is asymptomatic, she may be treated with appropriate antimicrobal therapy to erradicate the organisms or observed without therapy. The IUD should not be removed from an asymptomatic woman who is colonized but not infected with actinomycosis.

Overall Safety

Several long-term studies have indicated that the IUD is not associated with an increased incidence of endometrial or cervical carcinoma and may actually be associated with a reduction in risk of developing these neoplasms during and after its insertion.[194, 195] The IUD is a particularly useful method of contraception for women who have completed their families and do not wish permanent sterilization and have contraindications to, or do not wish to use, other effective methods of reversible contraception. An analysis reported that after 5 years of use, the IUD was the most cost-effective method of all methods of contraception including sterilization.[196] Women in the United States who use an IUD have a higher level of satisfaction with their method of contraception than do women using any of the other methods of reversible contraception.

Figure 25–16 ■ Relationship between incidence of positive endometrial cultures and duration of IUD use before hysterectomy. (From Mishell DR Jr, Bell JH, Good RG, et al. The intrauterine device: A bacteriologic study of the endometrial cavity. Am J Obstet Gynecol 96:119–126, 1966.)

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