Kirk-Othmer Encyclopedia of Chemical Technology.

CONTRACEPTIVES

Women have searched for effective methods of birth control since antiquity. From the earliest times, most have considered the ideal method one that would safely avert unwanted pregnancy while also avoiding inconvenience during intercourse. Some of the contraceptive methods practiced historically were based on superstitions and taboos; eg, the ancient Chinese advised women to swallow 24 live tadpoles in early spring, believing that this would ensure conception-free years. Other methods evolved that were more effective, and had a basis in rational chemical concepts. For example, the use of chemical agents placed in the vagina to prevent pregnancy was recorded in ancient Egyptian and Greek writings (1).

Today, millions of people throughout the world use a variety of methods to regulate human fertility, including chemical methods, eg, oral contraceptives, vaginal contraceptives, injectable/implantable contraceptives, and contragestational agents; intrauterine devices; intravaginal barrier methods; male and female condoms; surgical sterilization; induced abortion; and natural family planning. Each of these has its advantages and disadvantages, and it is generally accepted that none of these methods represents an ideal method of fertility regulation (2–4) for everyone.

This article reviews various contraceptive methods, with particular emphasis on the evolution of the chemical methods used in current hormonal contraceptives and contragestational products, and describes research efforts directed toward the development of new approaches to control human fertility.

1. Oral Contraceptives

Oral contraceptives were first introduced in the early 1960s. Since then there have been many changes in these products, including lowering of the contraceptive dose and the introduction of phasic oral contraceptives (5). Much has been written about the impact of oral contraceptives on the practice of family planning (6). The availability of an oral, hormonal contraceptive, ie, the pill, has permitted women to make responsible decisions in matters regarding size of family, spacing of children, and choice of lifestyle. The introduction of oral contraceptives also opened the door to intensified research in basic and applied reproductive biology. This led to the introduction of not only the second and third generation oral contraceptives used today, but also to today's broad range of other methods of fertility regulation.

Oral contraceptives are among the most popular form of reversible contraception in most countries. As of the early 1990s, over 60 million women around the world use the pill and almost 150 million women have used oral contraceptives sometime during their reproductive lives (7). The commercial market for oral contraceptives is large and expanding. U.S. drug store purchases alone will exceed $1 billion in 1992.

1.1. History

Detailed reviews of biological, chemical, and clinical research that led to the introduction of oral contraceptives are available in the scientific and medical literature (8, 9).

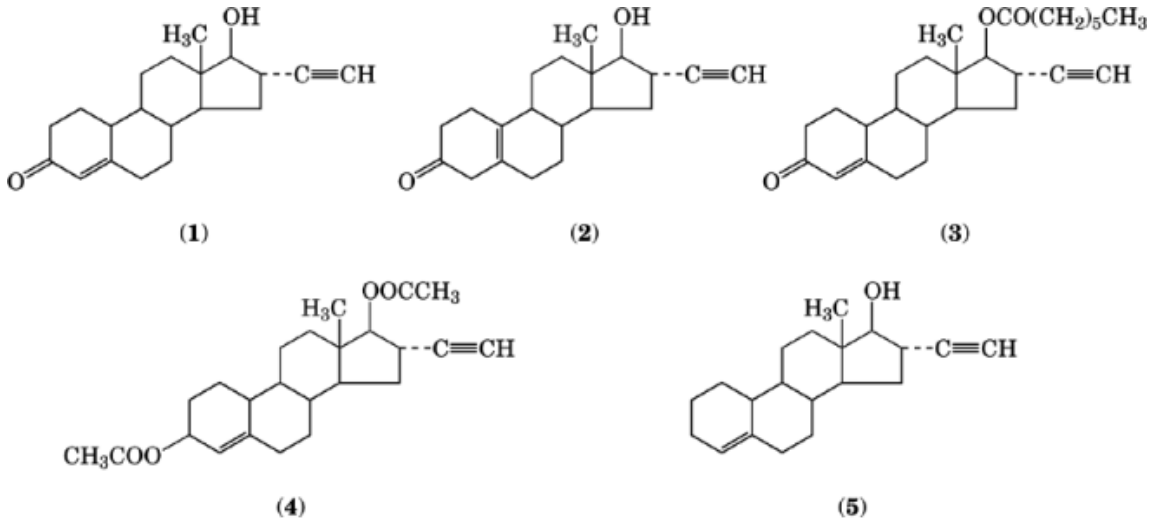


Fig. 1. Examples of estrane progestogens. (**1**) Norethindrone [68-22-4] (norethisterone, $C_{20}H_{26}O_2$); (**2**) norethynodrel [68-23-5] $C_{20}H_{26}O_2$; (**3**) norethindrone enanthate [3836-23-5], $C_{27}H_{38}O_3$; (**4**) ethynodiol diacetate [297-76-7], $C_{24}H_{32}O_4$; (**5**) ethinylestrenol [52-76-7] (lynestrenol, $C_{20}H_{28}O$).

The concept of hormonal control of ovulation first appeared in 1921 when Ludwig Haberlandt, a physiologist at the University of Innsbruck, showed that extracts of the corpus luteum, containing progesterone [57-83-0], $C_{21}H_{30}O_2$, could inhibit ovulation and make mice and rabbits infertile (10). Subsequent research showed that this phenomenon occurred in other species as well.

Making progesterone in the laboratory was both difficult and expensive, and progesterone could not be given orally because its natural form is destroyed in the digestive system. During the next 20 years, other sex hormones were isolated, identified, and synthesized. Unfortunately, evaluation of their clinical utility, like that of progesterone, was severely restricted by insufficient quantities of compounds. By 1943, Russell Marker, an American chemist, had developed a method for synthesizing progesterone and other steroid derivatives from disogenin, a naturally occurring steroid present in a species of *Dioscorea*. Marker's studies led to the synthesis of larger quantities of steroids that could be clinically evaluated for their effects on fertility regulation. It was discovered that elimination of the methyl group at C-19 of progesterone results in a progestational compound that is orally active. Also, structural modification of steroids from other hormone classes, such as the elimination of C-19 from testosterone, results in orally active compounds that have progesterone-like effects, ie, they induce secretory changes in estrogen-primed endometrium; induce the formation of thick, viscous cervical mucus; and suppress the release of luteinizing hormone and ultimately ovulation. These compounds are commonly termed progestogens or progestins. In 1951, Djerassi at Syntex and Coulton at Searle in the United States produced substituted 19-nor-synthetic progestogens which are still utilized in oral contraceptives, ie, norethisterone (**1**) (norethindrone in the United States) and norethynodrel (**2**), respectively (Fig. 1). Other progestogens which were subsequently synthesized include lynestrenol (**5**), chlormadinone acetate [302-22-7], $C_{23}H_{29}ClO_4$, medroxyprogesterone acetate (**6**), ethynodiol diacetate (**4**), levonorgestrel (**11**), desogestrel (**8**), norgestimate (**10**), and gestodene (**9**).

The first clinical study of an oral contraceptive began with a pill investigators believed contained only the progestogen norethynodrel. Early clinical data demonstrated that this preparation inhibited ovulation. In subsequent studies, utilizing newly synthesized batches of the progestogen, ovulation was inhibited, but significant intermenstrual vaginal bleeding also occurred. It was discovered that the original batch of progestogen, which

gave better cycle control, was contaminated with an estrogen, mestranol (**13**). It was subsequently shown that addition of estrogen to pure progestogen also increased efficacy. This realization led to the controlled inclusion of estrogen in oral contraceptives (11).

1.2. Second and Third Generation Oral Contraceptives

Most oral contraceptives are combinations of an estrogenic agent and a progestational agent (progestogen). Estrogens are found in the ovary, and are important in preventing pregnancy; they work in conjunction with the progestogen to suppress ovulation.

The estrogenic and progestational components provide their primary contraceptive effect by blocking ovulation, ie, preventing the selection of a dominant follicle in the ovary by a negative feedback action on the hypothalamus and pituitary. This inhibits pituitary secretion of follicle-stimulating hormone (FSH) [9002-18-0] and luteinizing hormone (LH) [9002-67-9], with the resultant inhibition of ovulation. The estrogen component also provides stability to the endometrium so that unwanted breakthrough bleeding can be avoided. This combination also provides several ancillary contraceptive mechanisms by interfering with fertilization and implantation processes should ovulation occur (7).

Early clinical investigators were concerned primarily about the contraceptive efficacy of the first oral contraceptive products. These original oral contraceptives were relatively high dose products as judged by later standards. Epidemiological studies during the 1960s and 1970s indicated that oral contraceptive usage was associated with an increased risk of thromboembolic disease. These cardiovascular complications were associated with the relatively high doses of estrogen used in original oral contraceptives, especially in women who smoke. These findings led to the development of low estrogen dose combination oral contraceptives. Early oral contraception formulations contained up to 100–150 μg of estrogen. By the early 1990s the majority of oral contraceptives contained only 30 or 35 μg of estrogen (Table 1). These low dose products are commonly referred to as second-generation oral contraceptives, ie, new products which have almost totally replaced the original high dose oral contraceptives. Numerous review articles and reports on cohort studies describing the use of oral contraceptives and the incidence of side effects are available (12–22).

As companies continued to conduct studies to find the lowest doses of estrogen and progestogen effective as contraceptives, women began to experience increased levels of intermenstrual bleeding. This observation led to the development of multiphasic oral contraceptives, a new approach to low-dose contraception (Table 2). Multiphasic oral contraceptives vary the dose of active ingredients or the ratio of progestogen to estrogen throughout the cycle, instead of remaining constant as in conventional combination oral contraceptives, to utilize the lowest effective dose of active ingredients yet still control intermenstrual bleeding. Some, but not all, of the low dose multiphasic oral regimens studied significantly reduce intermenstrual bleeding and spotting (23). The success of this approach was seen in the marketplace when the first triphasic oral contraceptive was introduced in the United States (Ortho-Novum 7/7/7) in 1984. It is now the most commonly prescribed oral contraceptive in that country. The products in Tables 1 and 2 are representative of products being sold throughout the world (Table 3).

New, pharmacologically more selective progestogens, which attempt to eliminate undesirable pharmacological activity but retain the needed progestational activity, have been investigated. Studies published in the 1970s and 1980s demonstrate that androgenicity associated with the progestational component of some of the original progestogens is associated with changes in lipid metabolism (24, 25). These changes may impact cardiovascular morbidity. Hence, oral contraceptives that do not disturb the various blood lipid fractions and do not lower HDL may be preferable to the ones that shift the lipid profile in an undesirable direction (26). Three companies, ie, Ortho Pharmaceutical Corporation, Organon, and Schering AG, have attempted to dissociate the androgenicity and progestational activities of steroidal progestogens using medicinal chemistry approaches. Norgestimate (**10**), desogestrel (**8**), and gestodene (**9**) emerged from this research (27–30). These more selective progestogens, in combination with ethinyl estradiol (**12**), compose the third generation oral contraceptives.

Table 1. Low Dose Monophasic Estrogen–Progestogen[a] Combination Oral Contraceptives Marketed in the United States

Trade name	Estrogen, μg	Progestogen, mg	Launch date	Manufacturer
Bevicon	35	0.50	10/75	Syntex
Demulen 1/35	35	1.00[b]	1/82	Searle
Demulen 1/50	50	1.00[b]	12/70	Searle
Desogen	30	0.15	1/93	Organon
Genora 0.5/35	35	0.50	10/89	Rugby Labs
Genora 1/35	35	1.00	12/86	Rugby Labs
Genora 1/50	50[c]	1.00	10/86	Rugby Labs
Levlen	30	0.15[d]	1/86	Berlex
Loestrin 1.5/30	30	1.50[e]	10/73	Parke-Davis
Loestrin 1/20	20	1.00[e]	10/73	Parke-Davis
Lo-ovral	30	0.30[d]	3/75	Wyeth
M.E.E.	35	1.00	3/88	Lexis Pharm
Modicon	35	0.50	12/74	Ortho
Nelova 0.5/35E	35	0.50	11/87	Warner-Chilcott
Nelova 1/35E	35	1.00	11/87	Warner-Chilcott
Nelova 1/50M	50[c]	1.00	11/88	Warner-Chilcott
Norcept-E 1/35	35	1.00	8/89	Gynopharma
Nordette	30	0.15[d]	5/82	Wyeth
Norinyl + 35	35	1.00	12/83	Syntex
Norinyl + 50	50[c]	1.00	12/83	Syntex
OrthoCept	30	0.15	1/93	Ortho
Ortho Novum 1/35	35	1.00	1/80	Ortho
Ortho Novum 1/50	50[c]	1.00	4/67	Ortho
Ortho-Cyclen	35	0.25[f]	10/92	Ortho
Ovcon 35	35	0.40	4/76	Mead Johnson
Ovcon 50	50	1.00	9/78	Mead Johnson
Ovral	50	0.50[d]	9/76	Wyeth

[a] Ethinyl estradiol-norethindrone unless otherwise noted.
[b] Ethynodiol diacetate (**4**).
[c] Mestranol (**13**).
[d] Norgestrel (**11**).
[e] Norethindrone acetate.
[f] Norgestimate.

During the 1990s and beyond, the usage of oral contraceptives containing these progestins will continue to grow.

1.3. Chemical Analysis

Chemically, the various progestogens belong to one of three classes. Estranes are 19-nortestosterone derivatives (Fig. 1); gonanes are 19-nortestosterone derivatives with a C-13 ethyl group (Fig. 2); and pregnanes are 17-alpha-OH progesterone derivatives similar in structure to progesterone itself.

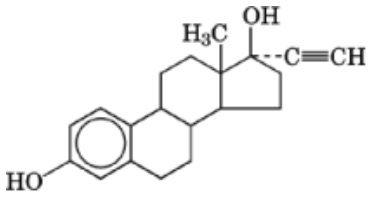
The pregnanes include megestrol, medroxyprogesterone acetate [71-58-9], $C_{24}H_{34}O_4$ (**6**), chlormadinone acetate [302-22-7], $C_{23}H_{29}ClO_4$, and cyproterone acetate [427-51-0], $C_{24}H_{29}ClO_4$ (**7**).

The second active ingredient in combination oral contraceptives is estrogen. In the early 1990s, one of two related estrogens is utilized, ie, ethinyl estradiol [57-63-6] (19-nor-17-pregna-1,3,5(10)-trien-20-yne-3,17-diol), $C_{20}H_{24}O_2$, (**12**), and mestranol [72-33-3] (3-methoxy-19-nor-17-pregna-1,3,5(10)-trien-20-yne-17-ol), which has the molecular formula $C_{21}H_{26}O_2$ (**13**).

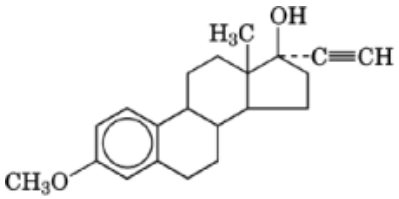
Table 2. Low Dose Multiphasic Estrogen–Progestogen Combination Oral Contraceptives Marketed in the United States

	Ethinyl estradiol		Progestogen[a]			
Trade name	Regimen, days	Dosage, μg	Regimen, days	Dosage, mg	Launch date	Manufacturer
			Levonorgestrel			
Triphasil	1–6	30	1–6	0.050	12/84	Wyeth
	7–11	40	7–11	0.075		
	12–21	30	12–21	0.125		
Tri-levlen	1–6	30	1–6	0.050	1/86	Berlex
	7–11	40	7–11	0.075		
	12–21	30	12–21	0.125		
			Norethindrone			
Jenest	1–21	35	1–7	0.50		Organo
			8–21	1.00		
Ortho Novum 10/11	1–21	35	1–10	0.50	3/82	Ortho
			11–21	1.00		
Ortho Novum 7/7/7	1–21	35	1–7	0.50	4/84	Ortho
			8–16	0.75		
			17–21	1.00		
Tri-norinyl	1–21	35	1–7	0.50	4/84	Syntex
			8–16	1.00		
			17–21	0.50		
			Norgestimate			
Ortho Tri-cyclen	1–21	35	1–7	0.180	10/92	Ortho
			8–16	0.215		
			17–21	0.250		

[a] Products are grouped by progestogen.



(12)



(13)

Mestranol was the original estrogen contaminant discovered during contraceptive efficacy testing of the progestogen, norethynodrel. Drug metabolism studies indicate that most of the estrogenic activity of this compound could be attributed to its active metabolite, ethinyl estradiol, which has largely replaced mestranol as the estrogen component of oral contraceptives. Ethinyl estradiol differs from naturally occurring estradiol-17β

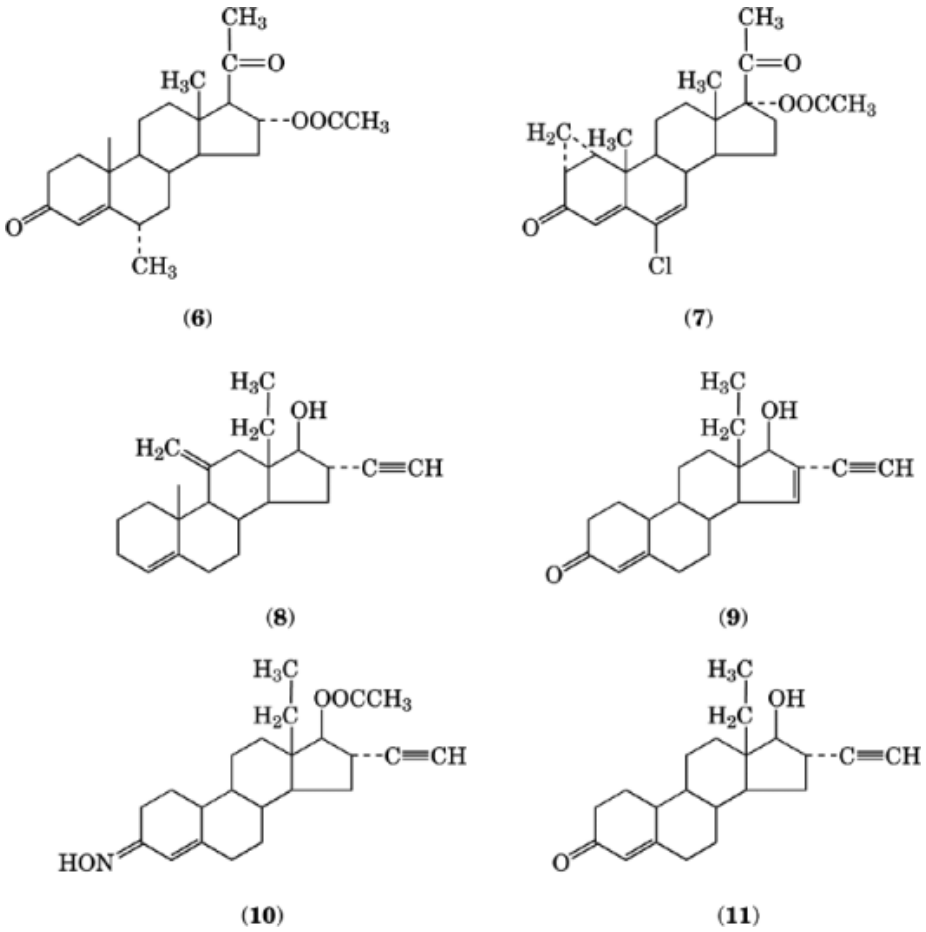


Fig. 2. Selected gonane progestogens. (**8**) desogestrel [54024-22-5], $C_{22}H_{30}O$; (**9**) gestodene [60282-87-3], $C_{21}H_{26}O_2$; (**10**) norgestimate [35189-28-7], $C_{23}H_{31}NO_3$; (**11**) norgestrel [6533-00-2] (levonorgestrel, $C_{21}H_{28}O_2$).

by having an ethinyl group attached to C-17, whereas mestranol differs from ethinyl estradiol by methylation of the hydroxyl group at C-3. Both ethinyl estradiol and mestranol resemble the natural estrogens qualitatively in their pharmacological actions on target tissues, including the reproductive tract, pituitary, and hypothalamus.

1.4. Progestogen-Only Oral Contraceptives

Progestogen-only oral contraceptives, ie, minipills, are available but are not used as extensively as combination oral contraceptives. These preparations contain 19-norsteroids such as norethindrone, lynestrenol, ethynodiol diacetate, or norgestrel, and 17-β-acetoxy progesterone derivatives such as chlormadinone acetate and megestrol acetate. The contraceptive effectiveness of these products is not as high as that of combination oral contraceptives; intermenstrual or breakthrough bleeding and spotting occur more frequently with these products. Progestogen-only oral contraceptives are prescribed for breast-feeding women since progestins do not influence milk production, and for women for whom estrogens are contraindicated.

Table 3. Oral Contraceptives Marketed in Selected Countries

Trade name	Regimen, total days breakdown	Dose, mg and ingredients: Progestogen[a]	Dose, mg and ingredients: Estrogen[b]	Launch date	Manufacturer
		Argentina			
Tridestan	21			9/82	Gador
	6	0.05 (**11**)	0.03[c]		
	5	0.075 (**11**)	0.04[c]		
	10	0.125 (**11**)	0.03[c]		
		Australia			
Biphasil	28			1/79	Wyeth
	11	0.05 (**11**)	0.05		
	10	0.125 (**11**)	0.05		
	7	placebo			
Neogynon	21	2.5 (**11**)	0.05	4/70	Schering
		Austria			
Cilest[d]	21	0.25 (**10**)	0.035	8/89	Cilag
Gynovin	21	0.075 (**9**)	0.03	5/88	Schering
Micronovum[e]	28	0.35 (**1**)		9/72	Cilag
Ortho Novum 1/50[f]	21	1.0 (**1**)	0.05[c]	3/69	Cilag
Ovysmen 1/35[g]	21	1.0 (**1**)	0.035	6/78	Cilag
Perikursal	21			6/77	Wyeth
	11	0.05 (**11**)	0.05		
	10	0.125 (**11**)	0.05		
Trinovum[h]	21			9/84	Cilag
	7	0.50 (**1**)	0.035		
	7	0.75 (**1**)	0.035		
	7	1.0 (**1**)	0.035		
		Belgium			
Microgynon-50	21	0.125 (**11**)	0.05	9/67	Schering
Micronor[i]	28	0.35 (**1**)		3/73	Cilag
Microval	28	0.03 (**11**)		12/72	Wyeth
		Brazil			
Anfertil	21	0.50 (**11**)	0.05	5/67	Wyeth
Evanor	21	0.25 (**11**)	0.05	8/70	Wyeth
Microdiol	21	0.15 (**8**)	0.03	7/85	Organon
Neovlar	21	0.25 (**11**)	0.05	2/71	Schering
Primovlar	21	0.50 (**11**)	0.03	6/67	Schering
		Canada			
Micronor	28	0.35 (**1**)		5/72	Cilag
Norlestrin 1/50	21	1.0 (**1**)	0.05	8/64	Parke-Davis
Norlestrin 2.5/50	21	2.5[j]	0.05	8/64	Parke-Davis
Ortho Novum 1/35	21	1.0 (**1**)	0.035	6/80	Cilag
Ortho Novum 1/50	21	1.0 (**1**)	0.035[c]	6/62	Cilag
Ortho 7/7/7	21			9/83	Cilag
	7	0.50 (**1**)	0.035		
	7	0.75 (**1**)	0.035		
	7	1.0 (**1**)	0.035		
Ortho 10/11	21			11/81	Cilag
	10	0.50 (**1**)	0.035		
	11	1.0 (**1**)	0.035		
		France			
Adepal	21			10/76	Wyeth
	7	0.5 (**11**)	0.03		
	14	0.20 (**11**)	0.04		

Table 3. ***Continued***

Trade name	Regimen, total days breakdown	Dose, mg and ingredients: Progestogen[a]	Dose, mg and ingredients: Estrogen[b]	Launch date	Manufacturer
Gynophase	21			1/74	Schering
	11	1.0[j]	0.05		
	10	2.0[j]	0.05		
Milligynon	21	0.60[j]		7/78	Schering
Minidril	21	0.15 (**11**)	0.03	1/76	Wyeth
Miniphase	21			3/77	Schering
	11	1.0[j]	0.03		
	10	2.0[j]	0.04		
Ogyline	28	0.35 (**1**)		10/80	Roussel
Ortho Novum 1/35[k]	21	1.0 (**1**)	0.035	9/81	Cilag
Ovanon	22			6/69	Organon
	7		0.05		
	15	2.5 (**5**)	0.05		
Phaeva	21			12/88	Wyeth
	6	0.05 (**9**)	0.03		
	5	0.07 (**9**)	0.04		
	10	1.0 (**9**)	0.03		
Physiostat	22			3/76	Organon
	7		0.05		
	15	0.05 (**5**)			
Planor	21	2.0 (**1**)	0.05	8/67	Roussel
Tretntovlane	21	1.0[j]	0.03	11/75	Schering
Triella	21			7/84	Cilag
	7	0.50 (**1**)	0.035		
	7	0.75 (**1**)	0.035		
	7	1.0 (**1**)	0.035		
Triminulet	21			12/88	Wyeth
	6	0.05 (**9**)	0.03		
	5	0.07 (**9**)	0.04		
	10	0.10 (**9**)	0.03		
Varnoline	21	0.15 (**8**)	0.03	4/84	Organon
		Germany			
Anacyclin	22			5/70	Geigy
	16	1.0 (**5**)	0.05		
	6	placebo			
Conceplan M	21	0.50 (**1**)	0.03	9/78	Gruenenthal
Ediwal 21	21	0.125 (**11**)	0.05	4/76	Schering
Etalontin 21	21	2.5[j]	0.05	1/63	Parke-Davis
Eugynon	21	0.50 (**11**)	0.05	11/66	Schering
Eunomin	21	2.0[l]	0.1[c]	10/75	Gruenenthal
Femranette	21	0.15 (**11**)	0.03	10/88	Brenner/Efeka
Lyndiol 2.5	22	2.5 (**5**)	0.05	1/62	Organon
Lyn-Ratiopharm	21	2.5 (**5**)	0.05	1/81	Ratiopharm
Marvelon[m]	21	0.15 (**8**)	0.03	6/81	Organon
Microlut	21	0.03 (**11**)		5/72	Schering
Neo-Eunomin	21	1.0[l]	0.05	1/85	Gruenenthal
Noerlest 21	21	0.60[j]	0.03	9/74	Parke-Davis
Noracyclin	22	2.5 (**5**)	0.05	1/64	Geigy
Orlest 28	28			7/67	Parke Davis
	21	1.0[j]	0.05		
	7	placebo			
Oviol	22			6/81	Nourypharma

Table 3. ***Continued***

Trade name	Regimen, total days breakdown	Dose, mg and ingredients: Progestogen[a]	Dose, mg and ingredients: Estrogen[b]	Launch date	Manufacturer
	7	0.125 (**8**)			
	15		0.05		
Ovoresta	22	1.0 (**5**)		10/72	Organon
Ovysmen 0.5/35[n]	21	0.50 (**1**)	0.035	3/75	Cilag
Pregnon 28	28			10/76	
	22	1.0 (**5**)	0.05		
	6	placebo			
Sequilar	21			3/74	Schering
	11	0.05 (**11**)	0.05		
	10	0.125 (**11**)	0.05		
Sinovula	21	1.0[j]	0.05	3/73	Asche
Synfase	21			9/86	Gruenenthal
	7	0.50 (**1**)	0.035		
	9	1.0 (**1**)	0.035		
	5	0.50 (**1**)	0.035		
Tetragynon	21	0.25 (**11**)	0.05	9/85	Schering
Trinordiol	21			10/79	Wyeth
	6	0.05 (**11**)	0.03		
	5	0.075 (**11**)	0.04		
	10	0.125 (**11**)	0.03		
Triguilar	21			10/79	Schering
	6	0.05 (**11**)	0.03		
	5	0.075 (**11**)	0.04		
	10	0.125 (**11**)	0.03		
Tristep	21			10/83	Asche
	6	0.05 (**11**)	0.03		
	5	0.05 (**11**)	0.05		
	10	0.125 (**11**)	0.04		
		Italy			
Bivlar	21	0.50 (**11**)	0.05	4/80	Schering
Evanor D	21	0.25 (**11**)	0.05	2/73	Wyeth
Ginoden	21	0.075 (**9**)	0.03	10/87	Schering
Ovranet	21	0.15 (**11**)	0.03	9/78	Wyeth
Planum	21	0.15 (**8**)	0.03	4/84	Menarini
Practil 21	21	0.15 (**8**)	0.03	3/84	Organon
		The Netherlands			
Binordiol	21	0.05 (**11**)	0.05	2/75	Wyeth
Exluton	21	0.50 (**5**)		11/72	Organon
Modicon[o]	21	0.50 (**1**)	0.035	11/78	Cilag
Stediril	21	0.125 (**11**)	0.05	2/76	Wyeth
Trigynon	21			12/80	Schering
	6	0.05 (**11**)	0.03		
	5	0.075 (**11**)	0.04		
	10	0.125 (**11**)	0.03		
		Puerto Rico			
Brevicon	21	0.50 (**1**)	0.035	10/75	Syntax
Ortho Novum 7/7/7	21			6/84	Cilag
	7	0.50 (**1**)	0.035		
	7	0.75 (**1**)	0.035		
	7	1.0 (**1**)	0.035		
		South Africa			
Normovlar Ed	28			2/76	Schering

Table 3. ***Continued***

Trade name	Regimen, total days breakdown	Dose, mg and ingredients: Progestogen[a]	Dose, mg and ingredients: Estrogen[b]	Launch date	Manufacturer
	11	0.05 (**11**)	0.05		
	10	0.125 (**11**)	0.05		
	7	placebo			
		Sweden			
Desolett	21	0.15 (**8**)	0.03	9/87	Organon
Follimin	21	0.15 (**11**)	0.03	3/76	Kabivitrum
Follinett	21	0.25 (**11**)	0.05	9/71	Kabivitrum
Follistrel	21	0.03 (**11**)		6/74	Kabivitrum
Lyndiolett	21	1.0 (**5**)	0.05	6/77	Organon
Mini-Pe	21	0.35 (**1**)		3/72	Syntex
Neovletta	21	0.15 (**11**)	0.03	12/75	Schering
Regunon	21	0.125 (**11**)	0.05	9/76	Schering
Trionetta	21			6/81	Schering
	7	0.05 (**11**)	0.03		
	5	0.05 (**11**)	0.04		
	10	0.125 (**11**)	0.03		
		Switzerland			
Femovan	21	0.075 (**9**)	0.03	5/87	Schering
Gynera	21	0.075 (**9**)	0.03	4/87	Schering
Minulet	21	0.075 (**9**)	0.03	4/87	Wyeth
Ovostat	22	1.0 (**5**)	0.05	10/69	Organon
Stediril	21	0.50 (**11**)	0.05	1/66	Wyeth
Yermonil	21	2.0 (**5**)	0.04	8/73	Geigy
		United Kingdom			
Binovum	21			3/82	Cilag
	10	0.50 (**1**)	0.035		
	11	1.0 (**1**)	0.035		
Brevinor	21	0.50 (**1**)	0.035	1/77	Syntex
Conova 30	21	2.0 (**4**)	0.03	1/78	Gold Cross
Femodene	21	0.075 (**9**)	0.03	5/87	Schering
Gynovlar 21	21	3.0[j]	0.05	10/64	Schering
Logynon Ed	28			6/80	Schering
	6	0.05 (**11**)	0.03		
	5	0.075 (**11**)	0.04		
	10	0.125 (**11**)	0.03		
	7	placebo			
Mercilon	21	0.15 (**8**)	0.03	4/88	Organon
Microgynon-30	21	0.15 (**11**)	0.03	3/74	Schering
Minovlar Ed	28			1/69	Schering
	21	1.0[j]	0.05		
	7	placebo			
Minovlar 30	21	0.15 (**11**)	0.03	1/69	Schering
Norgeston	21	0.03 (**11**)		5/79	Schering
Noriday 28	21	0.35 (**1**)		10/72	Syntex
Norimin	21	1.0 (**1**)	0.035	11/78	Syntex
Ovran	21	0.25 (**11**)	0.05	11/72	Wyeth
Ovysmen	21	0.50 (**1**)	0.035	9/75	Cilag

[a] Levonorgestrel (**11**); Norethisterone (**1**); Norgestimate (**10**); Lynestrenol (**5**); Ethynodiol diacetate (**4**); Desogestrel (**8**); Gestodene (**9**); Norgestrel (**11**).

[b] Ethinyl estradiol unless noted.

[c] Mestranol.

[d] Belgium (8/89), France (9/88), Germany (11/86), Italy (10/90), Netherlands (12/90), Switzerland (1/87), UK (5/91).
[e] Germany (11/71), Switzerland (7/74).
[f] Belgium (9/69), Germany (6/70), Netherlands (6/71), Puerto Rico (1/63), Switzerland (7/67).
[g] Germany (3/75).
[h] Belgium (2/86), Germany (3/83), Italy (4/88), Mexico (7/84), Netherlands (2/85), Switzerland (3/84), UK (1/84).
[i] Puerto Rico (1/73), UK (10/72).
[j] Norethisterone acetate [51-98-9], $C_{22}H_{28}O_3$.
[k] Mexico (7/83), Puerto Rico (9/80).
[l] Chlormadinone acetate [302-22-7], $C_{23}H_{29}ClO_4$.
[m] UK (1/82).
[n] Switzerland (6/76).
[o] Puerto Rico (1/75).

1.5. Areas of Continued Research

Research continues in many academic and pharmaceutical laboratories throughout the world with the objective of improving oral contraceptives and better understanding their pharmacological and clinical actions.

Epidemiological studies with oral contraceptive users have had a bearing on the utilization of oral contraceptives by the public. The possible association of oral contraceptive use with the incidence of breast cancer has been the subject of numerous epidemiologic studies and reviews by the World Health Organization (WHO), National Institutes of Health (NIH), and the U.S. Food and Drug Administration (FDA). While the incidence of breast cancer in some small subgroups of users may have increased slightly, it has been concluded that the overall incidence in oral contraceptive users does not appear to have increased (31, 32). Epidemiological studies on oral contraceptives have also demonstrated clear noncontraceptive health benefits, including protection against pelvic inflammatory disease (PID), ectopic pregnancy, endometrial cancer, cancer of the ovaries, benign breast disease, and benign ovarian cysts (33, 34). Relief from a wide range of menstrual disorders, such as heavy menstrual flow, also is a beneficial effect of oral contraceptive use (29, 30).

Toxicology studies are utilized to study the safety of new oral contraceptives. Because oral contraceptives are utilized by healthy, normal, young women, they have historically been required by regulatory agencies to undergo extremely intensive toxicological studies to confirm safety. Different countries have different requirements for the demonstration of product safety; the U.S. has historically been the most demanding, eg, safety had to be demonstrated in three animal species in very long-term chronic studies, utilizing different dosage schedules and different dosing intervals. For a number of years, issues such as species differences in pharmacokinetics and pharmacodynamics were not important considerations in the design of toxicological studies. A better understanding of the effect of kinetics, dynamics, and drug metabolism on drug safety has led to revisions in guidelines for the toxicological assessment of oral contraceptive safety (35, 36). For example, use of the female beagle has traditionally been required for assessment of the carcinogenic potential of new progestins. A combination of laboratory and epidemiological studies has led to the conclusion that the female beagle cannot be used as a totally valid toxicological model for assessing the safety of new combination oral contraceptives (37). New FDA and WHO guidelines have been proposed.

Intensive research continues for new active ingredients that can be used in combination oral contraceptives. This research has been targeted at both new estrogens and more selective progestogens, including nonsteroidal agents; Norgestimate, Desogestrel, and Gestodene are all more selective pharmacologically than the original progestogens.

The potential use of natural estrogens, such as estradiol and estriol, as components of oral contraceptives has been described (38, 39), but there has been little focus on the introduction of new natural estrogens into oral contraceptive formulations. The use of natural estrogens is based on the suggestion that the natural estrogens may have a lesser effect on coagulation factors and thus lesser predisposition to thrombus formation. The problem is that these natural steroids are poorly active as oral agents and require relatively high doses, in milligrams rather than micrograms, to provide adequate cycle control. Research continues in the synthesis

of new, more selective steroidal estrogens that retain the endocrine activity necessary for control of ovulation and cycle control, but lack any other pharmacological activities. The potential exists to further dissociate these pharmacological actions through medicinal chemistry approaches.

A final area of research focuses on how the pill can best be used by women. Physicians used to recommend pill-free holidays, but it is now known that there is no valid reason for this practice. Similarly, further research indicated that the U.S. FDA's restrictive guidelines for prescribing the pill to women over the age of 35 are not justified, and those guidelines have been changed. Finally it is clear that cigarette smoking increases the risk of cardiovascular side effects, especially in women over 35 who utilize combination oral contraceptives.

2. Long-Acting Contraceptives

The establishment of fertility regulation with hormonally active oral contraceptives led to other routes of long-acting contraceptive drug administration. Long-acting contraceptives avoid compliance issues, and are useful in countries with fewer health professionals. Their popularity is based on simplicity of administration and a relatively high degree of effectiveness (see Controlled-release technology, pharmaceutical).

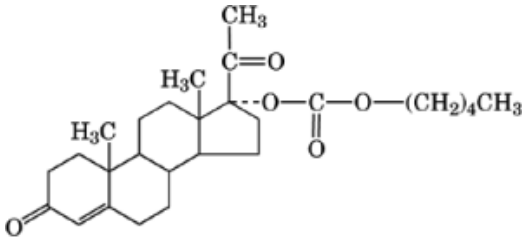
The currently (ca 1992) marketed injectable and implantable contraceptives are designed to be effective for maximum periods of three months and five years, respectively. There is little evidence from programmatic or health reasons that an injectable formulation with a longer effective life span, eg, six months, would not be equally effective. The acceptability and effectiveness of long-acting contraceptives may be determined by the means by which a community delivers contraceptive products to the public; the active life of a product may be determined by economic rather than programmatic or health related factors.

2.1. Injectable Contraceptives

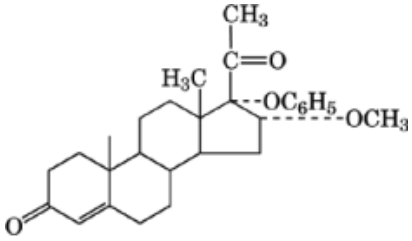
Injections of contraceptive drugs must be sufficiently spaced to make the approach attractive to the user. The average contraceptive user is not willing to endure daily injections or injection intervals of one or two weeks; the minimum acceptable injection interval has been found to be at least four weeks.

Long-acting activity of injectable contraceptives can be accomplished via a number of different approaches. Steroid activity can be extended over a period of time by chemical modifications, such as esterification, which result in products that require enzymatic hydrolysis over time for conversion to active products. Long-acting activity is also achieved by the presentation of drugs, with limited aqueous solubility, to the injection site in a microcrystalline aqueous suspension.

Two well-known injectable long-acting products are medroxyprogesterone acetate (Depo Provera) (**6**) and norethindrone enanthate (NET EN) (**3**). Both of these products are progestational in nature. Depo Provera (Upjohn Company) is a once-every-three-months injectable administered as a microcrystalline aqueous suspension. NET EN (Schering AG) is a two-month injectable administered as solution in caster oil. Depo Provera is approved for use as a contraceptive in more than ninety countries including the United States; NET EN is used in more than forty countries. Other products developed by chemically modifying known progestogens include 17α-hydroxyprogesterone caproate [630-56-8], $C_{27}H_{40}O_4$ (**14**) and dihydroxyprogesterone acetophenide [24356-94-3], $C_{29}H_{36}O_4$ (**15**). These monthly injectables are widely used in Latin America.



(14)



(15)

Long-acting progestins act primarily as ovulation inhibitors. An important secondary component is their effect on the cervical mucus and endometrium, achieved at circulating blood drug levels below those required for ovulation inhibition (40).

The acceptability of long-acting injectable contraceptives is tempered by the effects of these drugs on endometrial function and the presence of nuisance side effects such as intermenstrual spotting and bleeding. Under normal circumstances the cyclical changes in endometrial morphology are the result of changes in ovarian function. Estrogens and progesterone, produced by the ovary, are responsible for the change from an estrogen dominated proliferative endometrium to the secretory progesterone dominated endometrium of the luteal phase. Dimunition in progesterone production toward the end of a normal menstrual cycle leads to a breakdown of endometrial integrity and menses. Following the injection of long-acting progestins, ovarian function is inhibited and secretion of estrogens by developing follicles is diminished. Consequently, endometrial morphology no longer resembles that observed during menstrual cycles, and unpredictable bleeding episodes occur. This type of dysfunctional uterine bleeding frequently leads to the discontinuation of these contraceptive methods. Another outcome of the injectables is amenorrhea, ie, total absence of menstrual-like bleeding. Amenorrhea may be tolerated by patients better than dysfunctional bleeding, especially when this condition is explained to the patient prior to initiation of the therapy. However, amenorrhea is disturbing to some women because absence of menses is frequently associated with pregnancy.

The importance of predictable withdrawal bleeding has led to the development of combined progestin–estrogen injectable formulations. These products contain a relatively small dose of a long-acting progestin combined with a shorter acting estradiol ester. The progestational drug is programmed to have an effective life span of about thirty days and the estrogen of about a week. These types of formulations are administered on a monthly basis. Regularized bleeding occurs approximately one week after each injection and is the result of decreasing levels of estrogen. This is termed an estrogen withdrawal bleeding. Once-a-month injectables are popular in some Latin and South American countries; their introduction into other developing countries is being attempted by WHO (41).

The cost-effectiveness of injectable contraceptives has spurred the search for additional products that could be utilized for fertility regulation. The butanoate ester of levonorgestrel has undergone extensive studies

in laboratory animals and has been the subject of clinical studies. The pharmacokinetic profile of this drug can be controlled, to a degree, by changing particle size distribution. A product containing an aqueous suspension of particles in the 15–20 μm range can provide effective contraception for a three month period at a total dose of approximately 15 mg. This product is being developed by the World Health Organization (42).

Incorporation of a short-acting drug into a long-acting drug delivery system via microencapsulation technology is used to improve the pharmacokinetic profile of long-acting progestins. Biodegradable polymers such as polylactides and polyglycolides have been utilized to produce microcapsules or microspheres with the polymer surrounding the drug (42). The kinetic profile of such preparations approaches zero order release for the desired period of time. Most of these formulations have been programmed to release the progestin for approximately three months. While clinical studies with norethindrone-releasing microcapsules have been ongoing for a number of years, reproducibility of the product has sometimes been a problem. Improved manufacturing processes should eliminate batch to batch variations. Finally, the cost-effectiveness of delivery via microencapsulation of a product with superior pharmacokinetic characteristics is yet to be documented. The overall process of delivering a microencapsulated contraceptive to the client is more complex than for a micronized aqueous suspension. Consequently the improvement in pharmacokinetic profile may have to be weighed against higher cost and dosage form complexity.

2.2. Implanted Contraceptives

Controlled release of contraceptive progestins also can be accomplished by incorporating the drug into an implantable cylinder or rod. The best known implant is Norplant, developed by the Population Council. Norplant is composed of six matchlike silastic cylinders with the progestogen levonorgestrel (**11**) incorporated on the inside of each cylinder. After implantation under the skin, the product can provide effective contraception for a period of five years (43, 44). Since silastic is not biodegradable, the implant can be removed from a patient at any time.

Clinical studies with Norplant attest to its high contraceptive efficacy and safety. The main reason patients request the removal of Norplant is unpredictable vaginal bleeding episodes followed by amenorrhea. The bleeding problem is an unavoidable sequela of progestogen-only contraception.

While the effective life of Norplant I is at least five years, most of the users have the implants removed at an earlier time. Norplant II was developed to have a shorter life-span, and is composed of only two rods. Levonorgestrel is dispersed in the silastic matrix which is then inserted into a thin silastic tubing. This product has an effective life-span of two to three years (36). Because it is composed of only two rods, Norplant II also is easier to implant and remove.

Clinical studies also have been carried out with nonbiodegradable implants releasing the progestin desogestrel (**8**). Unlike levonorgestrel, desogestrel possesses lower androgenic activity and thus has less adverse effect on blood lipids.

2.2.1. Biodegradable Implants

Utilization of biodegradable polymers obviates the need for implant removal. However, biodegradation should not take place before the drug release is essentially finished; before that, structural integrity permitting surgical removal of the implant must be maintained. The time-course for biodegradation and the disappearance of the implant are still being studied.

The Capronor device has walls composed of sigma caprolactone and releases levonorgestrel. It is a single implant with projected life span of 12–18 months (42). Capronor I had the drug dissolved in ethyl oleate. Once the ethyl oleate diffused through the device wall, the rate of drug release decreased to levels below those required for ovulation inhibition. Clinical studies carried out by the National Institute for Health (NIH), WHO, and the Indian Council of Medical Research indicated that the presence of ethyl oleate reduced the useful life of the device to 8–10 months. Since the use of excipients such as ethyl oleate is undesirable, investigators have

attempted to regulate the rate of drug release by reducing the wall thickness. Studies in animals indicate that the thinner walled Capronor II may have an effective life of at least 12 months.

2.2.2. Fused Pellets

Another form of an implant is a fused pellet. The pellets may be composed of either the drug alone, or the drug fused with cholesterol (29, 36), and are formed as small cylinders by melting the drug and then solidifying it under pressure. Clinical studies with norethindrone pellets have been in progress for a number of years. Effective rates of release of the drug from the implantation site were originally difficult to achieve.

Polymeric implants and pellets require minor surgery for both their insertion and removal.

2.3. Vaginal Rings

Vaginal epithelium is readily permeable to contraceptive steroids. Since the vascular drainage of the vagina bypasses the liver, this route of administration potentially permits utilization of drugs that have low oral activity.

Contraceptive vaginal rings consist of silastic shells or core rings of various sizes and membrane thicknesses. They have been developed for delivery of progestins alone or progestins combined with estrogens. Progestin-alone rings are conceptionally similar to implants, but are under direct control of the patient since they can be removed at any time. Rings releasing both a progestin and an estrogen resemble combined oral contraceptives. After the ring is removed, a predictable withdrawal bleeding takes place. Contraceptive efficacy of vaginal rings has been linked to the weight of the subject. Higher release rates are required for heavier women than for lower weight women. Vaginal rings have been under development for nearly fifteen years, by the World Health Organization and Population Council (45, 46). Acceptability of this route of contraceptive drug administration in developed countries must still be determined.

3. Contragestational Drugs

Pharmacological substances that either inhibit implantation or interrupt pregnancy after implantation have been investigated during the 1980s and 1990s. A number of different terms have been used to describe these compounds (47–63), including anti-implantive agents, postcoital contraceptives, morning-after pills, once-a-week pills, interceptives, abortifacients, and contragestational agents. This medical approach to fertility regulation presents several principal advantages, including potentially fewer long-term side effects as a result of short-term periodic administration, and greater convenience.

However, in the decision to develop and market contragestational drugs, social, political, legal, ethical, and religious factors have been of critical importance.

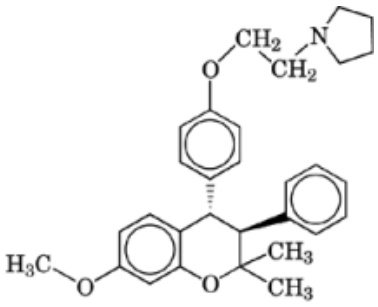
3.1. Post-Coital Contraception

Post-coital contraception historically has been viewed as an emergency measure where regular contraceptives were not used or where the primary contraceptives may have failed. A number of different approaches have been utilized in post-coital regimens. Early regimens utilized high doses of the estrogens (63), diethyl stilbestrol [56-53-1], ethinyl estradiol (**12**), and the conjugated equine estrogens (Premarin) (7). Characteristically, the drugs are taken for a period of three days. When given later than 72 hours after coitus, the effectiveness is reduced; the drugs are ineffective if implantation has been established. Although the estrogens are highly effective, users suffer from a high incidence of nausea and vomiting; cycle regularity also is disturbed. A similar approach has been reported for levonorgestrel-containing contraceptives (64).

It has been demonstrated that Danazol [17230-88-5], $C_{22}H_{27}NO_2$, is highly effective in post-coital regimens, and has a very low incidence of side effects. Danazol is marketed in many countries for the treatment of endometriosis and its availability is unrestricted. It does not appear that there is a significant difference in effectiveness when doses of 800 to 1200 mg have been utilized daily for three days (64, 65). When utilized in the post-coital mode, the precise mechanism of action of Danazol is not well-understood.

Clinical studies with the antiprogestin RU-486 indicate that, when used in a post-coital mode, this drug may be effective in preventing pregnancy.

A nonsteroidal weekly pill, centchroman [31477-60-8] (**16**), has recently been launched by the Central Drug Research Institute, Lucknow, India, and is being marketed as Choice-7 and Sahali (Hindustan Latex). Centchroman, (3,4-*trans*-2,2-dimethyl-3-phenyl-4-[*p*-(β-pyrrolidino-ethoxy)-phenyl]-7-methoxy-chromane) inhibits implantation of the fertilized egg, thus avoiding pregnancy (66). It exerts its antifertility effect via weak estrogenic and potent anti-estrogenic activity (67). Although the synthesis and pharmacological actions of centchroman have been well-documented (68), overall efficacy and side effects are not known or described except in a brief description of the product. It is reported that the Pearl index has been calculated to be 3.05 when weekly doses of centchroman (30 mg) were administered to approximately 1,600 women for a total of 20,000 months (66).



(**16**)

3.2. Abortifacients

It is estimated that between 30 and 40 million legal abortions and the same number of illegal abortions are carried out each year worldwide (69). In the mammal, removal of the corpus luteum during early pregnancy results in termination of pregnancy. Pharmacologically, this can be accomplished by various methods, including inhibition of gonadotropin support of the corpus luteum, inhibition of progesterone biosynthesis in the ovary, inhibition of progesterone binding to the uterine progestin receptor, and increase in the metabolism of progesterone. Many compounds that affect these processes have been reported (71); some of these compounds have been introduced for clinical use. Chemically induced abortion originally involved the administration of the natural prostaglandin F_2-α [551-11-1] (Dinoprost, $C_{20}H_{34}O_5$) (**17**), or synthetic analogues such as sulprostone [60325-46-4], $C_{23}H_{31}NO_7S$ (**18**) and prostaglandin ONO 802, [64318-79-2] (Gemeprost, $C_{23}H_{38}O_5$) (**19**) (Fig. 3) (71). After administration of relatively small amounts of these prostaglandins, the muscular tone of the uterus increases, followed by contractions, cervical dilation, and expulsion of the uterine contents. The usefulness of prostaglandins for termination of pregnancy is limited, because of a high frequency of gastrointestinal side effects.

In 1988, the French government approved the marketing of an abortion pill. RU486 [84371-65-3] (Mifepristone) (**20**), an antiprogestin developed by the French pharmaceutical company Roussel-UCLAF, is the first clinically useful progesterone antagonist (Fig. 4). A review of the chemistry, pharmacology, and clinical applications of this compound (72) is available, as is a review on the use of RU486 alone or in combination with a

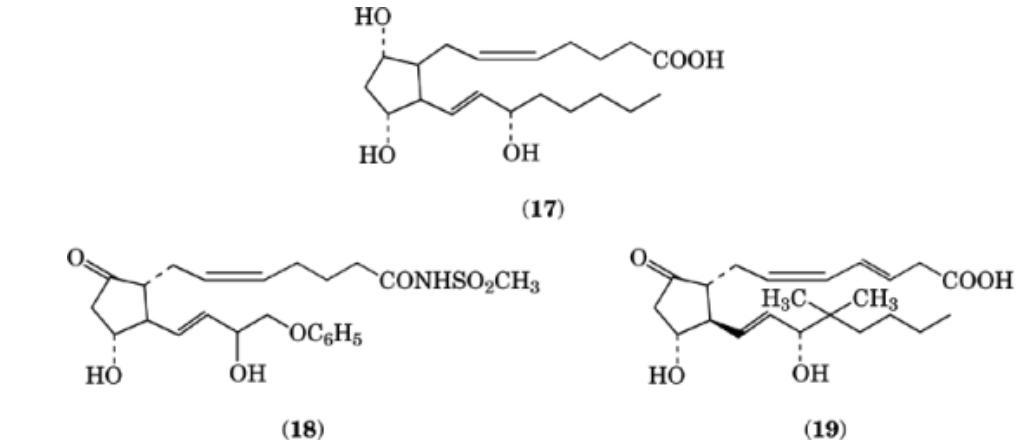


Fig. 3. Prostaglandins used in chemically induced abortion.

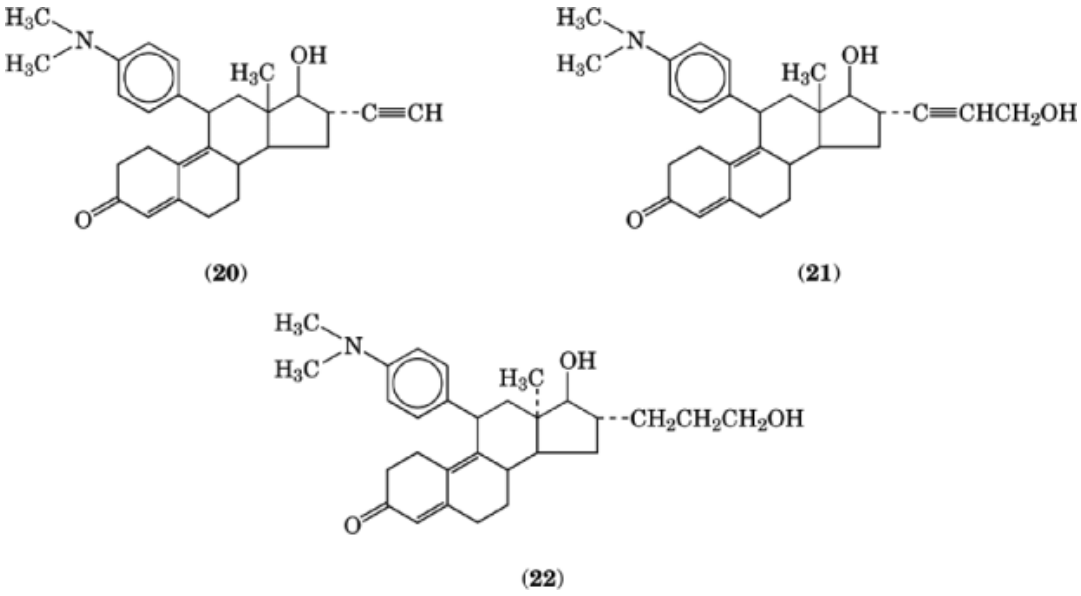
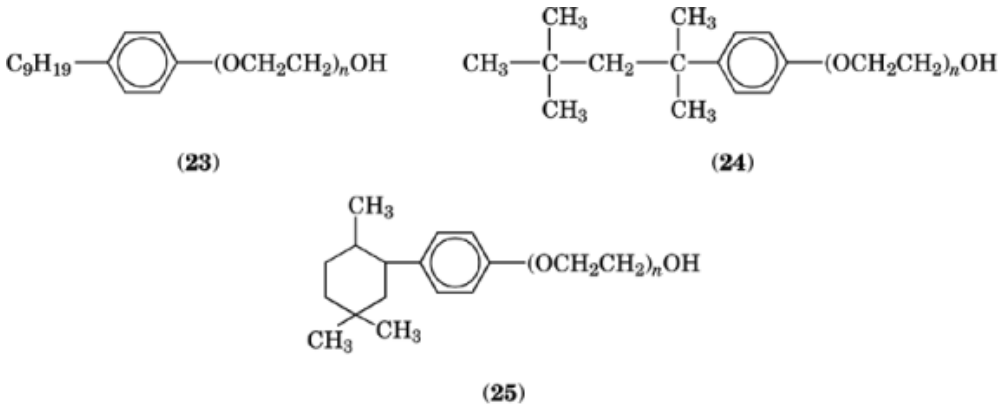


Fig. 4. Progesterone antagonists, ie, antiprogestins. (**20**) RU 486; (**21**) lilopristone [97747-88-1] (ZK 98, 734); (**22**) onapristone [96346-61-1] (ZK 98, 299).

prostoglandin analogue for termination of early pregnancy (73). Other studies suggest the use of antiprogestins for contraception and for treatment of gynecological disorders related to hormone production (74). The discovery of RU486 was followed by laboratory and clinical studies with other antiprogestins, including ZK98,299 (**22**) and ZK98,734 (**21**) (Fig. 4) (76). Many issues, not only scientific, but also political and religious, surround the clinical application of progesterone antagonists (5), and it is difficult to project worldwide availability of RU486 and related products.

Another approach to pregnancy termination has been the utilization of progesterone synthesis inhibitors. These compounds block production of progesterone by the corpus luteum and the early placenta. When administered with a prostaglandin, their use can result in medically induced abortions.



(23) (24) (25)

Fig. 5. Surface active spermicidal agents.

4. Vaginal Contraceptives

Vaginal contraception dates back to 1850 B.C. when written instructions for vaginal contraceptives appeared in Egyptian papyri. Vaginal contraceptives are simple, safe, require little medical supervision, and are among the most widely used forms of birth control available. Where used consistently and properly, reasonable efficacy rates are achieved (76, 77). The disadvantages of this method are that its use is coitally related and its efficacy depends on proper usage.

In 1855, the effects of chemical agents on sperm motility (78) were reported, prompting the first studies in modern-day vaginal contraceptive research. In 1880, the first commercial vaginal contraceptive, a suppository of cocoa butter containing the spermicide quinine sulfate [804-63-7] was produced (79). Subsequently, several vaginal gels and suppositories containing a variety of spermicidal chemicals, for use alone or in combination with a diaphragm, were marketed throughout the world. The International Planned Parenthood Contraceptive Directory for 1981 lists over 100 vaginal contraceptive products available worldwide (80).

The active agents employed in vaginal contraceptive products may be classified as weak acids, organometallic compounds, and surfactants (81). Because of the inferior spermicidal potency of the weak acids, and the growing concerns over the potential toxicity of mercury-containing compounds, surface active agents constitute the most important class of spermicidal compounds in vaginal contraceptive products. A review of the history of vaginal contraceptives that provides description of selected products and reviews the literature on clinical efficacy and various aspects of use and distribution is available (1).

The basis for *in vitro* spermicidal assays, used to evaluate new spermicidal agents, was introduced in 1932 (82). The Sander Cramer test (83) (Ortho Pharmaceutical Corporation), developed in the late 1930s, has been widely used to screen new spermicidal agents and compare spermicidal formulations. In the 1940s, the first surface active spermicidal agents, nonoxynol-9 [26027-38-3] (7-nonylphenoxypolyethoxyethanol, Triton N) (**23**) and octoxynol [9002-93-1] (4-diisobutylphenoxy-polyethoxy ethanol, Triton X-100) (**24**) were developed at Ortho (84). During the next two decades, these two agents became the principal active ingredients utilized in vaginal contraceptives throughout the world. A third surfactant spermicidal agent, menfegol [57821-32-6] (4-menthanylphenylpoly oxyethylene [8,8] ether) (**25**) was discovered and developed in the late 1960s (Fig. 5) (85).

In the last several decades, physical properties of vaginal contraceptive formulations have been improved to deliver spermicide more effectively and enhance consumer compliance. The formulation that delivers the spermicide can affect the efficacy of vaginal contraceptives (86, 87). Formulations currently available include

jellies, creams, suppositories, aerosol foams, and foaming tablets. Each consists of a relative inert base material that serves as a carrier for the chemically active spermicide and blocks to some extent the passage of sperm.

There are indications that a number of new investigational agents being developed by several groups promise greater efficacy, simpler use, longer duration, and fewer adverse effects.

5. Intrauterine Devices

Intrauterine devices are medical products that prevent conception when placed in the uterus. In spite of their ancient origins, modern intrauterine devices (IUDs) have been widely used only in the last 30 years. The two generic subclasses of IUDs are nonmedicated (inert) devices and medicated IUDs, ie, progestin-releasing and copper IUDs.

IUDs are used throughout the world, with an estimated 79 million users in 1989 (88). They are a highly effective contraceptive method with protection rates for some devices reported to be 94–99 per 100 women during one year of exposure to pregnancy. Excellent reviews have been written on the efficacy and safety of this contraceptive method (95).

Complications associated with IUDs include uterine perforation and pelvic inflammatory disease (95). Uterine bleeding and cramping are the most common causes for discontinuation of this method.

The IUD's relationship to pelvic infection, fueled by the high rate of septic abortion and pelvic inflammatory disease (PID) among users of the Dalkon Shield IUD, led to a decline in the popularity of IUDs in the U.S. All IUDs, except the progesterone-releasing Progestasert, were withdrawn from the U.S. market in the mid-1980s. In 1988 the copper T-380A (Paragard) was introduced into the U.S.

5.0.1. Inert Devices

Inert IUDs act by creating an environment hostile to sperm or fertilized ova and by blocking implantation (89, 90). The exact mechanism of action of IUDs is not totally clear, but convincing evidence is mounting to support the idea that IUDs act primarily as contraceptives and not abortifacients (83). Compared with noncontraceptors, IUD users have fewer recoverable sperm in the uteri and tubes after intercourse. In addition, there are fewer recoverable ova in the uteri and tubes at mid-cycle. Those ova found are rarely fertilized. In non-human primates, the rate of recovery of degenerating embryos is not significantly different from that seen among controls, in contrast to what might be expected if the IUD works by preventing embryo implantation. Transient elevations of human chorionic gonadotropin (hCG), which may indicate early pregnancy, were not more frequent among IUD users than among noncontraceptors (91).

After insertion of an IUD, polymorphonuclear leukocytes and macrophages accumulate in the uterine cavity. These cells appear to phagocytize sperm and liberate a blastotoxic toxin (92, 93). Intrauterine devices also may create a hostile environment, perhaps because antibodies are produced that interfere with implantation of the fertilized ovum (93).

There are eight types of inert IUDs used around the world; two are unmedicated and six are copper. Outside of China, the Lippes Loop, made of polyethylene, is the most widely used unmedicated IUD. The other main type of unmedicated IUD, used mostly in China, is a flexible stainless steel ring, ie, the Chinese IUD.

5.1. Medicated Devices

Medicated IUDs consist of an inert base reservoir for a uterus-affecting or spermicidal agent. Medicated IUDs as of this writing are either metal-bearing or progestogen-bearing devices. Copper-bearing IUDs have spermicidal activity and interfere with implantation (85). Two of these, the TCu-200 and the Multiload-250 (MLCu-250), are widely available except in China and the U.S. The inclusion of progestogens in IUDs does not

Table 4. Leading Contraceptive Methods in the United States (Ages 15–44)t[a], %

Method	1988	1989	1990	1991
pill	24	25	26	28
sterilization	23	24	23	24
female sterilization	14	14	14	15
vasectomy	10	10	10	10
condom	12	15	17	16
hysterectomy/menopause	6	5	6	5
withdrawal	4	5	5	5
rhythm	3	3	4	3
diaphragm	4	4	3	3
pregnant	3	3	3	3
trying to conceive	2	2	3	3
sponge	2	2	2	2
vaginal suppository	2	2	2	2
foam	1	1	2	1
IUD	1	1	1	1
douche	1	1	1	1
cream/jelly alone		1	1	1
cervical cap				
Norplant	na	na	na	na
no method	24	22	20	19

[a](Courtesy of Ortho Pharmaceutical, Raritan, N.J.)

appear to improve their efficacy, but may reduce menstrual cramping and bleeding associated with IUD usage (94).

The second generation of copper IUDs have more copper wire, copper sleeves, and/or a silver core to the copper wire, denoted by Ag in the IUD name. Significant second-generation IUDs include the TCu-380A, TCu-220C, Nova T, and Multiload-375 (MLCu-375); these are available worldwide except China.

Progestasert is a hormone-releasing IUD containing 38 mg progesterone, released at a rate of 65 μg per day for one year. It is available only in France and the U.S.

LNG-20, a long-lasting levonorgestrel-releasing IUD, is still under development at the Population Council. Other IUDs in development are the Multiload Mark II (marketed in Finland), the Uterine-Occluding Device, and two new copper devices, the Ombrelle and the Fincoid-350.

6. Sterilization

During the 1970s and 1980s, voluntary surgical sterilization of both men and women increased in popularity. Sterilization is the most used contraceptive method in the world, predominantly because of usage in developing countries, including China, and is the second leading contraceptive method in the U.S. for contraceptors ages 15–44 (Table 4). Although sterilization procedures in the male and female can be reversed under certain circumstances, the procedure is irreversible in most cases. Worldwide, an estimated 42 million couples rely on vasectomy; nearly 140 million rely on female sterilization (88). Vasectomy is a principal family planning method in only six developed countries, ie, the U.S., New Zealand, Australia, UK, Canada, and the Netherlands; and in three developing countries, ie, China, India, and South Korea. The method is hardly used in other countries and few people have heard of vasectomy compared with other methods (96).

In the 1970s questions were raised about certain immunological complications as a consequence of male sterilization or vasectomy. Clinical epidemiological data do not appear to indicate that this actually occurs in clinical practice. No significant long-term side effects of male sterilization have been demonstrated.

Voluntary female sterilization is the world's most widely used family planning method. An estimated 138 million women of reproductive age used the method in 1990, 43 million more than in 1984. Millions more are expected to ask for the method during the 1990s (97).

Because of the increasing worldwide interest and demand for simple, effective, and inexpensive female sterilization, a variety of procedures and methods have been developed. These approaches differ whether they are performed postpartum, postabortum, or in interval situations. The choice of methods also largely depends upon the physician's prior training, knowledge, and experience. Excellent reviews have been written on sterilization (98).

7. Physical Barrier Methods

Various physical barrier devices are available for contraceptive use by men and women. Modern barrier methods such as diaphragms, condoms, and cervical caps were made possible by the discovery of the vulcanization of rubber.

Diaphragms, shallow rubber cups with a flexible metal rim which are placed in the vagina and cover the cervix, are both a mechanical barrier to sperm and a receptable for spermicidal agent. The mechanism of action is believed to be a combination of spermicidal and mechanical barrier actions. To be effective, the diaphragm must fit correctly, be inserted properly, and remain in place sufficiently long for the spermicide to act (99).

The cervical cap birth control device has been available in Europe for many years and in the U.S. since late 1988. It is a small, rubber, dome-shaped device that fits snugly over the cervix. The cervical cap has some advantages over the diaphragm, but has not lived up to widespread expectations that it would become an overwhelmingly popular method of contraception (100).

The male barrier contraceptive device is known as the condom, or rubber, and is widely available in most countries. The condom is a rubber or latex sheath, sometimes packaged with a lubricant and spermicide, which serves as a cover for the penis and a receptacle for semen. The method is very effective if the condom is of good quality, remains on, and is replaced for each subsequent intercourse. It was reported that 6 billion condoms were used in 1990 (101). Usage appears to be increasing as adjunctive use with other methods of contraception for prevention of HIV or other sexually transmitted diseases. By rough estimate, condoms may have been used in more than 13 billion acts of sexual intercourse that risked unwanted pregnancy, HIV, and/or other sexually transmitted diseases (101).

Two new female condoms, ie, vaginal pouches, are in early stages of development. These devices still require thorough preclinical and clinical studies to demonstrate safety and effectiveness before they reach the market (102).

Another type of barrier contraceptive device is the vaginal contraceptive sponge. Clinicians do not appear to be hailing this method. Studies show that the failure rate for the contraceptive sponge in parous women is higher than the failure rate for the diaphragm. A U.S. study of the contraceptive sponge found a first-year failure rate of 13.9% in nulliparous sponge users and a 28.3% first-year failure rate in parous sponge users. Other disadvantages of the method include allergic reactions in a small percentage of women, and a slightly increased risk of nonmenstrual toxic shock syndrome (TSS). When compared with other over-the-counter methods, the sponge can be expensive (103).

8. Natural Methods

Natural methods, ie, natural family planning, are methods based on awareness of the fertile and infertile segments of the menstrual cycle. This awareness can be utilized to avoid pregnancy or to become pregnant.

In order to avoid conception, abstinence from sexual intercourse during the fertile period of the menstrual cycle must be practiced (77, 104). It has been determined that the fertile period in women occurs before menstruation (105, 106), and formulas have been developed to determine the fertile and infertile days of the menstrual cycle. Ovulation has been linked to a cyclic shift in basal body temperature (107), which can be used retrospectively to determine the time of ovulation.

The primary difficulty with periodic abstinence is the month-to-month variation in the time of ovulation. Whereas the ovum can only be fertilized during the first 12 to 24 hours after its release from the ovary, sperm remain viable longer in the female reproductive tract, able to fertilize an ovum for 5–7 days and perhaps longer. Thus, intercourse several days prior to ovulation can result in pregnancy.

Recent findings may lead to better identification of the fertile period. Changes in the quality and quantity of cervical mucus occurring 5–6 days prior to the mid-cycle surge of luteinizing hormone (LH), which initiates ovulation, can be used to predict the fertile period. However, it is sometimes difficult to recognize the changes in mucus. Various devices have been marketed to automate the daily temperature monitoring or to assist in cervical mucus collection (68). However, such devices produce only marginal improvement because of the inherently variable nature of temperature and mucus texture as fertility markers. Colorimetric enzyme immunoassays have been developed for the measurement of LH in urine. Since LH is rapidly excreted, the increase in urine LH levels can be used as a marker to predict impending ovulation. However, because of the life span of sperm, one must be cautious in predicting the usefulness of this method. Research on methods of consistently and accurately predicting ovulation is ongoing (108).

9. Breast-Feeding

In many societies, it is believed that women who are breast-feeding are incapable of becoming pregnant. Suckling leads to a release of prolactin and endorphins that interfere with the hormones necessary for ovulation. This disruption of ovulation lasts for several postpartum months; in some populations it may last as long as a year or more. A study of lactating women in the United States and the Philippines concluded that during the first six months postpartum women who were fully breast-feeding had only between 1 and 5% risk of ovulation; women who were partially breast-feeding had less than a 10% risk (109). However, although breast-feeding does affect ovulation, the duration of lactational amenorrhea and infertility is variable (110), and lactation appears to be unreliable as the sole method of fertility regulation.

10. New Approaches

There continues to be great interest in developing new and improved contraceptives. In addition to utilizing new technology, new contraceptives should be superior to existing products, eg, oral contraceptives, used by millions of women over the last 30 years, are not only safe and effective but even protect women against some cancers. Because oral contraceptives are so effective, they become a very high standard that other products must meet. However, improved methods of contraception are still needed by segments of the world's population.

10.1. Contraceptive Vaccines

Major research efforts involve immunological approaches to fertility control; excellent reviews of this area are available (111–114). The development of contraceptive vaccines is directed towards the immunoneutralization of reproductive process or the interference of fertilization by inducing antibodies against oocytes and spermatozoa. Attempts have been made to develop vaccines against leutinizing hormone releasing hormone (LHRH) (also known as gonadotropin releasing hormone, GnRH), LH, follicle stimulating hormone (FSH), human chorionic gonadotropin (hCG), placenta antigen, the zona pellucida of the ovum, and different sperm antigens.

Research on an hCG vaccine has been conducted over the past 15 years. WHO has conducted a phase I clinical study in Australia, using a vaccine based on a synthetic C-terminal peptide (109–140)of β-hCG conjugated to Diptheria Toxoid (CTP-DT), that showed potentially effective contraceptive levels of antibodies were produced in vaccinated women without any adverse side effects. Phase II clinical studies are under consideration to determine if the immune response, raised to its prototype anti-hCG vaccine, is capable of preventing pregnancy in fertile women volunteers (115). While research on the C-terminal peptide from the β-subunit of hCG has been carried out under the auspices of WHO, research supported by the Population Council and the National Institutes of Health has involved two alternative vaccine candidates (109, 116, 118).

Using recent advanced technologies, unique sperm antigens have been identified and partially characterized. Sperm antigens shown to have high immunocontraceptive potential are human sperm membrane antigen (SP-10) and guinea pig sperm membrane protein (PH-20). SP-10 is a sperm membrane-specific antigen of 24-34 kD, isolated using a monoclonal antibody (MHS-10) that cross-reacts with the entire acrosomal region. It is associated with the outer aspect of the inner acrosomal membrane and the inner aspect of the outer acrosomal membrane of mature human sperm (119). It has been produced recombinantly in an *Escherichia coli* expression system. The recombinant SP-10 fusion protein is under study in the baboon.

PH-20, a guinea pig sperm protein of 64 kD, is present on both the plasma membrane and inner acrosomal membrane of sperm. It is essential for adhesion of sperm to the zona pellucida, the initial step in the fertilization process. Active immunization with PH-20 causes infertility in both male and female guinea pigs for a period ranging from 6 to 15 months (120).

Another interesting sperm specific antigen is lactic dehydrogenase-x (LDH-x or $LDHC_4$), an isoenzyme of LDH confined to male germ cells. LDH-x is one of the best characterized antigens and its amino acid sequence is known. A synthetic peptide based on a portion of the molecule has been shown to reduce fertility in laboratory animals. The nucleotide sequence coding for human LDH-x has been defined and engineered into an expression vector system (121).

The zona pellucida (ZP) is the complex extracellular glycoprotein matrix that surrounds the oocyte. It plays an important role in sperm penetration and fertilization. It is a composite of several antigenic glycoproteins designated ZPI, ZPII, ZPIII, and, in some species, ZPIV. Immunologically, it does not cross-react with any other body tissues, but interspecies cross-reactivity has been observed among several species including primates. Numerous studies indicate the immunocontraceptive potential of zona pellucida (122).

Several other antigens with good immunocontraceptive potential have been identified and investigated in laboratory animals. In most studies, the rate and duration of the immunocontraceptive effect are less than acceptable. A potential problem in immunological approaches to antifertility research is the need for a safe, effective adjuvant and suitable animal models for evaluating the efficacy and safety of methods (111). Newer and more effective adjuvants are required for contraceptive vaccines and vaccines in general.

10.2. Luteinizing Hormone Releasing Hormone

The isolation and synthesis of luteinizing hormone releasing hormone (LHRH) was an important advance in reproductive research (123). LHRH is a peptide hormone produced and secreted by the hypothalamus that

stimulates the secretion of FSH and LH. A decapeptide with an amino acid sequence of pyroGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH_2, it is chemically and functionally similar in both males and females of all mammalian species studied thus far. More than 1000 analogues of LHRH have been synthesized by deletion or substitution of amino acids to introduce agonist or antagonist properties. A large number of reviews have appeared discussing their therapeutic importance (124–126).

These agonists and antagonists may provide useful therapy for several clinical conditions such as prostatic carcinoma, precocious puberty, and endometriosis. Scientists also continue to study LHRH analogues for contraception. Treatment with LHRH analogues blocks ovulation in women and spermatogenesis in men. However, it also results in a loss of estrogen and testosterone and causes other related side effects. Scientists are attempting to assess the use of these agents in combination with replacement estrogen, progesterone, and testosterone to determine if the side effects can be avoided. Several small nonhuman primate and clinical studies have suggested possible utility in this area, but large-scale clinical efficacy studies have not been conducted.

10.3. Inhibin and Activin

Inhibin, a water-soluble, gonadal factor known for over 50 years to inhibit pituitary function, has been isolated and identified (127–130). Inhibin is a glycoprotein hormone that preferentially inhibits the secretion of FSH. It consists of an α-chain subunit, mol wt 14,000, linked by disulfide bonds to a β-chain subunit, mol wt 18,000. There exist two forms of the β-chain subunit, β-A and β-B. The smaller subunit combines with either the β-A or β-B subunit to form inhibin-A or inhibin-B, respectively.

During the isolation of inhibin from follicular fluid, some chromatographic fractions stimulated FSH release from cultured anterior pituitary cells, suggesting the existence of FSH releasing proteins (FRPs). Two FRPs, given the generic term activins, were subsequently isolated (131, 132). One is composed of two disulfide-linked β-A subunits (activin A); the other consists of similarly linked β-A and β-B subunits (activin AB).

Studies confirm that inhibin plays a role in regulating FSH secretion. However, the importance of this role in the human has not yet been determined. If inhibin-regulated FSH secretion is pivotal in follicular recruitment and growth, then it may be possible to block ovulation by means of inhibin antagonists.

Activin has the potential to serve the same therapeutic uses as GnRh analogues. This is because of its ability to suppress steroidogenesis directly at the gonadal level. Although the spectrum of functions of inhibin and activin are not completely understood at present, this peptide family has already demonstrated, by the nature of its differential subunit association, a powerful mechanism for the generation of dimers with opposing biologic actions. These characteristics of the inhibin peptide family warrant further study and evaluation as alternative approaches to fertility control.

10.4. Progesterone Antagonists as Contraceptives

Another area of antifertility research involves progesterone antagonists or inhibitors. This hormone is required to maintain pregnancy, and infertility results from failure of the corpus luteum to produce adequate amounts of progesterone. Inhibitors of progesterone synthesis, such as epostane (133), and inhibitors of progesterone-receptor binding, such as RU486, have been investigated for termination of pregnancy. Studies in the nonhuman primate indicate that progesterone antagonist may have antifertility potential other than as an abortifacient (65).

10.5. Male Fertility Control

There is interest in male fertility control, both from a scientific as well as a sociological viewpoint. Many compounds have been identified as having male antifertility activityin various species, eg, gossypol [303-45-7], ORF 5513, 5-thio-D-glucose [20408-97-3], and 6-chlorodeoxyglucose (134). A principal program centering around the use of androgens has been conducted (135).

Organic molecules thus far identified, such as those listed above, appear either to have irreversible antifertility effects, to be inherently toxic, or to affect libido. It has been demonstrated that sperm count could be depressed in men injected with large doses of androgens. However, questions about the potential utility of androgens as male antifertility agents are still debated.

The ideal male contraceptive would produce azoospermia without compromising libido and sexual potency. While not totally fulfilling the criteria for a perfect male contraceptive, GnRH antagonists hold a greater potential than GnRH agonists. Unlike the agonists, GnRH antagonists inhibit gonadotropin secretion, decrease androgen levels, and induce azoospermia in male primates (136, 137). Similar effects on hormone secretion have been reported in men (130).

In monkeys, testosterone replacement delays, but does not prevent, GnRH antagonist-induced azoospermia (139). In men, the combination of testosterone and a GnRH antagonist results in a more complete gonadotropin and gonadal suppression than either agent alone (140). These results suggest that GnRH antagonists, given in conjunction with androgens to maintain libido and sexual potency, have potential as male contraceptives.

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