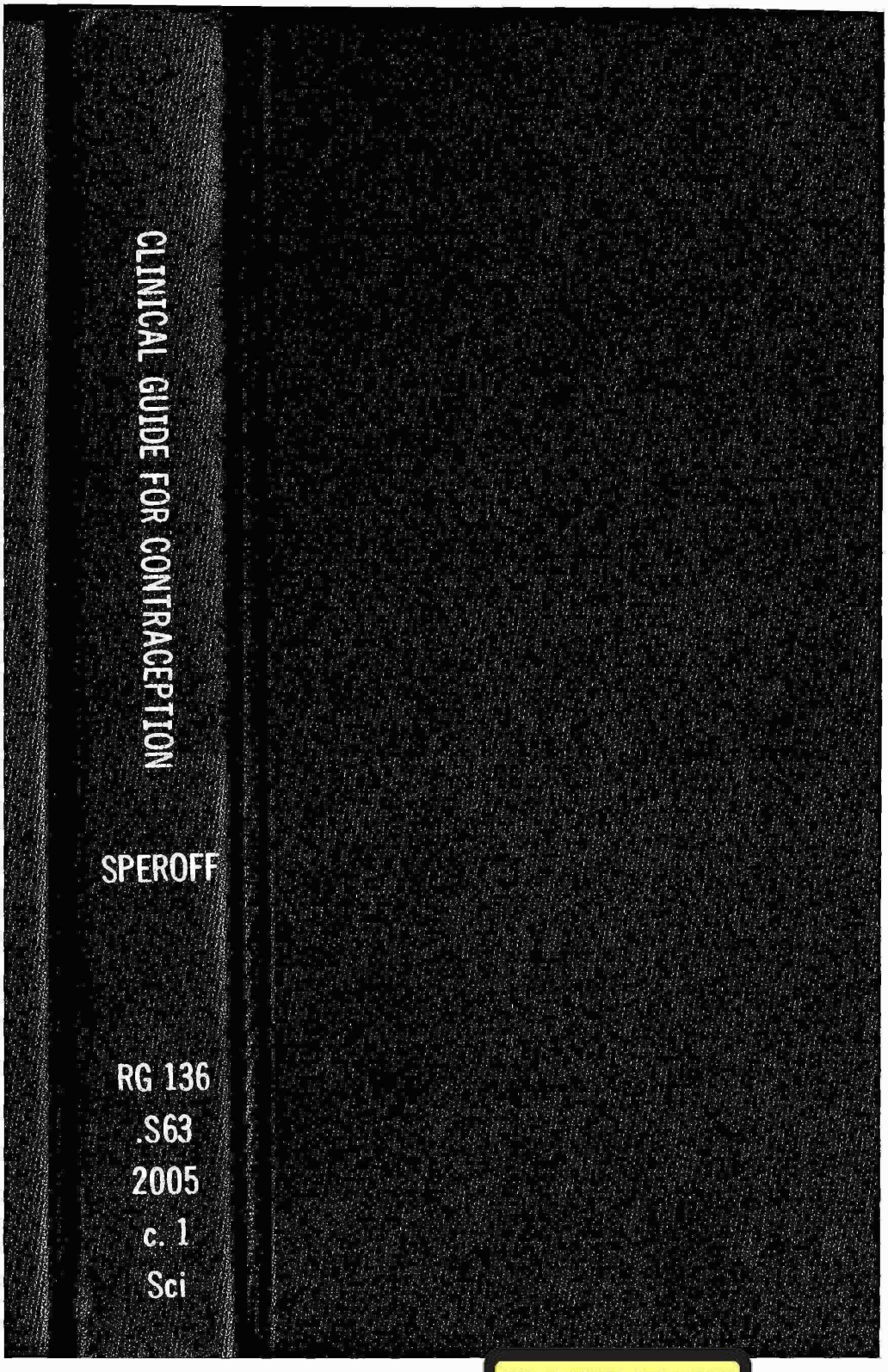
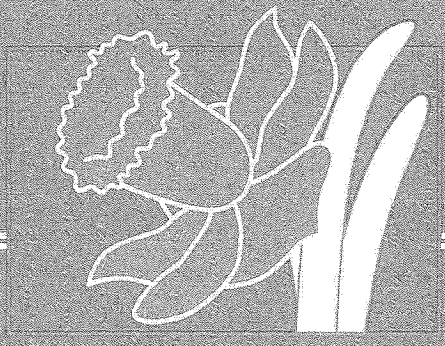


A CLINICAL GUIDE FOR CONTRACEPTION

FOURTH EDITION



LEON SPEROFF

PHILIP D. DARNEY

LIPPINCOTT WILLIAMS & WILKINS

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Dedication

This book is dedicated to our children, one son, seven daughters, and three grandchildren. As Sherlock Holmes said: "You know my methods, use them!"

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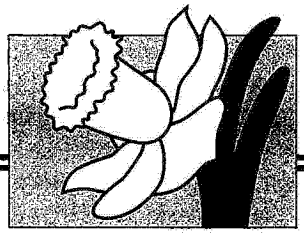


2 Oral Contraception

Contraception is commonly viewed as a modern event, a recent development in human history. On the contrary, efforts to limit reproduction predate our ability to write about it. It is only contraception with synthetic sex steroids that is recent.

History[1-4]

It wasn't until the early 1900s that inhibition of ovulation was observed to be linked to pregnancy and the corpus luteum. Ludwig Haberlandt, professor of physiology at the University of Innsbruck, Austria, was the first to demonstrate that ovarian extracts given orally could prevent fertility (in mice). In the 1920s, Haberlandt and a Viennese gynecologist, Otfried Otto Fellner, were administering steroid extracts to a variety of animals and reporting the inhibition of fertility. By 1931, Haberlandt was proposing the administration of hormones for birth control. An extract was produced, named Infecundin, ready to be used, but Haberlandt's early death in 1932, at age 47, brought an end to this effort. Fellner disappeared after the annexation of Austria to Hitler's Germany.

The concept was annunciated by Haberlandt, but steroid chemistry wasn't ready. The extraction and isolation of a few milligrams of the sex steroids required starting points measured in gallons of urine or thousands of pounds of organs. Edward Doisy processed 80,000 sow ovaries to produce 12 mg of estradiol.

Russell Marker

The supply problem was solved by an eccentric chemist, Russell E. Marker, who completed his thesis, but not his course work, for his Ph.D. Marker, born in 1902 near Hagerstown, Maryland, received his bachelor's degree in organic chemistry and his master's degree in colloidal chemistry from the University of Maryland. After leaving the University of Maryland, Marker worked with the Ethyl Gasoline Corporation and in 1926 developed the process of octane rating, based on the discovery that knocking in gasoline was due to hydrocarbons with an uneven number of carbons.

From 1927 to 1935, Marker worked at the Rockefeller Institute, publishing a total of 32 papers on configuration and optical rotation as a method of identifying compounds. He became interested in solving the problem of producing abundant and cheap amounts of progesterone, but he was told to continue with his work in optical technology. In 1935, he moved to Pennsylvania State University at a reduced salary but with the freedom to pursue any field of research. At that time, the ovaries from 2,500 pregnant pigs were required to produce 1 mg of progesterone. In 1939, Marker devised the method (called the Marker degradation) to convert a sapogenin molecule into a progestin. Marker became convinced that the solution to the problem of obtaining large quantities of steroid hormones was to find plants (in the family that includes the lily, the agave, and the yam) that contained sufficient amounts of diosgenin, a plant steroid (a sapogenin) that could be used as a starting point for steroid hormone production. This conviction was strengthened with his discovery that a species of *Trillium,* known locally as Beth's root, was collected in North Carolina and used in the preparation of Lydia Pinkham's Compound, popular at the time to relieve menstrual troubles. A principal ingredient in Beth's root was diosgenin, but the rhizome was too small to provide sufficient amounts for commercial production. Marker's search for an appropriate plant took him to California, Arizona, and Texas.

On a visit to Texas A & M University, Marker found a picture of a large dioscorea *(Dioscorea mexicana)* in a book that he just happened to pick up and browse through while spending the night at the home of a retired botanist. After returning to Pennsylvania, he decided to go to Veracruz, Mexico (it took 3 days by train), to search for this dioscorea. He made several attempts in 1941 and early 1942 but was frustrated first by the lack of a plant-collecting permit from the Mexician government and then by his failure to find the plant. He remembered that the book with the picture reported that this dioscorea was known locally as "cabeza de negro," black tubers that grew near Orizaba and Cordoba. Marker took a bus to Cordoba, and near Orizaba, an Indian who owned a small store brought him two plants. Each tuber was 9–12 inches high and consisted of white material like a turnip, used by local Mexicans as a poison to catch fish.

Marker managed to get one bag of tubers back to Pennsylvania State University and isolated diosgenin. Unable to obtain support from the pharmaceutical industry, Marker used his life savings, and in 1942, he returned to Veracruz, collected the roots of the Mexican yam, and prepared a syrup from the roots. Marker paid Mexican medical students to collect the yams. The students were arrested when farmers reported that their yams were being stolen, but not before Marker had enough to prepare a syrup. Back in Pennsylvania with his 5-gallon cans of syrup, Marker worked out the degradation of diosgenin to progesterone. One 5-gallon can yielded 3 kg of progesterone. United States pharmaceutical companies still refused to back Marker, and even the University refused, despite Marker's urging, to patent the process.

In 1943, Marker resigned from Pennsylvania State University and went to Mexico where he collected the roots of *Dioscorea mexicana,* 10 tons worth! Looking through the yellow pages in a Mexico City telephone directory, Marker found a company called Laboratorios Hormona, owned by a lawyer, Emeric Somlo, and a physician, Frederick Lehman. Marker arranged a meeting, and the three agreed to form a Mexican company to produce hormones. In an old pottery shed in Mexico City (the laboratories of Laboratorios Hormona), in 2 months he prepared several pounds of progesterone (worth $300,000) with the help of four young women who had little education and spoke no English (Marker did not speak Spanish). The two partners and Marker formed a company in 1944 that they called Syntex (from synthesis and Mexico). In 1944, Marker produced over 30 kg of progesterone. The price of progesterone fell from $200 to $50 a gram.

During this time, Marker received expenses, but he was not given his share of the profits or the 40% share of stock due to him. Failing to reach a settlement, Marker left Syntex after only 1 year and started a new company in Texcoco, called Botanica-Mex. He changed to *Dioscorea barbasco,* which gave a greater yield of diosgenin, and the price of progesterone dropped to $10 a gram, and later to $5. This company was allegedly harassed (legally and physically) by Syntex, and in 1946 was sold, eventually coming under the ownership of Organon of Holland, which still uses it.

In 1949, Marker retired to Pennsylvania to devote the rest of his life to making replicas of antique works in silver, a successful business that allowed him, in the 1980s, to endow scientific lectureships at both Pennsylvania State University and the University of Maryland. However, he took his know-how with him. Fortunately for Syntex, he had published a scientific description of his process, and there still was no patent on his discoveries. Syntex recruited George Rosenkranz, a Hungarian immigrant living in Cuba, to reinstitute the commercial manufacture of progesterone (and testosterone) from Mexican yams, a task that took him (with the help of the women left behind by Marker) 2 years.

In 1970, the Mexican government honored Marker and awarded him the Order of the Aztec Eagle; he declined. In 1984, Pennsylvania State University established the annual Marker Lectures in Science and, in 1987, the Russell and Mildred Marker Professorship of Natural Product Chemistry. In 1987, Marker was granted an honorary doctorate in science from the University of Maryland, the degree he failed to receive in 1926. At the age of 92, Russell Earl Marker died in Wernersville, Pennsylvania, in 1995, from complications after a broken hip.

Carl Djerassi[5]

The Djerassi family lived in Bulgaria for hundreds of years after escaping Spain during the Inquisition. Carl Djerassi, the son of a Bulgarian physician, was born in Vienna (as was his physician mother). Djerassi, at the age of 16, and his mother emigrated to the United States in 1939. A Jewish refugee aid organization placed Djerassi with a family in Newark, New Jersey. With a scholarship to Tarkio College in Tarkio, Missouri, he was exposed to middle America, where he earned his way giving talks to church groups about Bulgaria and Europe. His education was further supported by another scholarship from Kenyon College in Ohio, where he pursued chemistry. After a year working for CIBA, Djerassi received his graduate degree from the University of Wisconsin. Returning to CIBA and being somewhat unhappy, he responded to an invitation to visit Syntex. Rosenkranz proposed that Djerassi head a research group to concentrate on the synthesis of cortisone.

In 1949, it was discovered that cortisone relieved arthritis, and the race was on to develop an easy and cheap method to synthesize cortisone. Carl Djerassi, at age 26, joined Syntex to work on this synthesis using the Mexican yam plant steroid diosgenin as the starting point. This was quickly achieved (in 1951), but soon after, an even better method of cortisone production using microbiologic fermentation was discovered at Upjohn. This latter method used progesterone as the starting point, and, therefore, Syntex found itself as the key supplier to other companies for this important process, at the rate of 10 tons of progesterone per year and a price of 48 cents per gram.

Djerassi and other Syntex chemists then turned their attention to the sex steroids. They discovered that the removal of the 19-carbon from yam-derived progesterone increased the progestational activity of the molecule. Ethisterone had been available for a dozen years, and the Syntex chemists reasoned that removal of the 19-carbon would increase the progestational potency of this orally active compound. In 1951, norethindrone was synthesized; the patent for this drug is the first patent for a drug listed in the National Inventor's Hall of Fame in Akron, Ohio. A closely related

compound, norethynodrel, was actually the first orally active progestational agent to receive a patent, assigned to Frank Colton, a chemist at G.D. Searle & Company.

Djerassi eventually left Syntex to become a professor at Stanford University, and is now a playwright and novelist, living in San Francisco.

Gregory Pincus

Gregory Goodwin (Goody) Pincus was born in 1903 in New Jersey, the son of Russian Jewish immigrants who lived on a farm colony founded by a German-Jewish philanthropic organization. Pincus was the oldest of 6 children and grew up in a home of intellectual curiosity and energy, but even his family regarded him as a genius.

Pincus graduated from Cornell and went to Harvard to study genetics, joining Hudson Hoagland and B. F. Skinner as graduate students of W. J. Crozier in physiology, receiving degrees in 1927. Crozier's hero was Jacques Loeb who discovered artificial parthenogenesis working with sea urchin eggs. Most importantly, Loeb was a strong believer in applying science to improve human life. Thus, Crozier, influenced by Loeb, taught Pincus, Hoagland, and Skinner (respectively, in reproductive biology, neurophysiology, and psychology) to apply science to human problems. This was to be the cornerstone of Pincus's own philosophy.

Hoagland, after a short stay at Harvard, spent a year in Cambridge, England, and then moved to Clark University in Worcester, Massachusetts, to be the chair of biology at the age of 31. Pincus went to England and Germany, and returned to Harvard as an assistant professor of physiology.

Pincus performed pioneering studies of meiotic maturation in mammalian oocytes, in both rabbit and human oocytes. In 1934, Pincus reported the achievement of in vitro fertilization of rabbit eggs, earning him a headline in the *New York Times* that alluded to Haldane and Huxley. An article in *Colliers* depicted him as an evil scientist. By 1936, Harvard had cited Pincus's work as one of the university's outstanding scientific achievements of all time, but Harvard denied him tenure in 1937.

At Clark University, Hudson Hoagland was in constant conflict with the president of the university, Wallace W. Atwood, the senior author of a widely used textbook on geography. In 1931, the Department of Biology consisted of one faculty member and his graduate student, and their chair, Hudson Hoagland. Hoagland, upset and angry over Harvard's refusal to grant tenure to his friend (suspecting that this was because of anti-Semitism), invited Pincus to join him. Hoagland secured funds for Pincus from philanthropists

in New York City, enough for a laboratory and an assistant. This success impressed the two men, especially Hoagland, planting the idea that it would be possible to support research with private money.

Min-Chueh Chang received his Ph.D. from Harvard on an infamous day, December 7, 1941, and thus he was forced to remain in this country. He was drawn to Pincus because of Pincus's book, *The Eggs of Mammals*, published in 1936, a book that had a major impact on biologists at that time. The successful recruitment of M-C Chang by Hoagland and Pincus was to pay great dividends.

Soon Hoagland had put together a group of outstanding scientists, but because of his on-going antagonism with President Atwood, the group was denied faculty status. Working in a converted barn, they were totally supported by private funds. By 1943, 12 of Clark's 60 faculty were in the Department of Biology.

Frustrated by the politics of academia, Hoagland and Pincus (who both enjoyed stepping outside of convention) had a vision of a private research center devoted to their philosophy of applied science. Indeed, the establishment of the Worcester Foundation for Experimental Biology, in 1944, can be attributed directly to Hoagland and Pincus, their friendship for each other, and their confidence, enthusiasm, ambition, and drive. It was their spirit that turned many members of Worcester society into financial supporters of biologic science. Hoagland and Pincus accomplished what they set out to do. They created and sustained a vibrant, productive scientific institution in which it was a pleasure to work.

Although named the Worcester Foundation for Experimental Biology, the Foundation was located in the summer of 1945 across Lake Quinsigamond in a house on an estate in Shrewsbury. The board of trustees was chaired by Harlow Shapley, a distinguished astronomer, vice-chaired by Rabbi Levi Olan, and included three Nobel laureates and a group of Worcester businessmen.

From 1945 to the death of Pincus in 1967, the staff grew from 12 to 350 (scientists and support people), 36 of whom were independently funded and 45 were postdoctoral fellows. The annual budget grew from $100,000 to $4.5 million. One hundred acres of adjoining land were acquired, and the campus grew to 11 buildings. In its first 25 years, approximately 3,000 scientific papers were published.

But in those early years, Pincus was the animal keeper, Mrs. Hoagland the bookkeeper, M-C. Chang was the night watchman, and Hoagland

mowed the lawn. During the years of World War II, Pincus and Hoagland combined their interests in hormones and neurophysiology to focus on stress and fatigue in industry and the military.

The initial discoveries that led to an oral contraceptive can be attributed to M-C. Chang (also the first to describe the capacitation process of sperm). In 1951, he confirmed the work of Makepeace (in 1937) demonstrating that progesterone could inhibit ovulation in rabbits. When norethindrone and norethynodrel became available, Chang found them to be virtually 100% effective in inhibiting ovulation when administered orally to rabbits.

Katherine Dexter McCormick (1875–1967) was a very rich woman; in 1904, she married Stanley McCormick, the son of Cyrus McCormick, the founder of International Harvester. She was also intelligent, the second woman to graduate from the Massachusetts Institute of Technology, socially conscious, and a generous contributor to family planning efforts. McCormick's husband suffered from schizophrenia, and she established the Neuroendocrine Research Foundation at Harvard to study schizophrenia. This brought her together with Hoagland, who told her of the work being done by Chang and Pincus.

Pincus attributed his interest in contraception to his growing appreciation for the world's population problem and to a 1951 visit with Margaret Sanger, at that time president of the Planned Parenthood Federation of America. At that visit, Sanger expressed hope that a method of contraception could be derived from the laboratory work being done by Pincus and Chang.

In 1952, Margaret Sanger brought Pincus and Katherine McCormick together. During this meeting, Pincus formulated his thoughts derived from his mammalian research. He envisioned a progestational agent in pill form as a contraceptive, acting like progesterone in pregnancy. Sanger and McCormick provided a research grant for further animal research. By the time of her death, McCormick had contributed more than $2 million to the Worcester Foundation, and left another $1 million in her will. In his book, *The Control of Fertility*, published in 1965, Pincus wrote: "This book is dedicated to Mrs. Stanley McCormick because of her steadfast faith in scientific inquiry and her unswerving encouragement of human dignity."[6]

It was Pincus who made the decision to involve a physician because he knew human experiments would be necessary. John Rock, chief of gynecology and obstetrics at Harvard, met Pincus at a scientific conference and discovered their mutual interest in reproductive physiology. Rock and his colleagues pursued Pincus's work. Using oocytes from oophorectomies,

they reported in vitro fertilization in 1944, the first demonstration of fertilization of human oocytes in vitro. Rock was interested in the work with progestational agents, not for contraception, however, but because he hoped the female sex steroids could be used to overcome infertility.

Sanger and McCormick needed some convincing that Rock's Catholicism would not be a handicap, but they were eventually won over because of his stature. Rock was a physician who literally transformed his personal values in response to his recognition of the problems secondary to uncontrolled reproduction. With the help of Luigi Mastroianni, the first administration of synthetic progestins to women was to Rock's patients in 1954. Of the first 50 patients to receive 10–40 mg of synthetic progestin (a dose extrapolated from the animal data) for 20 days each month, all failed to ovulate during treatment (causing Pincus to begin referring to the medication as "the pill"), and 7 of the 50 became pregnant after discontinuing the medication (pleasing Rock, who all along was motivated to treat infertility).

Pincus and Chang decided to announce their findings at the International Planned Parenthood meeting in Tokyo, in the fall of 1955. Rock refused to join in this effort, believing that Pincus and Chang were moving too fast. Despite this disagreement (which apparently was spirited and strong), it was done, and the Tokyo presentation generated worldwide publicity.

In 1956, with Celso-Ramon Garcia and Edris Rice-Wray, working in Puerto Rico, the first human trial was performed. The initial progestin products were contaminated with about 1% mestranol. In the amounts being used, this added up to 50–500 μg of mestranol, a sufficient amount of estrogen to inhibit ovulation by itself. When efforts to provide a more pure progestin lowered the estrogen content and yielded breakthrough bleeding, it was decided to retain the estrogen for cycle control, thus establishing the principle of the combined estrogen-progestin oral contraceptive. Early clinical trials were conducted by J. W. Goldzieher in San Antonio and E. T. Tyler in Los Angeles.

Pincus, a longtime consultant to Searle, picked the Searle compound for extended use, and with great effort, convinced Searle that the commercial potential of an oral contraceptive warranted the risk of possible negative public reaction. Pincus also convinced Rock, and together they pushed the U.S. Food and Drug Administration for acceptance of oral contraception. In 1957, Enovid was approved for the treatment of miscarriages and menstrual disorders and, in 1960, for contraception. Neither Pincus nor the Worcester Foundation got rich on the pill; alas, there was no royalty agreement.

The pill did bring Pincus fame and travel. There is no doubt that he was very much aware of the accomplishment and its implications. As he trav-

eled and lectured in 1957, he said: "How a few precious facts obscurely come to in the laboratory may resonate into the lives of men everywhere, bring order to disorder, hope to the hopeless, life to the dying. That this is the magic and mystery of our time is sometimes grasped and often missed, but to expound it is inevitable."[6]

Pincus was the perfect person to bring oral contraception into the public world, at a time when contraception was a private, suppressed subject. Difficult projects require people like Pincus. A scientific entrepreneur, he could plow through distractions. He could be hard and aggressive with his staff. He could remain focused. He hated to lose, even in meaningless games with his children. Yet he combined a gracious, charming manner with his competitive hardness. He was filled with the kind of self-confidence that permits an individual to forge ahead, to translate vision into reality. Pincus died in 1967 (as did Katherine McCormick at the age of 92) of aplastic anemia that some have argued was caused by his long-term exposure to solvents and chemicals. Rock died in 1984 at the age of 94. Chang died in 1991 at the age of 82 and was buried in Shrewsbury, near his laboratory and close to the grave of Pincus.

Pincus wrote his book, *The Control of Fertility,* in 1964–65, only because "a break came in the apparent dam to publication on reproductive physiology and particularly its subdivisions concerned with reproductive behavior, conception, and contraception."[6]

> "We have conferred and lectured in many countries of the world, seen at first hand the research needs and possibilities in almost every European, Asiatic, Central, and South American country. We have faced the hard fact of overpopulation in country after country, learned of the bleak demographic future, assessed the prospects for the practice of efficient fertility control. This has been a saddening and a heartening experience; saddening because of the sight of continuing poverty and misery, heartening because of the dedicated colleagues and workers seeking to overcome the handicap of excess fertility and to promote healthy reproductive function. Among these we have made many friends, found devoted students."[6]

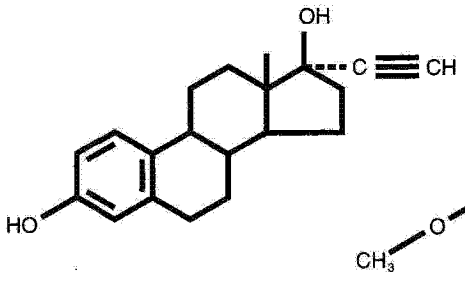
Syntex, a wholesale drug supplier, was without marketing experience or organization. By the time Syntex had secured arrangements with Ortho for a sales outlet, Searle marketed Enovid in 1960 (150 μg mestranol and 9.85 mg norethynodrel). Ortho-Novum, using norethindrone from Syntex, appeared in 1962. Wyeth Laboratories introduced norgestrel in 1968, the same year in which the first reliable prospective studies were initiated. It

was not until the late 1970s that a dose-response relationship between problems and the amount of steroids in the pill was appreciated. As a result, health care providers and patients, over the years, have been confronted by a bewildering array of different products and formulations. The solution to this clinical dilemma is relatively straightforward, the theme of this chapter: use the lowest doses that provide effective contraception.

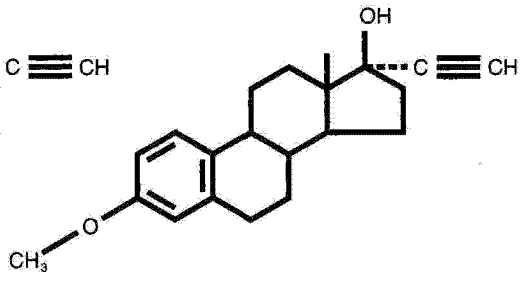
Pharmacology of Steroid Contraception

The Estrogen Component of Combination Oral Contraceptives

Estradiol is the most potent natural estrogen and is the major estrogen secreted by the ovaries. The major obstacle to the use of sex steroids for contraception was inactivity of the compounds when given orally. A major breakthrough occurred in 1938 when it was discovered that the addition of an ethinyl group at the 17 position made estradiol orally active. Ethinyl estradiol is a very potent oral estrogen and is one of the two forms of estrogen used in every oral contraceptive. The other estrogen is the 3-methyl ether of ethinyl estradiol, mestranol.



Ethinyl estradiol



Mestranol

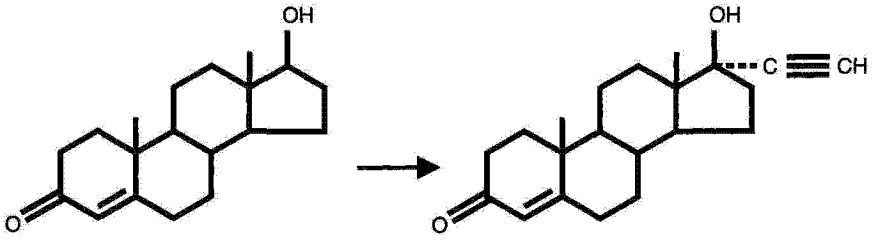
Mestranol and ethinyl estradiol are different from natural estradiol and must be regarded as pharmacologic drugs. Animal studies have suggested that mestranol is weaker than ethinyl estradiol, because mestranol must first be converted to ethinyl estradiol in the body. Indeed, mestranol does not bind to the cellular estrogen receptor. Therefore, unconjugated ethinyl estradiol is the active estrogen in the blood for both mestranol and ethinyl estradiol. In the human body, differences in potency between ethinyl estradiol and mestranol do not appear to be significant, certainly not as great as indicated by assays in rodents. This is now a minor point because all of the low-dose oral contraceptives contain ethinyl estradiol.

The metabolism of ethinyl estradiol (particularly as reflected in blood levels) varies significantly from individual to individual and from one population to another.[7] There is even a range of variability at different sampling times within the same individual. Therefore, it is not surprising that the same dose can cause side effects in one individual and not in another.

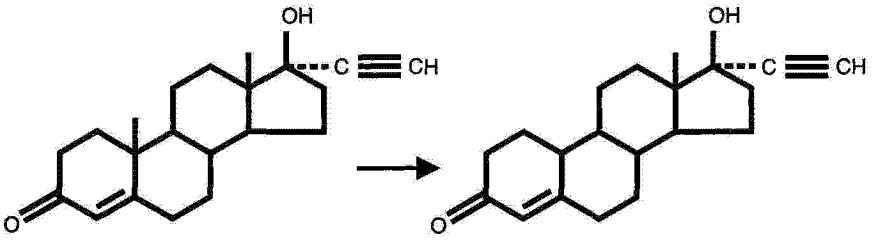
The estrogen content (dosage) of the pill is of major clinical importance. Thrombosis is one of the most serious side effects of the pill, playing a key role in the increased risk of death (in the past with high doses) from a variety of circulatory problems. This side effect is related to estrogen, and it is dose related; therefore, the dose of estrogen is a critical issue in selecting an oral contraceptive.

The Progestin Component of Combination Oral Contraceptives

The discovery of ethinyl substitution and oral potency led (at the end of the 1930s) to the preparation of ethisterone, an orally active derivative of testosterone. In 1951, it was demonstrated that removal of the 19-carbon from ethisterone to form norethindrone did not destroy the oral activity, and most importantly, it changed the major hormonal effect from that of an androgen to that of a progestational agent. Accordingly, the progestational derivatives of testosterone were designated as 19-nortestosterones (denoting the missing 19-carbon). The androgenic properties of these compounds, however, were not totally eliminated, and minimal anabolic and androgenic potential remains within the structure.



Testosterone Ethisterone



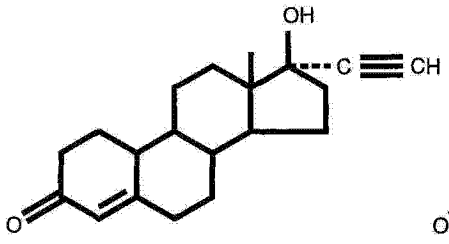
Ethisterone Norethindrone

The "impurity" of 19-nortestosterone, i.e., androgenic as well as progestational effects, was further complicated in the past by a belief that they were metabolized within the body to estrogenic compounds. This question was restudied, and it was argued that the previous evidence for metabolism to estrogenic compounds was due to an artifact in the laboratory analysis. More recent studies indicate that norethindrone can be converted to ethinyl estradiol; however, the rate of this conversion is so low that insignificant amounts of ethinyl estradiol can be found in the circulation or urine following the administration of the commonly used doses of norethindrone.[8] Any estrogenic activity, therefore, would have to be due to a direct effect. In animal and human studies, however, only norethindrone, norethynodrel, and ethynodiol diacetate have estrogen activity, and it is very slight due to weak binding to the estrogen receptor.[9] Clinically, androgenic and estrogenic activities of the progestin component, therefore, are insignificant due to the low dosage in the current oral contraceptives. As with the estrogen component, serious side effects have been related to the high doses of progestins used in old formulations, not the particular progestin, and routine use of oral contraceptives should now be limited to the low-dose products.

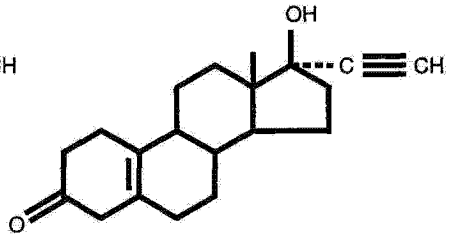
The norethindrone family contains the following 19-nortestosterone progestins: norethindrone, norethynodrel, norethindrone acetate, ethynodiol diacetate, lynestrenol, norgestrel, norgestimate, desogestrel, and gestodene.

Most of the progestins closely related to norethindrone are converted to the parent compound. Thus the activity of norethynodrel, norethindrone acetate, ethynodiol diacetate, and lynestrenol is due to rapid conversion to norethindrone.

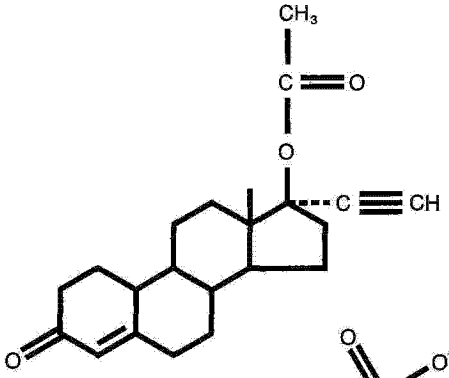
Norgestrel is a racemic equal mixture of the dextrorotatory enantiomer and the levorotatory enantiomer. These enantiomers are mirror images of each other and rotate the plane of polarized light in opposite directions. The dextrorotatory form is known as d-norgestrel, and the levorotatory form is l-norgestrel (known as levonorgestrel). Levonorgestrel is the active isomer of norgestrel.



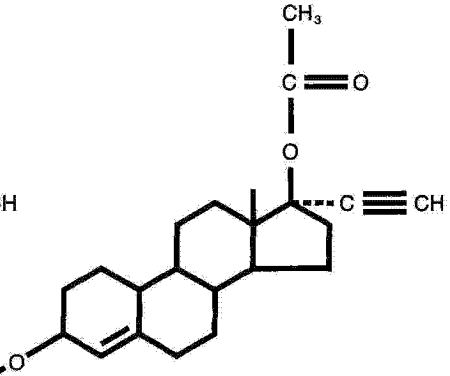
Norethindrone



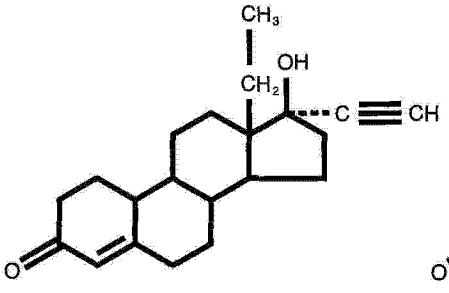
Norethynodrel



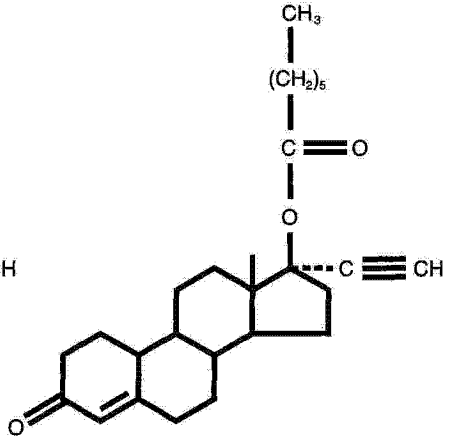
Norethindrone acetate



Ethynodiol diacetate



Levonorgestrel



Norethindrone enanthate

Desogestrel undergoes two metabolic steps before the progestational activity is expressed in its active metabolite, 3-keto-desogestrel, now known as etonogestrel. This metabolite differs from levonorgestrel only by a methylene group in the 11 position. Gestodene differs from levonorgestrel by the presence of a double bond between carbons 15 and 16; thus, it is Δ-15 gestodene. It is metabolized into many derivatives with progestational activity, but not levonorgestrel. Several metabolites have the potential to contribute to the activity of norgestimate. Although norgestimate is a "new" progestin, epidemiologists included it in the oral contraceptive second-generation family because its activity was believed to be largely due to levonorgestrel and levonorgestrel metabolites.[10, 11] Almost all of the biologic effects are now attributed to the 17-deacetylated metabolite, now known as norelgestromin; the levonorgestrel metabolite is tightly bound to sex hormone-binding globulin (unlike norelgestromin) severely limiting its biologic activity.[12]

DEFINITIONS USED IN EPIDEMIOLOGIC STUDIES

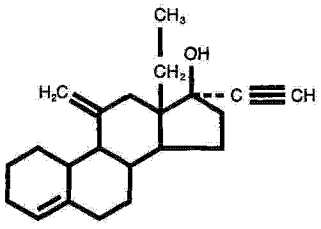
Low-Dose Oral Contraceptives
Products containing less than 50 μg ethinyl estradiol

First-Generation Oral Contraceptives
Products containing 50 μg or more of ethinyl estradiol

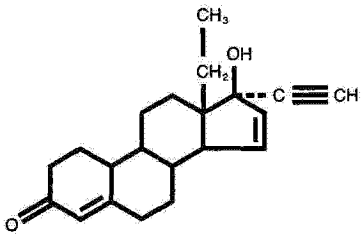
Second-Generation Oral Contraceptives
Products containing levonorgestrel, norgestimate, and other members of the norethindrone family and 20, 30, or 35 μg ethinyl estradiol

Third-Generation Oral Contraceptives
Products containing desogestrel or gestodene with 20, 25, or 30 μg ethinyl estradiol

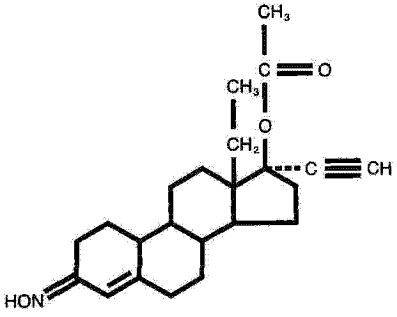
A second group of progestins became available for use when it was discovered that acetylation of the 17-hydroxy group of 17-hydroxyprogesterone produced an orally active but weak progestin. An addition at the 6 position is necessary to give sufficient progestational strength for human use, probably by inhibiting metabolism. Derivatives of progesterone with substituents at the 17 and 6 positions include the widely used medroxyprogesterone acetate.



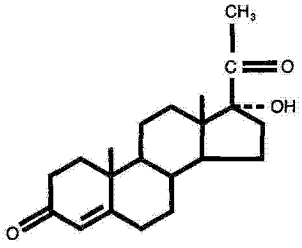
Desogestrel



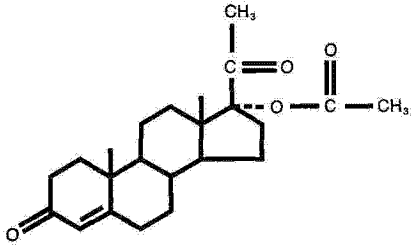
Gestodene



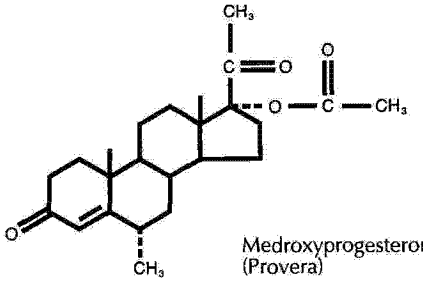
Norgestimate



17α-Hydroxyprogesterone

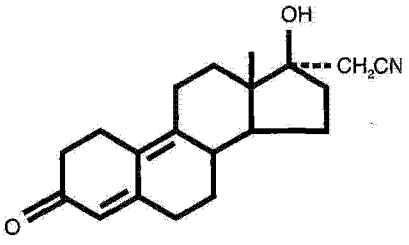


17-Acetoxy progesterone

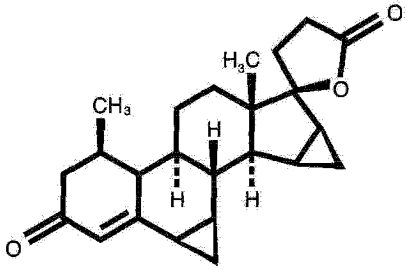


Medroxyprogesterone acetate
(Provera)

Dienogest is a 19-nortestosterone that has a cyanomethyl group instead of an ethinyl group in the 17 position, combining the properties of both the 19-nortestosterone family and the derivatives of progesterone.[13] It exerts antiandrogenic activity and is used in a 2-mg dose combined with ethinyl estradiol as an oral contraceptive.



Dienogest



Drospirenone

New Progestins

Probably the greatest influence on the effort that yielded the new progestins was the belief throughout the 1980s that androgenic metabolic effects were important, especially in terms of cardiovascular disease. Cardiovascular side effects are now known to be due to a dose-related stimulation of thrombosis by estrogen. In the search to find compounds that minimize androgenic effects, however, the pharmaceutical companies succeeded.

The new progestins include desogestrel, gestodene, and norgestimate, and even newer progestins are in development.[14] In regard to cycle control (breakthrough bleeding and amenorrhea), the new formulations are

comparable with previous low-dose products. All progestins derived from 19-nortestosterone have the potential to decrease glucose tolerance and increase insulin resistance. The impact on carbohydrate metabolism of the previous low-dose formulations was very minimal, and the impact of the new progestins is negligible. Most changes are not statistically significant, and when they are, they are so subtle as to be of no clinical significance. The decreased androgenicity of the progestins in the new products is reflected in increased sex hormone–binding globulin and decreased free testosterone concentrations to a greater degree than the older oral contraceptives. This difference could be of greater clinical value in the treatment of acne and hirsutism, but comparative clinical studies have indicated similar effects for all oral contraceptives.[15]

The new progestins, because of their reduced androgenicity, predictably do not adversely affect the cholesterol-lipoprotein profile. Indeed, the estrogen-progestin balance of combined oral contraceptives containing one of the new progestins even promotes favorable lipid changes. Thus, the new formulations have the potential to offer protection against cardiovascular disease, an important consideration as we enter an era of women using oral contraceptives for longer durations and later in life. But one must be cautious regarding the clinical significance of subtle changes, and it will be difficult to accumulate data with these rare events.

Drospirenone is a progestin that is an analogue of spironolactone. Its biochemical profile is very similar to progesterone, including a high affinity for the mineralocorticoid receptor that produces an antimineralocorticoid effect.[16, 17] Contraceptive efficacy equal to that of other formulations is achieved in the combination of 3.0 mg drospirenone and 30 μg ethinyl estradiol (Yasmin). Because drospirenone is spironolactone-like with antiandrogenic and antimineralocorticoid activity, caution is recommended in regard to serum potassium levels, avoiding its use in women with abnormal renal, adrenal, or hepatic function. It has been suggested that the oral contraceptive that contains drospirenone is effective for treating premenstrual syndrome/premenstrual dysphoric disorder (PMDD).

In an open-label, 1-year study of 326 women, Yasmin was associated with a significant reduction in scores assessing negative affect, water retention, and increased appetite during the premenstrual and menstrual phases of their cycles.[18] A similar effect was observed in new users and in those who switched from oral contraceptives. We have learned over the last decade that treatments for premenstrual syndrome must be studied in comparison with a placebo because of the powerful placebo response associated with this disorder. In the only double-blind, placebo-controlled randomized

trial, 82 women with established diagnoses of PMDD were assessed using the Calendar of Premenstrual Experiences scale.[19] A statistically significant reduction associated with the oral contraceptive treatment was achieved in only one category, that measuring acne, appetite, and food cravings. The authors interpreted their results as indicating a general and consistent trend in all symptom groups, suggesting a beneficial effect of the oral contraceptive for the treatment of PMDD. However, a close look at the results easily reveals very wide standard deviations around each point, and by no means, can this study be considered conclusive or definitive.

In a multicenter 2-year study in Europe of 900 women, Yasmin was compared to Marvelon (the same dose of ethinyl estradiol and 150 μg desogestrel).[20] Marvelon was associated with a small increase in body weight after the fifth cycle; the average body weight associated with Yasmin remained throughout the 2 years below the baseline level at the beginning of the study but increased to a level above the baseline at the end of the study. The early weight loss amounted to only 1% of body weight and may reflect diuretic action. This study also showed a small reduction in premenstrual symptoms with Yasmin. There is evidence, therefore, to indicate favorable effects that could be expected to have a beneficial impact on PMDD. However, the strength of this activity in the only double-blind, placebo-controlled trial was minimal. Whether these effects are sufficient to have a meaningful clinical impact requires further study with appropriate numbers and placebo controls.

New Formulations

The multiphasic preparation alters the dosage of both the estrogen and progestin components periodically throughout the pill-taking schedule. The aim of these new formulations is to alter steroid levels in an effort to achieve lesser metabolic effects and minimize the occurrence of breakthrough bleeding and amenorrhea, while maintaining efficacy. We are probably at or very near the lowest dose levels that can be achieved without sacrificing efficacy. Metabolic studies with the multiphasic preparations indicate no differences or slight improvements over the metabolic effects of low-dose monophasic products. Low-dose oral contraceptives now include products with ethinyl estradiol daily doses of 20, 25, 30, and 35 μg.

An estrophasic approach (Estrostep) combines a continuous low dose of a progestin with a low, but gradually increasing dose of estrogen.[21] This approach minimizes estrogen exposure at the beginning of the cycle, yielding a low rate of side effects such as nausea. The increasing estrogen results in a marked increase in sex hormone–binding globulin that produces a very low androgenic state by reducing the bioavailability of circulating free androgens, and this formulation is very effective for treating acne.[22,23]

Reduction of the pill-free interval is a strategy aimed at the concern that pill omission with low-dose oral contraceptives might more readily result in "escape" ovulation. Utilizing a 4-day pill-free interval (rather than the usual 7 days) is associated with greater ovarian suppression.[24] Another approach adds estrogen for 5 of the usual 7 pill-free days.[25] However, these approaches have failure rates and breakthrough bleeding rates that are comparable to the standard regimens, and no clear-cut advantage for these alterations can be established.

Generic Products

Generic products are therapeutically equivalent drugs, containing the same amount of active ingredients in the same concentration and dosage form. These products are less expensive, marketed by pharmaceutical companies after patent expiration of the original drug. Generic oral contraceptives need only meet the test of bioequivalence; studies to demonstrate efficacy, side effects, and safety are not required. Meeting the test of bioequivalence requires demonstration in a small number of subjects that absorption, concentrations, and time curves are comparable to the reference drug. The generic product is approved if the bioequivalence testing ranges from 80% to 120% of the values for the reference drug (differences no greater than 20%). Approved, patented products must not vary more than ±10%; therefore, a generic oral contraceptive could contain only 72% of the standard dose. In the lowest-dose oral contraceptives, this could impair efficacy. We should hasten to point out that there has been no evidence or even anecdotal suggestions that generic oral contraceptives have reduced efficacy or caused more side effects such as breakthrough bleeding.

Potency

For many years, clinicians, scientists, medical writers, and even the pharmaceutical industry have attempted to assign potency values to the various progestational components of oral contraceptives. An accurate assessment, however, has been difficult to achieve for many reasons. Progestins act on numerous target organs (e.g., the uterus, the mammary glands, and the liver), and potency varies depending on the target organ and end point being studied. In the past, animal assays, such as the Clauberg test (endometrial change in the rabbit) and the rat ventral prostate assay, were used to determine progestin potency. Although these were considered acceptable methods at the time, a better understanding of steroid hormone action and metabolism and a recognition that animal and human responses differ have led to greater reliance on data collected from human studies.

Historically, this has been a confusing issue because publications and experts used potency ranking to provide clinical advice. There is absolutely

no need for confusion. Oral contraceptive progestin potency is no longer a consideration when it comes to prescribing oral contraception, because the potency of the various progestins has been accounted for by appropriate adjustments of dose. In other words, the biologic effect (in this case the clinical effect) of the various progestational components in current low-dose oral contraceptives is approximately the same. The potency of a drug does not determine its efficacy or safety, only the amount of a drug required to achieve an effect.

Clinical advice based on potency ranking is an artificial exercise that has not stood the test of time. There is no clinical evidence that a particular progestin is better or worse in terms of particular side effects or clinical responses. Thus oral contraceptives should be judged by their clinical characteristics: efficacy, side effects, risks, and benefits. Our progress in lowering the doses of the steroids contained in oral contraceptives has yielded products with little serious differences.

Mechanism of Action

The combination pill, consisting of estrogen and progestin components, is given daily for 3 of every 4 weeks. The combination pill prevents ovulation by inhibiting gonadotropin secretion via an effect on both pituitary and hypothalamic centers. The progestational agent in the pill primarily suppresses luteinizing hormone (LH) secretion (and thus prevents ovulation), while the estrogenic agent suppresses follicle-stimulating hormone (FSH) secretion (and thus prevents the emergence of a dominant follicle). Therefore, the estrogenic component significantly contributes to the contraceptive efficacy. However, even if follicular growth and development were not sufficiently inhibited, the progestational component would prevent the surge-like release of LH necessary for ovulation.

The estrogen in the pill serves two other purposes. It provides stability to the endometrium so that irregular shedding and unwanted breakthrough bleeding can be minimized, and the presence of estrogen is required to potentiate the action of the progestational agents. The latter function of estrogen has allowed reduction of the progestational dose in the pill. The mechanism for this action is probably estrogen's effect in increasing the concentration of intracellular progestational receptors. Therefore, a minimal pharmacologic level of estrogen is necessary to maintain the efficacy of the combination pill.

Because the effect of a progestational agent always takes precedence over estrogen (unless the dose of estrogen is increased many, many fold), the endometrium, cervical mucus, and perhaps tubal function reflect progestational stimulation. The progestin in the combination pill produces

an endometrium that is not receptive to ovum implantation, a decidualized bed with exhausted and atrophied glands. The cervical mucus becomes thick and impervious to sperm transport. It is possible that progestational influences on secretion and peristalsis within the fallopian tubes provide additional contraceptive effects. Even if there is some ovarian follicular activity (especially with the lowest dose products), these actions serve to ensure good contraceptive efficacy.[26]

Efficacy

A clinician's anecdotal experience with contraceptive methods is truly insufficient to provide the accurate information necessary for patient counseling. The clinician must be aware of the definitions and measurements used in assessing contraceptive efficacy and must draw on the talents of appropriate experts in this area to summarize the accurate and comparative failure rates for the various methods of contraception. The publications by Trussell et al., summarized below, accomplish these purposes and are highly recommended.[27-29]

Contraceptive failures do occur and for many reasons. Thus, "method effectiveness" and "use effectiveness" have been used to designate efficacy with correct and incorrect use of a method. It is less confusing to simply compare the very best performance (the lowest expected failure rate) with the usual experience (typical failure rates) as noted in the table of failure rates during the first year of use. The lowest expected failure rates are determined in clinical trials, where the combination of highly motivated subjects and frequent support from the study personnel yields the best results. It should be noted that slightly more than half of the unintended pregnancies in the United States are due to contraceptive failures.

In view of the multiple actions of oral contraceptives, it is hard to understand how the omission of a pill or two can result in a pregnancy. Indeed, careful review of failures suggests that pregnancies usually occur because initiation of the next cycle is delayed allowing escape from ovarian suppression. Strict adherence to 7 pill-free days is critical to obtain reliable, effective contraception. For this reason, the 28-day pill package, incorporating 7 pills that do not contain steroids, is a very useful aid to ensure adherence to the necessary schedule. The most prevalent problems that can be identified associated with apparent oral contraceptive failures are vomiting and diarrhea.[30, 31] ***Even if no pills have been missed, patients should be instructed to use a backup method for at least 7 days after an episode of gastroenteritis. An alternative is to place the pill in the vagina during the illness (discussed later).***

The contraceptive effectiveness of the new progestin oral contraceptives, multiphasic formulations, and lowest estrogen dose products are unequivocally comparable with older low-dose (less than 50 μg estrogen) and higher dose monophasic combination birth control pills.[26] While carefully monitored studies with motivated subjects achieve an annual failure rate of 0.1%, typical usage is associated with a 7.6% failure rate during the first year of use.[29] Contraceptive failure rates have been estimated using the data from the 1995 National Survey of Family Growth and correcting for the underreporting of induced abortion.[29, 32, 33]

Failure Rates During the First Year of Use, United States[29,32,33]

Method	Percent of Women with Pregnancy Lowest Expected	Typical
No method	85.0%	85.0%
Combination pill	0.1	7.6
Progestin-only	0.5	3.0
IUDs		
Levonorgestrel IUD	0.1	0.1
Copper T 380A	0.6	0.8
Implant	0.2	0.2
Injectable	0.3	0.3
Female sterilization	0.2	0.4
Male sterilization	0.1	0.15
Spermicides	6.0	25.7
Periodic abstinence		20.5
Calendar	9.0	
Ovulation method	3.0	
Symptothermal	2.0	
Post-ovulation	1.0	
Withdrawal	4.0	23.6
Cervical cap		
Parous women	20.0	40.0
Nulliparous women	9.0	20.0
Sponge		
Parous women	20.0	40.0
Nulliparous women	9.0	20.0
Diaphragm and spermicides	6.0	12.1
Condom		
Male	3.0	13.9
Female	5.0	21.0

Metabolic Effects of Oral Contraception

Cardiovascular Disease

In October 1995, the United Kingdom Committee on Safety of Medicines sent a letter to all U.K. physicians and pharmacists stating that women taking oral contraceptives containing desogestrel or gestodene should be urged to complete their current cycle and to continue a formulation with these progestins only if prepared to accept an increased risk of venous thromboembolism. The Committee on Safety of Medicines took this action because of observational studies that indicated a 2-fold increase in the risk of venous thromboembolism when desogestrel- and gestodene-containing contraceptives were compared with products with other progestins (mostly levonorgestrel). This action and the studies on which it was based immediately became controversial. The controversy went beyond the validity of the epidemiologic data. The publicity surrounding these events reverberated throughout Europe, leading to an immediate overall decrease in oral contraceptive use, an increase in unwanted pregnancies, and an increase in induced abortions.[34, 35]

The controversy involving new progestin oral contraceptives that began in late 1995, continued through 1996, and began to reach resolution in 1997. The fundamental question is whether oral contraceptives containing desogestrel and gestodene have a different risk of thrombosis compared with oral contraceptives containing older progestins. Thrombosis can be divided into two major categories, venous thromboembolism and arterial thrombosis. Venous thromboembolism includes both deep vein thrombosis and pulmonary embolism. Arterial thrombosis includes acute myocardial infarction and stroke.

The Coagulation System

The goal of the clotting mechanism is to produce thrombin, which converts fibrinogen to a fibrin clot. Thrombin is generated from prothrombin by factor Xa in the presence of factor V, calcium, and phospholipids. The vitamin K–dependent factors include factors VII, IX, and X, as well as prothrombin. Antithrombin III is one of the body's natural anticoagulants, an irreversible inhibitor of thrombin and factors IXa, Xa, and XIa. Protein C and protein S are two other major inhibitors of coagulation and are also vitamin K–dependent. Protein C, and its helper, protein S, inhibit clotting at the level of factors V and VIII. Tissue plasminogen activator (t-PA) is produced by endothelial cells and released when a clot forms. Both t-PA and plasminogen bind to the fibrin clot. The t-PA converts the plasminogen to plasmin, which lyses the clot by degrading the fibrin. Deficiencies of antithrombin III, protein C, and protein S are inherited in an autosomal dominant pattern, accounting for 10–15% of familial thrombosis. The most common inherited causes of venous thromboembolism are the factor V Leiden mutation, followed distantly by a mutation in the prothrombin gene.[36]

Coagulation Factors:
- **Factors that favor clotting when increased**
  - **Fibrinogen**
  - **Factors VII, VIII, X**
- **Factors that favor clotting when decreased**
  - **Antithrombin III**
  - **Protein C**
  - **Protein S**

Fibrinolysis Factors:
- **Factors that favor clotting when increased**
  - **Plasminogen**
  - **Plasminogen activator inhibitor-1 (PAI-1)**
- **Factor that favors clotting when decreased**
  - **Antiplasmin**

An inherited resistance to activated protein C has been identified as the basis for about 50% of cases of familial venous thrombosis, due in almost all cases to a gene alteration recognized as the factor V Leiden mutation.[37, 38] The factor V Leiden mutation is found in approximately 30% of individuals who develop venous thromboembolism.[39] Activated protein C inhibits coagulation by degrading factors V and VIII. One of the three cleavage sites in factor V is the precise site of a mutation (known as the factor V Leiden mutation) that substitutes glutamine instead of arginine at this site (adenine for guanine at nucleotide 1691 in the gene).[39] This mutation makes factor V resistant to degradation (and activation in fibrinolysis). The entire clotting cascade is then resistant to the actions of the protein C system.

Heterozygotes for the factor V Leiden mutation have an 5–8-fold increased risk of venous thrombosis, and homozygotes have an 80-fold increased risk, and this risk is further enhanced by oral contraceptive use.[40–42] The highest prevalence (3–4% of the general population) of factor V Leiden is found in Europeans, and its occurrence in populations not of European descent is very rare, perhaps explaining the low frequency of thromboembolic disease in Africa, Asia, and in Native Americans.[43] The mutation is believed to have arisen in a single ancestor approximately 21,000 to 34,000 years ago.[44] It has been suggested that this was a useful adaptation in heterozygotes in response to life-threatening bleeding, such as with childbirth.

The next most common inherited disorder after the factor V Leiden mutation is a mutation, a guanine to adenine change, in the gene encoding prothrombin.[36, 45] The prevalence of this abnormality in the white population is estimated to range from 0.7% to 4%.[46] Oral contraceptive

use has been reported to markedly increase the risk of venous thrombosis in carriers of the prothrombin mutation.[47] Perhaps other unidentified disorders make a contribution because an increased risk of venous thrombosis with oral contraceptives has been reported in women with elevated prothrombin levels despite an absence of the prothrombin gene mutation.[48]

The administration of pharmacologic amounts of estrogen as in high-dose oral contraceptives causes an increase in the production of clotting factors such as factor V, factor VIII, factor X, and fibrinogen.[49] The progestin component also influences the clotting factor responses.[50] Some studies of the blood coagulation system have concluded that both monophasic and multiphasic low-dose oral contraceptives have no significant clinical impact on the coagulation system. Slight increases in thrombin formation are offset by increased fibrinolytic activity.[51, 52] Other studies of formulations containing 30 and 35 μg of ethinyl estradiol indicate an increase in clotting factors associated with an increase in platelet activity.[53] However, these changes are essentially all within normal ranges and their clinical significance is unknown.[50]

Smoking produces a shift to hypercoagulability.[54] A 20 μg estrogen formulation has been reported to have no effect on clotting parameters, even in smokers.[54, 55] One study comparing a 20 μg product with a 30 μg product found similar mild procoagulant and fibrinolytic activity, although there was a trend toward increased fibrinolytic activity with the lower dose.[56] These mixed reports make it essential to base clinical decisions on the epidemiologic studies of clinical events.

There is no evidence of an increase in risk of cardiovascular disease among past users of oral contraception.[57–59] In the Nurses' Health Study, the Royal College of General Practitioners' Study, and the Oxford Family Planning Association Study, long-term past use of oral contraceptives was not associated with an increase in overall mortality.[60–62] Part of the concern for a possible lingering effect of oral contraceptive use was based on a presumed adverse impact on the atherosclerotic process, which would then be added to the effect of aging and, thus, would be manifested later in life. Instead, the findings have been consistent with the contention that cardiovascular disease due to oral contraception is secondary to acute effects, specifically estrogen-induced thrombosis, a dose-related event.

Venous Thromboembolism — The Conventional Wisdom

Older epidemiologic evaluations of oral contraceptives and vascular disease indicated that venous thrombosis was an effect of estrogen, limited to current users, with a disappearance of the risk by 3 months after discontinuation.[63, 64] Thromboembolic disease was believed to be a consequence of the pharmacologic administration of estrogen, and the level of risk was

believed to be related to the estrogen dose.[65–67] Smoking was documented to produce an additive increase in the risk of arterial thrombosis [68–70] but had no effect on the risk of venous thromboembolism.[71, 72]

Is there still a risk of venous thromboembolism with the current low-dose (less than 50 μg ethinyl estradiol) formulations of oral contraceptives? In the first years of oral contraception, the available products, containing 80 and 100 μg ethinyl estradiol (an extremely high dose), were associated with a 6-fold increased risk of venous thrombosis.[73] Because of the increased risks for venous thrombosis, myocardial infarction, and stroke, lower dose formulations (less than 50 μg estrogen) came to dominate the market, and clinicians became more careful in their screening of patients and prescribing of oral contraception. Two forces, therefore, were at work simultaneously to bring greater safety to women utilizing oral contraception: (1) the use of lower dose formulations, and (2) the avoidance of oral contraception by high-risk patients. Because of these two forces, the Puget Sound study in the United States documented a reduction in venous thrombosis risk to 2-fold.[74] The new studies also reflect the importance of these two forces, but they still indicate an increased risk.

Venous Thromboembolism — The Controversial Studies

The World Health Organization (WHO) Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception was a hospital-based, case-control study with subjects collected from 21 centers in 17 countries in Africa, Asia, Europe, and Latin America.[75] As part of this study, the risk of idiopathic venous thromboembolism associated with a formulation containing 30 μg ethinyl estradiol and levonorgestrel (doses ranging from 125 to 250 μg) was compared with the risk with preparations containing 20 or 30 μg ethinyl estradiol and either desogestrel or gestodene (data from 10 centers in 9 countries).[76] There were only 9 cases and 3 controls using combined oral contraceptives with other progestins, precluding precise analysis. The users of the levonorgestrel formulations had an increased odds ratio (an estimation of relative risk used in case-control studies) of 3.5 compared with nonusers. Current users of a desogestrel product had an increased risk of 9.1 compared with nonusers, and with gestodene, the odds ratio was also 9.1. Thus, the increased risk for desogestrel and gestodene was 2.6 times that of levonorgestrel, when adjusted for body weight and height. Also of note, the increased risk for the desogestrel formulation containing 20 μg ethinyl estradiol was 38.2, a number that is obviously not reliable because it was based upon only 8 cases and 1 control; the confidence interval (CI) of 4.5–325 reflected this imprecision. Overall, these increased risks were lower than those estimated by earlier case-control studies of higher dose oral contraceptives.

The Transnational Study on Oral Contraceptives and the Health of Young Women analyzed 471 cases of deep vein thrombosis and/or venous thromboembolism from the United Kingdom and Germany.[77] Second-generation oral contraceptives were defined as products containing 35 μg or less of ethinyl estradiol and a progestin other than desogestrel or gestodene. Comparing users of second-generation products to nonusers, the odds ratio was 3.2 (CI = 2.3–4.3). Comparing users of desogestrel and gestodene products to users of second-generation oral contraceptives, the risk of venous thromboembolism was 1.5-fold greater.

A third major study was from Boston University, but the data were derived from ***the General Practice Research Database,*** a computerized system involving the general practitioners in the United Kingdom.[78] Using this cohort, the authors calculated the death rate from pulmonary embolism, stroke, and acute myocardial infarction in the users of levonorgestrel, desogestrel, and gestodene low-dose oral contraceptives. Over a 3-year period, they collected a total of 15 unexpected idiopathic cardiovascular deaths in users of these products, a nonsignificant change, and no difference in the risk comparing desogestrel and gestodene with levonorgestrel. The risk estimates for venous thromboembolism (adjusted for smoking and body size) were about 2 times greater for desogestrel and for gestodene, compared with levonorgestrel uses. There were only 4 cases and 9 controls using the 20 μg ethinyl estradiol and desogestrel product, and although the risk was similar to that associated with the 30 μg ethinyl estradiol and desogestrel product, this is too small a number for analysis. In an updated analysis from this same group and database, the findings were unchanged, except that smoking was found to be a risk factor for venous thromboembolism.[79]

Similar results were reported when women with deep vein thrombosis in the ***Leiden Thrombophilia Study*** in the Netherlands were reanalyzed for their use of oral contraceptives.[80] As expected, the risk of deep vein thrombosis was markedly higher in women who were carriers of the factor V Leiden mutation and in women with a family history of thrombosis.

Venous Thromboembolism — Subsequent Studies

The reports in late 1995 and early 1996 were followed by a flood of letters to editors, as well as reviews and editorials, highlighting confounding and bias problems in these studies.[81–83] Some prominent figures were convinced the reports of increased risks with desogestrel and gestodene were real;[84, 85] others were skeptical, pointing out possible confounding biases. Subsequently, reanalysis and new studies did reveal confounders and biases in the initial studies.

In Denmark, Lidegaard and colleagues performed a hospital-based, case-control study of women with confirmed diagnoses of venous

thromboembolism in 1994 and 1995 (in Denmark, all women with this diagnosis are hospitalized, and, therefore, very few, if any, cases were missed).[86] A 2-fold increased risk of venous thromboembolism was found in current users of oral contraceptives, regardless of estrogen doses ranging from 20 to 50 μg. The increased risk was concentrated in the first year of use. ***Because there were more short-term users of the new progestins and more long-term users of the older progestins, adjustment for duration of use resulted in no significant differences between the different types of progestins.*** Those factors associated with an increased risk of thromboembolism included coagulation disorders, treated hypertension during pregnancy, family history of venous thromboembolism, and an increasing body mass index. Notably, conditions not associated with an increased risk of venous thromboembolism included smoking, migraine, diabetes, hyperlipidemia, parity, or age at first birth. There was still insufficient strength in this study to establish the absence or presence of a dose-response relationship comparing the 20 μg estrogen dose to higher doses; however, a 5-year update reported the following useful information:[87]

- The risk of venous thrombosis associated with current use of oral contraceptives declined with increasing duration of use.
- The risk was slightly greater with desogestrel or gestodene.
- Smoking more than 10 cigarettes per day increased the risk.
- Oral contraceptives with 20 μg estrogen had a lower risk than products with 30–40 μg.
- Progestin-only contraceptive products did not increase the risk.

Case-control studies using cases of venous thromboembolism derived from the computer records of general practices in the U.K. concluded that the increased risk associated with oral contraceptives was the same for all types, and that the pattern of risk with specific oral contraceptives suggested confounding because of "preferential prescribing" (defined later).[88, 89] *In these studies, matching cases and controls by year of birth eliminated differences between different types of oral contraceptives.* A similar analysis based on 42 cases from a German database again found no difference between new progestin and older progestin oral contraceptives.[90] Thus, in these two studies, more precise adjustments for age eliminated a confounding bias. An assessment of the incidence of venous thromboembolism in the United Kingdom before and after the decline in third-generation progestin use could detect no impact on the statistics (neither an increase nor a decrease).[91]

A reanalysis of the Transnational Case-Control Study considered the duration and patterns of oral contraceptive use.[92, 93] This reanalysis focused on first-time users of second- and third-generation oral contraceptives. *Statistical analysis with adjustment for duration of use in 105 cases who were first-time users could find no differences between second- and*

third-generation products. Similarly, a reanalysis of the U.K. General Practice Database could demonstrate no difference between different oral contraceptive formulations.[94]

A case-control study in Germany assessed the outcome when the cases were restricted to hospitalized patients compared to results when all cases, both in-hospital and out-of-hospital, were considered.[95] The conclusion indicated that hospital-based studies overestimated the risk of venous thromboembolism, and that there was no difference comparing progestins when all cases were included.

Evaluation of the Studies

An immediate problem with the initial studies was how to reconcile the results with the conventional wisdom that thrombosis is an estrogen dose-related complication. Progestational agents, and desogestrel and gestodene in particular, have no significant impact on clotting parameters.[14] Therefore, there was inherent biologic implausibility surrounding the new studies. The initial reports resurrected the claim by Kuhl in 1988 and 1989 that gestodene could cause more thrombosis because it affected ethinyl estradiol metabolism, resulting in higher estrogen levels.[96, 97] Other laboratories, however, could not replicate Kuhl's findings.[98, 99]

Former users discontinue oral contraceptives for a variety of reasons, and often are switched to what clinicians perceive to be "safer" products ("preferential prescribing").[100–102] Individuals who do well with a product tend to remain with that product. Thus, at any one point in time, individuals on an older product are relatively healthy and free of side effects ("healthy user effect"). This is also called attrition of susceptibles because higher risk individuals with problems are gradually eliminated from the group.[82] *Comparing users of older and newer products, therefore, can involve disparate cohorts of individuals.*

Because desogestrel- and gestodene-containing products were marketed as less androgenic and therefore "better" (a marketing claim not substantiated by epidemiologic studies), clinicians chose to provide these products to higher risk patients and older women.[100, 101] In addition, clinicians switched patients perceived to be at greater risk for thrombosis from older oral contraceptives to the newer formulations with desogestrel and gestodene. Furthermore, these products were prescribed more often to young women who were starting oral contraception for the first time (these young women will not have experienced the test of pregnancy or previous oral contraceptive use to help identify those who have a congenital predisposition to venous thrombosis). These changing practice patterns exert different effects over the lifetime of a product, and analytical adjustments are extremely difficult. The Transnational Group believed it accomplished an appropriate adjustment by focusing on first-time

users and duration of use.[92] It is also unlikely that the "healthy user effect" is dominant in first-time users. And, of course, this analysis found no differences between second- and third-generation oral contraceptives.

The challenge for a clinician is to make a decision: is an observational study with statistically significant results clinically (biologically) real? This controversy illustrates how difficult this can be. When faced with results from observational studies, clinicians want to see uniformity, consistency, agreement—all arguing in favor of a real clinical effect; an example is the protective effect of oral contraceptives on the risk of ovarian cancer. The initial studies were impressive in their agreement. All indicated increased relative risks associated with desogestrel and gestodene compared with levonorgestrel. Nevertheless, all of the early studies, somewhat similar in design, were influenced by the same unrecognized biases. *Persistent errors produce consistent conclusions.*

Forty cases of venous thrombosis in drospirenone (Yasmin) users (two of which were fatal) were reported in Europe in 2002.[103] The Dutch College of General Practitioners issued a statement encouraging clinicians not to prescribe Yasmin. However, this is the similar story we experienced with "third-generation" progestins, only to learn that preferential prescribing and the healthy user effect probably biased the early case-control studies. In postmarketing surveillance, only one case of venous thrombosis occurred in a million cycles of Yasmin compared with 5 among users of other oral contraceptives.[103]

The risk of venous thrombosis associated with modern oral contraceptives is increased but manifested primarily in the first years of use. The risk is influenced in a major way by the estrogen dose, and the difference between second-generation and third-generation progestin products is small, either real and not meaningful clinically or a reflection of biases and confounders. The impact of smoking on the risk of venous thrombosis is less than that on the risk of arterial thrombosis.

Venous Thromboembolism and the Factor V Leiden Mutation

A risk of idiopathic venous thrombosis persists with low-dose oral contraceptives, at a level of approximately 3–4-fold greater than the normal, general incidence.[76–78, 80, 104] However, an inherited resistance to activated protein C, the factor V Leiden mutation, may account for a significant portion of the patients who experience venous thrombosis while taking oral contraceptives.

Relative Risk and Actual Incidence of Venous Thromboembolism[40–42, 105, 109]

Population	Relative Risk	Incidence
Young women-general population	1	4–5 per 100,000 per year
Pregnant women	12	48–60
High-dose oral contraceptives	6–10	24–50
Low-dose oral contraceptives	3–4	12–20
Leiden mutation carrier	6–8	24–40
Leiden carrier and oral contraceptives	10–15	40–75
Leiden mutation - homozygous	80	320–400

An inherited resistance to activated protein C, the factor V Leiden mutation, is the most common inherited coagulation problem, transmitted in an autosomal-dominant fashion.[37, 106] Heterozygotes have a 5- to 8-fold increased risk of venous thromboembolism, and homozygotes an 80-fold increased risk. Oral contraceptive users who have this mutation have been reported to have a 30-fold increased risk of venous thrombosis.[107, 108] Some have argued, however, that this increase has been overestimated, and it may be closer to 10–15-fold.[41, 109] The risk of developing venous thrombosis is greatest in the initial months of use, and it has been suggested that venous thrombosis occurring in the first month of exposure should make the clinician suspect the presence of a clotting disorder.[110]

An American case-control study confirmed the approximately 3–4-fold increased risk of venous thrombosis with the current use of low-dose oral contraceptives.[42] The risk for women with Factor V Leiden mutations increased 11-fold (comparable to the risk in a pooled analysis of case-control studies[41]). Almost half of the cases in current users occurred in women with a BMI greater than 30.

Should screening for the factor V Leiden mutation (or for other inherited clotting disorders) be routine prior to prescribing contraceptives? The carrier frequencies of the Leiden mutation in the American population (the percentages are similar in men and women) are as follows:[105]

Caucasian Americans	—	5.27%
Hispanic Americans	—	2.21%
Native Americans	—	1.25%
Black Americans	—	1.23%
Asian Americans	—	0.45%

These estimates are consistent with the European assessments, indicating that this is a trait carried in people of European origin. In the United States, of the approximately 10 million women currently using oral contraceptives, about 450,000 are likely to carry the factor V Leiden mutation. However, because the incidence rate of venous thromboembolism is so low (4–5 per 100,000 young women per year),[40, 105] the number of women required to be screened to prevent one death is prohibitively large. The prevalence of all deficiencies is only about 0.5% in the asymptomatic population, and only one-third of patients at risk are detected by the present tests.[111]

Furthermore, because only a small number of women even with the Leiden mutation (less than 1 in 1,000) have a clinical event (99.85% of the individuals who test positively will NOT have a clinical event!), the finding of a positive screening test, especially considering the high rate of false-positive tests, would be a barrier to the use of oral contraceptives, and a subsequent increase in unwanted pregnancies (which has an even greater risk of venous thromboembolism) would likely follow. ***Most experts believe that screening for inherited disorders should be pursued only in women with a previous episode of venous thromboembolism or a close positive family history (parent or sibling) of venous thrombosis.***

Arterial Thrombosis

Because the incidence of cerebral thrombotic attacks (thrombotic strokes and transient ischemic attacks) among young women is higher than venous thromboembolism and myocardial infarction, and death and disability are more likely, cerebral arterial thrombosis is the most important possible side effect. A very low incidence of stroke in young women carries with it little increase in absolute risk. However, because the incidence of cerebral thrombotic attacks is higher in women over age 40, we should do our best, as the following discussion indicates, to make sure oral contraceptive users over age 40 are in good health and without significant risk factors for cardiovascular disease (especially hypertension, migraine with aura, and smoking).

It has been difficult to establish arterial thrombosis dose-response relationships with estrogen because these events are so rare. Nevertheless, the estrogen dose is important for the risk of myocardial infarction and thrombotic strokes.[112, 113] Thus, a rationale for advocating low-dose estrogen oral contraceptives continues to be valid.

Arterial Thrombosis — Myocardial Infarction

A population-based, case-control study analyzed 187 cases of myocardial infarction in users of low-dose oral contraceptives in the Kaiser Permanente Medical Care Program.[114] *There was no statistically significant*

increase in the odds ratio for myocardial infarction in current oral contraceptive users compared with past or never users.

In the Transnational case-control study of myocardial infarctions collected from 16 centers in Austria, France, Germany, Switzerland, and the United Kingdom, the results were as follows:[115, 116]

	Cases	Controls	Odds Ratio	Confidence Interval
Any OC use	57	156	2.35	1.42–3.89
50 μg estrogen OCs	14	22	4.32	1.59–11.74
Old progestin OCs	28	71	2.96	1.54–5.66
New progestin OCs	7	49	0.82	0.29–2.31

These data were interpreted as indicating no increased risk of myocardial infarction associated with oral contraceptives containing desogestrel or gestodene. However, the reduced risk with the new progestin oral contraceptives was also emphasized (the comparison of third-generation products to second-generation products yielded a reduced risk that was statistically significant), suggesting a possible saving of deaths from myocardial infarction with desogestrel and gestodene. The problem is that the small actual incidence makes it difficult to acquire sufficient numbers. The conclusion was based on only 7 cases and 49 controls using third-generation oral contraceptives and 28 cases and 71 controls using second-generation products, and, in our view, the power is too limited to make any conclusion regarding the new progestin oral contraceptives. A similar limitation was apparent in a case-control study from the Netherlands and another from the United Kingdom[117, 118] This is a good example of a conclusion that may be statistically significant but clinically not real. A meta-analysis of recent studies on the risk of myocardial infarction concluded that the third-generation progestins were not associated with an increase in risk, but again the numbers were inadequate to support a beneficial impact.[119] The rare occurrence of a myocardial infarction in young women, especially young women free of cardiovascular risk factors, makes it unlikely that epidemiologic studies will detect meaningful differences comparing different formulations of oral contraceptives.

The Transnational study found that cigarette smoking carried a higher risk for myocardial infarction than oral contraceptives, and that nonsmoking users of oral contraceptives had no evidence of an increased risk.[115] In addition, there was an indication that patient screening is important in minimizing the impact of hypertension on the risk of myocardial infarction. Similar results were

reported in a case-control study based on subjects in England, Scotland, and Wales and another in America.[117, 120]

In the WHO multicenter study, there were 368 cases of acute myocardial infarction.[121] Factors associated with an increased risk of myocardial infarction included smoking, a history of hypertension (including hypertension in pregnancy), diabetes, rheumatic heart disease, abnormal blood lipids, and a family history of stroke or myocardial infarction. Duration of use and past use of oral contraceptives did not affect risk. Although there was about a 5-fold overall increased odds ratio of myocardial infarction in current users of oral contraceptives, essentially all cases occurred in women with cardiovascular risk factors. There was no apparent effect of increasing age on risk; however, there were only 12 cases among oral contraceptives users less than 35 years old. There was no apparent relationship with estrogen dose, and there was no apparent influence of type or dose of progestin, but the rare occurrence of this condition produced such small numbers that there was insufficient statistical power to accurately assess the effects of progestin type, and estrogen and progestin doses. *The conclusion of this study was that the risk of myocardial infarction in women who use oral contraceptives is increased only in smokers.*

In a Danish case-control study of acute myocardial infarction in young women, a statistically significant increase in risk was noted only in current users of 50 μg ethinyl estradiol.[113] There was a progressive increase in risk with the number of cigarettes smoked, (accounting for 80% of the acute myocardial infarctions in young women), increasing body mass index, treated hypertension, treated hypertension in pregnancy, diabetes mellitus, hyperlipidemia, frequent migraine, and family history of myocardial infarction. However, only family history of myocardial infarction and smoking affected the risk associated with oral contraceptives; no influence on oral contraceptive risk was apparent with diabetes, hypertension, and heart disease. No differences could be demonstrated according to type of progestin.

A case-control study from the Netherlands found that the risk of myocardial infarction was highest among users of oral contraceptives who smoked, had diabetes mellitus, or who were hypercholesterolemic.[118] The risk of myocardial infarction was not affected by the presence of the factor V Leiden mutation or the prothrombin gene mutation.

Incidence of Myocardial Infarction in Reproductive Age Women [121]

Overall incidence [105]	5 per 100,000 per year
Women less than age 35	
Nonsmokers	4
Nonsmokers & OCs	4
Smokers	8
Smokers & OCs	43
Women 35 years old and older	
Nonsmokers	10
Nonsmokers & OCs	40
Smokers	88
Smokers & OCs	485

NOTE: The above incidences are estimates based on oral contraceptive use paired with cardiovascular risk factors prevalent in the general population. Effective screening would produce smaller numbers. The increased risks in the smokers and OC groups reflect the impact of undetected cardiovascular risk factors, especially hypertension.

Arterial Thrombosis — Stroke

Older case-control and cohort studies indicated an increased risk of cerebral thrombosis among current users of high-dose oral contraceptives.[123–125] However, thrombotic stroke did not appear to be increased in healthy, nonsmoking women with the use of oral contraceptives containing less than 50 μg ethinyl estradiol.[124, 125] A case-control study of all 794 women in Denmark who suffered a cerebral thromboembolic attack during 1985–1989 concluded that there was an almost 2-fold increased relative risk associated with oral contraceptives containing 30–40 μg estrogen, and the risk was significantly influenced by both smoking and the dose of estrogen in additive (not synergistic) fashion.[70] A case-control analysis of data collected by the Royal College of General Practitioners' Oral Contraception Study concluded that current users were at increased risk of stroke (with a persisting effect in former users); however, this outcome was limited mainly to smokers and to formulations with 50 μg or more of estrogen.[125]

A population-based, case-control study of 408 strokes from the California Kaiser Permanente Medical Care Program found no increase in risk for either ischemic stroke or hemorrhagic stroke.[126] The identifiable risk factors for ischemic stroke were smoking, hypertension, diabetes, elevated body weight, and low socioeconomic status. The risk factors for hemorrhagic stroke were the same plus greater body mass and heavy use of alcohol. *Current users of low-dose oral contraceptives did not have an increased risk of ischemic or hemorrhagic stroke compared with former users and with never users.* There was no evidence for an adverse effect of increasing age or for smoking (for hemorrhagic stroke, there was a suggestion of a positive interaction between current oral contraceptive use and smoking, but the numbers were small, and the result was not statistically significant).

The Transnational study analyzed their data for ischemic stroke in a case-control study of 220 ischemic strokes in the United Kingdom, Germany, France, Switzerland, and Austria.[127] Overall, there was a 3-fold increase in the risk of ischemic stroke associated with the use of oral contraceptives, with higher risks observed in smokers (more than 10 cigarettes per day), in women with hypertension, and in users of higher dose estrogen products. No differences were observed comparing second- and third-generation progestins. A Dutch case-control study also found no differences comparing second- and third-generation progestins.[128] A case-control study from the state of Washington concluded that there is no increased risk of stroke in current users of low-dose oral contraceptives.[129] A pooled analysis of the data from California and Washington concluded that low-dose oral contraceptives are not associated with an increase in the risk of stroke.[130]

The World Health Organization data on stroke come from the same collaborative study that yielded the publications on venous thromboembolism. The results with stroke were published as two separate reports, one on ischemic stroke and the other on hemorrhagic stroke.[131, 132]

This hospital-based, case-control study from 21 centers in 17 countries accumulated 697 cases of ischemic stroke, 141 from Europe and 556 from developing countries.[131] The overall odds ratio for ischemic stroke indicated about a 3-fold increased risk. In Europe, however, the risk was statistically significant only for higher-dose products and **NOT** statistically significant for products with less than 50 μg ethinyl estradiol. In developing countries, there was no difference in risk with low-dose and higher dose oral contraceptives. This is believed to be due to the strong influence of hypertension. In Europe, it was uncommon for women with a history of hypertension to be using oral contraceptives; however, this was not the case in developing countries. Duration of use and type of progestin had no impact, and past users did not have an increased risk, but smoking 10 or more cigarettes daily exerted a synergistic effect with oral contraceptives, increasing the risk of

ischemic stroke, approximating the effect of hypertension and oral contraceptives. The risk was greater in women 35 years and older; however, this, too, was believed to be due to an effect of hypertension. *Thus, the conclusion of this study was that the risk of ischemic stroke is extremely low, concentrated in those who use higher dose products, smoke, or have hypertension.*

In the WHO study on hemorrhagic stroke, there were 1,068 cases.[132] Current use of oral contraceptives was associated with a slightly increased risk of hemorrhagic stroke only in developing countries, not in Europe. This again probably reflects the presence of hypertension, because the greatest increased risk (about 10- to 15-fold) was identified in current users of oral contraceptives who had a history of hypertension. Current cigarette smoking also increased the risk in oral contraceptive users, but not as dramatically as hypertension. For hemorrhagic stroke, the dose of estrogen had no effect on risk, and neither did duration of use or type of progestin. *This study concluded that the risk of hemorrhagic stroke due to oral contraceptives is increased only slightly in older women, probably occurring only in women with risk factors such as hypertension.*

A second Danish case-control study included thrombotic strokes and transitory cerebral ischemic attacks analyzed together as cerebral thromboembolic attacks.[112] In this study, the 219 cases during 1994 and 1995 included 146 cases of cerebral infarction and 73 cases of transient ischemic attacks. There was a dose-response relationship with estrogen in the dose ranges of 20, 30–40, and 50 μg ethinyl estradiol, although the number of 20 μg users (5 cases, 22 controls) was not sufficient to establish a lower risk at this lower dose. This analysis claimed a reduced risk associated with desogestrel and gestodene; however, the odds ratio did not achieve statistical significance. An updated 5-year report of the Danish case-control study indicated that the odds ratio of cerebral thrombosis decreased from a high of 4.5 with 50 μg estrogen pills to 1.6 with 20–40 μg pills.[133] Hypertension increased the risk 5-fold, migraine 3.2 times, diabetes 5.6 times, and hyperlipidemia and coagulation disorders about 12-fold.

Incidence of Stroke in Reproductive Age Women[122, 126, 131, 132]

Incidence of ischemic stroke	5 per 100,000 per year
	1–3 per 100,000 per year in women under age 35
	10 per 100,000 per year in women over age 35
Incidence of hemorrhagic stroke	6 per 100,000 per year
Excess cases per year due to OCs, *including smokers and hypertensives*	2 per 100,000 per year in low-dose OC users
	1 per 100,000 per year in low-dose OC users under age 35
	8 per 100,000 per year in high-dose users

Arterial Thrombosis — Current Assessment

There has been no evidence with respectable statistical power that the new progestins have an appreciable difference in risk for arterial disease, an event that is already **NOT** increased with low-dose older-type progestin oral contraceptives. It is possible that as these studies continue and acquire greater statistical power, a difference will emerge, but even if this is the case, the difference will be minor and likely unmeasureable. Conclusions based on a limited number of cases are premature, and a critical attitude toward arterial thrombosis is appropriate just as such an approach finally revealed likely explanations for the initial findings with venous thrombosis.

Most importantly, the new studies fail to find any substantial risk of ischemic or hemorrhagic stroke with low-dose oral contraceptives in healthy, young women. The WHO study did find evidence for an adverse impact of smoking in women under age 35; the Kaiser study did not. This difference is explained by the confounding effect of hypertension, the major risk factor identified. In the WHO study, a history of hypertension was based on whether a patient reported ever having had high blood pressure (other than in pregnancy) and not validated by medical records. In the Kaiser study, women were classified as having hypertension if they reported using antihypertensive medication (less than 5% of oral contraceptive users had treated hypertension, and there were no users of higher dose products). In the WHO study, the effect of using oral contraceptives in the presence of a high-risk factor is apparent in the different odds ratios when European women who received good screening from clinicians were compared with women in developing countries who received little screening; therefore, more women with cardiovascular risk factors in developing countries were using oral contraceptives.

Over the years, there has been recurring discussion over whether to provide oral contraceptives over-the-counter on a nonprescription basis. The data in the WHO report make an impressive argument against such a move. The increased risk of myocardial infarction was most evident in developing countries where 70% of the cases received their oral contraceptives from a nonclinical source. Deprived of screening, women with risk factors in developing countries were exposed to greater risk.

Oral contraceptives containing less than 50 µg ethinyl estradiol do not increase the risk of myocardial infarction or stroke in healthy, nonsmoking women, regardless of age. The effect of smoking in women under age 35 is, as we have long recognized, not detectable in the absence of hypertension. After age 35, the subtle presence of hypertension makes analysis difficult, but the Kaiser study indicates that increasing age and smoking by themselves have little impact on the risk of stroke in low-dose oral contraceptive users. The screening of patients in the Kaiser program was excellent, resulting in few women with hypertension using oral contraceptives. ***The new studies indicate that hypertension should be a major concern, especially in regards to the risk of stroke.***

Smoking

Smoking continues to be a difficult problem, not only for patient management but for analysis of data as well. In large U.S. surveys in 1982 and 1988, the decline in the prevalence of smoking was similar in users and nonusers of oral contraception; however, 24.3% of 35- to 45-year-old women who used oral contraceptives were smokers![134] In this group of smoking, oral contraceptive-using women, 85.3% smoked 15 or more cigarettes per day (heavy smoking). Despite the widespread teaching and publicity that smoking is a contraindication to oral contraceptive use over the age of 35, more older women who used oral contraceptives smoked and smoked heavily, compared with young women. This strongly implies that older smokers are less than honest with clinicians when requesting oral contraception, and this further raises serious concern over how well this confounding variable can be controlled in case-control and cohort studies. ***A former smoker must have stopped smoking for at least 12 consecutive months to be regarded as a nonsmoker. Women who have nicotine in their bloodstream obtained from patches or gum should be regarded as smokers.***

Lipoproteins and Oral Contraception

The balance of estrogen and progestin potency in a given oral contraceptive formulation can potentially influence cardiovascular risk by its overall effect on lipoprotein levels. Oral contraceptives with relatively high doses of progestins (doses not used in today's low-dose formulations) do produce

unfavorable lipoprotein changes.[135] The levonorgestrel triphasic exerts no significant changes on HDL-cholesterol, LDL-cholesterol, apoprotein B, and no change or an increase in apoprotein A. The monophasic desogestrel and desogestrel pills have a favorable effect on the lipoprotein profile, while the triphasic norgestimate and gestodene pills produce beneficial alterations in the LDL/HDL and apoprotein B/apoprotein A ratios.[136–139] Like the triphasic levonorgestrel pills, norethindrone multiphasic pills have no significant impact on the lipoprotein profile over 6–12 months.[140] ***In summary, studies of low-dose formulations indicate that the adverse effects of progestins are limited to the fixed-dose combination with a dose of levonorgestrel that exceeds that in the multiphasic formulation or in the low-dose products.*** The formulation that contains 100 μg levonorgestrel and 20 μg ethinyl estradiol produces short-term changes in the lipid profile that are similar to those seen with other low-dose oral contraceptives, and with long-term use, the levels revert to those observed at baseline before treatment.[141]

An important study in monkeys indicated a protective action of estrogen against atherosclerosis, but by a mechanism independent of the cholesterol-lipoprotein profile. Oral administration of a combination of estrogen and progestin to monkeys fed a high-cholesterol, atherogenic diet decreased the extent of coronary atherosclerosis despite a reduction in HDL-cholesterol levels.[142–144] In somewhat similar experiments, estrogen treatment markedly prevented arterial lesion development in rabbits.[145–147] In considering the impact of progestational agents, lowering of HDL is not necessarily atherogenic if accompanied by a significant estrogen impact. These animal studies help explain why older, higher dose combinations, which had an adverse impact on the lipoprotein profile did not increase subsequent cardiovascular disease.[57, 60] The estrogen component provided protection through a direct effect on vessel walls, especially favorably influencing vasomotor and platelet factors such as nitric oxide and prostacyclin.

This conclusion is reinforced by angiographic and autopsy studies. Young women with myocardial infarctions who have used oral contraceptives have less diffuse atherosclerosis than nonusers.[148, 149] Indeed, a case-control study indicated that the risk of myocardial infarction in patients taking older, high-dose levonorgestrel-containing formulations is the same as that experienced with pills containing other progestins.[57] An analysis of the database in the Women's Health Initiative revealed a reduced risk of cardiovascular disease in postmenopausal women who had been previous users of oral contraceptives; a finding that should be viewed with some caution because the clinical trial was not designed to address this issue.[150]

In the past two decades, we have been subjected to considerable marketing hype about the importance of the impact of oral contraceptives on the

cholesterol-lipoprotein profile. If indeed certain oral contraceptives had a negative impact on the lipoprotein profile, one would expect to find evidence of atherosclerosis as a cause of an increase in subsequent cardiovascular disease. There is no such evidence. Thus, the mechanism of the cardiovascular complications is undoubtedly a short-term acute mechanism—thrombosis (an estrogen-related effect).

Hypertension

Oral contraceptive-induced hypertension was observed in approximately 5% of users of higher dose pills. More recent evidence indicates that small increases in blood pressure can be observed even with 30 μg estrogen, monophasic pills, including those containing the new progestins. However, an increased incidence of clinically significant hypertension has not been reported.[151–154] The lack of clinical hypertension in most studies may be due to the rarity of its occurrence. The Nurses' Health Study observed an increased risk of clinical hypertension in current users of low-dose oral contraceptives, providing an incidence of 41.5 cases per 10,000 women per year.[155] Therefore, an annual assessment of blood pressure is still an important element of clinical surveillance, even when low-dose oral contraceptives are used. Postmenopausal women in the Rancho Bernardo Study who had previously used oral contraceptives (probably high-dose products) had slightly higher (2–4 mm Hg) diastolic blood pressures.[156] Because past users do not demonstrate differences in incidence or risk factors for cardiovascular disease, it is unlikely this blood pressure difference has an important clinical effect.

Variables such as previous toxemia of pregnancy or previous renal disease do not predict whether a woman will develop hypertension on oral contraception.[157] Likewise, women who have developed hypertension on oral contraception are not more predisposed to develop toxemia of pregnancy. Overall, there is no evidence that previous oral contraceptive users have an increased risk of hypertension during a subsequent pregnancy.[158, 159] The exception is the Nurses' Health Study, which indicated that recent users for a long duration (8 or more years) have a 2-fold increased risk of preeclampsia, a finding that was based on a small number of cases.[160] These epidemiologic associations are hard to establish because of the role of underlying hypertension in pregnancy-induced hypertension and the difficulty in assessing the efficacy of hypertension screening in oral contraceptive users.

The mechanism for an effect on blood pressure is thought to involve the renin angiotensin system. The most consistent finding is a marked increase in plasma angiotensinogen, the renin substrate, up to 8 times normal values (on higher dose pills). In nearly all women, excessive vasoconstriction is prevented by a compensatory decrease in plasma

renin concentration. If hypertension does develop, the renin-angiotensinogen changes take 3–6 months to disappear after stopping combined oral contraception.

One must also consider the effects of oral contraceptives in patients with preexisting hypertension or cardiac disease. Women on oral contraceptives and with uncontrolled hypertension have an increased risk of arterial thrombosis.[121, 131, 132] Women with treated hypertension using oral contraceptives have been reported to have poor control of blood pressure with higher diastolic pressures.[161] In our view, with medical control of the blood pressure and close follow-up (at least every 3 months), the clinician and the nonsmoking patient who is under age 35 and otherwise healthy may choose low-dose oral contraception. Close follow-up is also indicated in women with a history of preexisting renal disease or a strong family history of hypertension or cardiovascular disease. It seems prudent to suggest that patients with marginal cardiac reserve should utilize other means of contraception. Significant increases in cardiac output and plasma volume have been recorded with oral contraceptive use (higher dose pills), probably a result of fluid retention.

Cardiovascular Disease — Summary

The outpouring of epidemiologic data in the last few years allows the construction of a clinical formulation that is evidence-based. The following conclusions are consistent with the recent reports.

SUMMARY: Oral Contraceptives and Thrombosis

- **Pharmacologic estrogen increases the production of clotting factors.**
- **Progestins have no significant impact on clotting factors.**
- **Past users of oral contraceptives do not have an increased incidence of cardiovascular disease.**
- **All low-dose oral contraceptives, regardless of progestin type, have an increased risk of venous thromboembolism, concentrated in the first 1–2 years of use. The actual risk of venous thrombosis with low-dose oral contraceptives is lower in the new studies compared with previous reports. Some have argued that this is due to preferential prescribing and the healthy user effect. However, it is also logical**

that the lower risk reflects better screening of patients and lower estrogen doses. The risk increases with increasing age and body weight.

•Smoking has a lesser effect on the risk of venous thrombosis compared with arterial thrombosis.

•Smoking and estrogen have an additive effect on the risk of arterial thrombosis. Why is there a difference between venous and arterial clotting? The venous system has low flow with a state of high fibrinogen and low platelets, in contrast to the high-flow state of the arterial system with low fibrinogen and high platelets. Thus, it is understandable why these two different systems can respond in different ways.

•Hypertension is a very important additive risk factor for stroke in oral contraceptive users.

•Low-dose oral contraceptives (less than 50 μg ethinyl estradiol) do not increase the risk of myocardial infarction or stroke in healthy, nonsmoking women, regardless of age.

•Almost all myocardial infarctions and strokes in oral contraceptive users occur in users of high-dose products, or users with cardiovascular risk factors over the age of 35. In the Oxford Family Planning Association cohort, cardiac deaths occurred only in women who smoked 15 or more cigarettes per day.[62]

•Arterial thrombosis (myocardial infarction and stroke) has a dose-response relationship with the dose of estrogen, but there are insufficient data to determine whether there is a difference in risk with products that contain 20, 30, or 35 μg ethinyl estradiol.

The recent studies reinforce the belief that the risks of arterial and venous thrombosis are a consequence of the estrogen component of combination oral contraceptives. Current evidence does not support an advantage or disadvantage for any particular formulation, except for the greater safety associated with any product containing less than 50 μg ethinyl estradiol. Although it is logical to expect the greatest safety with the lowest dose of

estrogen, the rare occurrence of arterial and venous thrombosis in healthy women makes it unlikely that there will be any measurable differences in the attributable incidence of clinical events with all low-dose products.

The new studies emphasize the importance of good patient screening. The occurrence of arterial thrombosis is essentially limited to older women who smoke or have cardiovascular risk factors, especially hypertension. The impact of good screening is evident in the repeated failure to detect an increase in mortality due to myocardial infarction or stroke in healthy, nonsmoking women.[62, 78, 122] Although the risk of venous thromboembolism is slightly increased, the actual incidence is still relatively rare, and the mortality rate is about 1% (probably less with oral contraceptives, because most deaths from thromboembolism are associated with trauma, surgery, or a major illness). The minimal risk of venous thrombosis associated with oral contraceptive use does not justify the cost of routine screening for coagulation deficiencies. Nevertheless, the importance of this issue is illustrated by the increased risk of a very rare event, cerebral sinus thrombosis, in women who have an inherited predisposition for clotting and use oral contraceptives.[36, 162]

If a patient has a close family history (parent or sibling) or a previous episode of idiopathic thromboembolism, an evaluation to search for an underlying abnormality in the coagulation system is warranted. It has been reported that family history of venous thromboembolism has low predictive value.[163] Another study indicated that testing for thrombophilia did not allow for prediction of recurrent events, but risk factors such as family history did provide prediction.[164] The conservative recommendation for a woman considering exposure to exogenous estrogen stimulation is to rule out an underlying thrombophilia. The following measurements are recommended, and abnormal results require consultation with a hematologist regarding prognosis and prophylactic treatment. The list of laboratory tests is long, and because this is a dynamic and changing field, the best advice is to consult with a hematologist. If a diagnosis of a congenital deficiency is made, screening should be offered to other family members.

HYPERCOAGUABLE CONDITIONS	THROMBOPHILIA SCREENING
Antithrombin III deficiency	Antithrombin III
Protein C deficiency	Protein C
Protein S deficiency	Protein S
Factor V Leiden mutation	Activated protein C resistance ratio
Prothrombin gene mutation	Activated partial thromboplastin time
Antiphospholipid syndrome	Hexagonal activated partial thromboplastin time
	Anticardiolipin antibodies
	Lupus anticoagulant
	Fibrinogen
	Prothrombin G mutation (DNA test)
	Thrombin time
	Homocysteine level
	Complete blood count

Combination oral contraception is contraindicated in women who have a history of idiopathic venous thromboembolism and in women who have a close family history (parent or sibling) of idiopathic venous thromboembolism. These women will have a higher incidence of congenital deficiencies in important clotting measurements, especially antithrombin III, protein C, protein S, and resistance to activated protein C.[165] Such a patient who screens negatively for an inherited clotting deficiency might still consider the use of oral contraceptives, but this would be a difficult decision with unknown risks for both patient and clinician, and it is more prudent to consider other contraceptive options. Other risk factors for thromboembolism that should be considered by clinicians include an acquired predisposition such as the presence of lupus anticoagulant or malignancy and immobility or trauma. Varicose veins are not a risk factor unless they are very extensive.[73]

The conclusion once again is that low-dose oral contraceptives are very safe for healthy, young women. By effectively screening for the presence of smoking and cardiovascular risk factors, especially hypertension, in older women, we can limit, if not eliminate, any increased risk for arterial disease associated with low-dose oral contraceptives. And it is very important to emphasize that there is no increased risk of cardiovascular events associated with duration of use (long-term). In large cohort studies, the risk of overall mortality comparing users and nonusers of oral contraceptives is identical.[60–62]

Carbohydrate Metabolism

With the older high-dose oral contraceptives, an impaired glucose tolerance test was present in many women. In these women, plasma levels of insulin as well as the blood sugar were elevated. Generally, the effect of oral contraception is to produce an increase in peripheral resistance to insulin action. Most women can meet this challenge by increasing insulin secretion, and there is no change in the glucose tolerance test, although 1-hour values may be slightly elevated.

Insulin sensitivity is affected mainly by the progestin component of the pill.[166] The derangement of carbohydrate metabolism may also be affected by estrogen influences on lipid metabolism, hepatic enzymes, and elevation of unbound cortisol. The glucose intolerance is dose-related, and once again effects are less with the low-dose formulations. ***Insulin and glucose changes with low-dose monophasic and multiphasic oral contraceptives are so minimal that it is now believed they are of no clinical significance.***[154, 167–170] This includes long-term evaluation with hemoglobin A1c.

The observed changes in studies of oral contraception and carbohydrate metabolism are in the nondiabetic range. To measure differences, investigators have resorted to analysis by measuring the area under the curve for glucose and insulin responses during glucose tolerance tests. A highly regarded cross-sectional study utilizing this technique reported that even lower dose formulations have detectable effects on insulin resistance.[166] The reason this is important is that it is now recognized that hyperinsulinemia due to insulin resistance is a contributor to cardiovascular disease. However, there are several critical questions that remain unanswered. Can the results from a cross-sectional study be duplicated in a study of sufficient size with patients serving as their own controls? Is a statistically significant hyperinsulinemia, detected in a study, clinically meaningful?

Because long-term, follow-up studies of large populations have failed to detect any increase in the incidence of diabetes mellitus or impaired glucose tolerance (even in past and current users of high-dose pills),[156, 171, 172] the concern now appropriately focuses on the slight impairment as a potential risk for cardiovascular disease. If slight hyperinsulinemia were meaningful, wouldn't you expect to see evidence of an increase in cardiovascular disease in past users who took oral contraceptives when doses were higher? As we have emphasized before, there is no such evidence. The data strongly indicate that the changes in lipids and carbohydrate metabolism that have been measured are not clinically meaningful.

It can be stated definitively that oral contraceptive use does not produce an increase in diabetes mellitus.[171–174] The hyperglycemia associated with oral

contraception is not deleterious and is completely reversible. Even women who have risk factors for diabetes in their history are not affected. In women with recent gestational diabetes, no significant impact on glucose tolerance could be demonstrated over 6–13 months comparing the use of low-dose monophasic and multiphasic oral contraceptives with a control group, and no increase in the risk of overt diabetes mellitus could be detected with long-term follow-up.[175, 176] A high percentage of women with previous gestational diabetes develop overt diabetes and associated vascular complications. Until overt diabetes develops, it is appropriate for these patients to use low-dose oral contraception.

In clinical practice, it may, at times, be necessary to prescribe oral contraception for the overt diabetic. No effect on insulin requirement is expected with low-dose pills.[177] According to the older epidemiologic data, the use of oral contraceptives increases the risk of thrombosis in women with insulin-dependent diabetes mellitus; therefore, women with diabetes have been encouraged to use other forms of contraception. However, this effect in women under age 35 who are otherwise healthy and nonsmokers is probably very minimal with low-dose oral contraception, and reliable protection against pregnancy is a benefit for these patients that outweighs the small risk. A case-control study could find no evidence that oral contraceptive use by young women with insulin-dependent diabetes mellitus increased the development of retinopathy or nephropathy.[178] In a 1-year study of women with insulin-dependent diabetes mellitus who were using a low-dose oral contraceptive, no deterioration could be documented in lipoprotein or hemostatic biochemical markers for cardiovascular risk.[179] And finally, no effect of oral contraceptives on cardiovascular mortality could be detected in a group of women with diabetes mellitus.[180]

The Liver

The liver is affected in more ways and with more regularity and intensity by the sex steroids than any other extragenital organ. Estrogen influences the synthesis of hepatic DNA and RNA, hepatic cell enzymes, serum enzymes formed in the liver, and plasma proteins. Estrogenic hormones also affect hepatic lipid and lipoprotein formation, the intermediary metabolism of carbohydrates, and intracellular enzyme activity. Nevertheless, an extensive analysis of the prospective cohorts of women in the Royal College of General Practitioners' Oral Contraception Study and the Oxford Family Planning Association Contraceptive Study could detect no evidence of an increased incidence or risk of serious liver disease among oral contraceptive users.[181]

The active transport of biliary components is impaired by estrogens as well as some progestins. The mechanism is unclear, but cholestatic jaundice and pruritus were occasional complications of higher dose oral contraception,

and are similar to the recurrent jaundice of pregnancy, i.e., benign and reversible. The incidence with lower dose oral contraception is unknown, but it must be a very rare occurrence.

The only absolute hepatic contraindication to oral contraceptive use is acute or chronic cholestatic liver disease. Cirrhosis and previous hepatitis are not aggravated. Once recovered from the acute phase of liver disease, a woman can use oral contraception.

Data from the Royal College of General Practitioners' prospective study indicated that an increase in the incidence of gallstones occurred in the first years of oral contraceptive use, apparently due to an acceleration of gallbladder disease in women already susceptible.[182] In other words, the overall risk of gallbladder disease was not increased, but in the first years of use, disease was activated or accelerated in women who were vulnerable because of asymptomatic disease or a tendency toward gallbladder disease. The mechanism appears to be induced alterations in the composition of gallbladder bile, specifically a rise in cholesterol saturation that is presumably an estrogen effect.[183] The Nurses' Health Study reported no significant increase in the risk of symptomatic gallstones among ever-users, but slightly elevated risks among current and long-term users.[184] Although oral contraceptive use has been linked to an increased risk of gallbladder disease, the epidemiologic evidence has been inconsistent. Indeed an Italian case-control study and a report from the Oxford Family Planning Association cohort found no increase in the risk of gallbladder disease in association with oral contraceptive use and no interaction with increasing age or body weight.[185, 186] Keep in mind that even though some studies found a statistically significant modest increase in the relative risk of gallbladder disease, even if the effect were real, it is of little clinical importance because the actual incidence of this problem is very low.

Liver Adenomas

Hepatocellular adenomas can be produced by steroids of both the estrogen and androgen families. Actually, there are several different lesions, peliosis, focal nodular hyperplasia, and adenomas. Peliosis is characterized by dilated vascular spaces without endothelial lining, and may occur in the absence of adenomatous changes. The adenomas are not malignant; their significance lies in the potential for hemorrhage. The most common presentation is acute right upper quadrant or epigastric pain. The tumors may be asymptomatic, or they may present suddenly with hematoperitoneum. There is some evidence that the tumors and focal nodular hyperplasia regress when oral contraception is stopped.[187, 188] Epidemiologic data have not supported the contention that mestranol increased the risk more than ethinyl estradiol.

The risk appears to be related to duration of oral contraceptive use and to the steroid dose in the pills. This is reinforced by the rarity of the condition ever since low-dose oral contraception became available. The ongoing prospective studies have accumulated many woman-years of use and have not identified an increased incidence of such tumors.[181] In a collaborative study of 15 German liver centers, no increase in risk for liver adenomas in contemporary oral contraceptive users could be detected.[189] An Italian case-control study found an increase in risk for focal nodular hyperplasia associated with low-dose oral contraceptives, a risk that reached statistical significance only with 3 or more years of use (with a very wide confidence interval because of only 13 cases).[190] In our view it is not even worth mentioning during the informed consent (choice) process.

No reliable screening test or procedure is currently available. Routine liver function tests are normal. Computed tomography (CT) scanning or magnetic resonance imaging (MRI) is the best means of diagnosis; angiography and ultrasonography are not reliable. Palpation of the liver should be part of the periodic evaluation in oral contraceptive users. If an enlarged liver is found, oral contraception should be stopped, and regression should be evaluated and followed by imaging.

Other Metabolic Effects

Nausea and breast discomfort continue to be disturbing effects, but their incidence is significantly less with low-dose oral contraception. Fortunately, these effects are most intense in the first few months of use and, in most cases, gradually disappear. In placebo-controlled trials with low-dose oral contraceptives, the incidence of "minor" side effects such as headache, nausea, dysmenorrhea, and breast discomfort actually occurred at the same rate in the treated group and the placebo group![191–193]

Weight gain usually responds to dietary restriction, but for some patients, the weight gain is an anabolic response to the sex steroids, and discontinuation of oral contraception is the only way that weight loss can be achieved. This must be rare with low-dose oral contraception because data in published studies, especially in placebo-controlled trials, fail to indicate a difference in body weight between users and nonusers.[193–201]

There is no association between oral contraception and peptic ulcer disease or inflammatory bowel disease.[202, 203] Oral contraception is not recommended for patients with problems of gastrointestinal malabsorption because of the possibility of contraceptive failure.

Chloasma, a patchy increase in facial pigment, was, at one time, found to occur in approximately 5% of oral contraceptive users. It is now a rare problem due to the decrease in estrogen dose. Unfortunately, once chloasma

appears, it fades only gradually following discontinuation of the pill and may never disappear completely. Skin-blanching medications may be useful.

Hematologic effects include an increased sedimentation rate, increased total iron-binding capacity due to the increase in globulins, and a decrease in prothrombin time. The use of oral contraceptives results in a decrease in iron deficiency anemia because of a reduction in menstrual bleeding.[204, 205] Indeed, in anemic women, an increase in hemoglobin and ferritin levels accompanies the use of oral contraceptives.[206]

The continuous, daily use of oral contraceptives may prevent the appearance of symptoms in porphyria precipitated by menses. Changes in vitamin metabolism have been noted: a small nonharmful increase in vitamin A and decreases in blood levels of pyridoxine (B6) and the other B vitamins, folic acid, and ascorbic acid. Despite these changes, routine vitamin supplements are not necessary for women eating adequate, normal diets.[207]

Mental depression is very rarely associated with oral contraceptives. In studies with higher dose oral contraceptives, the effect was due to estrogen interference with the synthesis of tryptophan that could be reversed with pyridoxine treatment. It seems wiser, however, to discontinue oral contraception if depression is encountered. Though infrequent, a reduction in libido is occasionally a problem and may be a cause for seeking an alternative method of contraception.

Adverse androgenic voice changes were occasionally encountered with the use of the first very high-dose oral contraceptives. Vocal virilization can be a serious and devastating problem for some women, especially when vocal performance is important. Careful study of women on low-dose oral contraceptives indicates that this is no longer a side effect of concern.[208]

The Risk of Cancer

Endometrial Cancer

The use of oral contraception protects against endometrial cancer. Use for at least 12 months reduces the risk of developing endometrial cancer by **50%**, with the greatest protective effect gained by use for more than 3 years.[209–214] This protection persists for 20 or more years after discontinuation (the actual length of duration of protection is unknown) and is greatest in women at highest risk: nulliparous and low parity women.[214, 215] This protection is equally protective for all 3 major histologic subtypes of endometrial cancer: adenocarcinoma, adenoacanthoma, and adenosquamous cancers. Finally, protection is seen with all monophasic formulations of oral contraceptives, including pills with less than 50 μg estrogen.[209, 211, 214, 216] There are no data as yet with multiphasic preparations or the new progestin formulations, but

because these products are still dominated by their progestational component, there is every reason to believe that they will be protective.

Ovarian Cancer

Protection against ovarian cancer, the most lethal of female reproductive tract cancers, is one of the most important benefits of oral contraception. Because this cancer is detected late and prognosis is poor, the impact of this protection is very significant. Indeed, a decline in mortality from ovarian cancer has been observed in several countries since the early 1970s, perhaps an effect of oral contraceptive use.[217] Cohorts of women with increased exposure to oral contraceptives have demonstrated a marked decrease in the incidence of ovarian cancer.[218–220] The risk of developing epithelial ovarian cancer of all histologic subtypes in users of oral contraception is reduced by **40%** compared with that of nonusers.[211, 213, 221–226] This protective effect increases with duration of use and continues for 20 or more years after stopping the medication. This protection is seen in women who use oral contraception for as little as 3 to 6 months (although at least 3 years of use are required for a notable impact), reaching an 80% reduction in risk with more than 10 years of use, and is a benefit associated with all monophasic formulations, including the low-dose products.[225–227] The protective effect of oral contraceptives is especially observed in women at high risk of ovarian cancer (nulliparous women and women with a positive family history).[228, 229] Continuous use of oral contraception for 10 years by women with a positive family history for ovarian cancer can reduce the risk of epithelial ovarian cancer to a level equal to or less than that experienced by women with a negative family history.[228] Again, the multiphasic and new progestin products have not been in use long enough to yield any data on this issue, but because ovulation is effectively inhibited by these formulations, protection against ovarian cancer should be exerted. The same magnitude of protection has been observed in one case-control study of women with BRCA1 or BRCA2 mutations but not in another.[230, 231]

Case-control studies have indicated that a reduced risk of ovarian cancer is not only associated with oral contraception but also tubal sterilization, IUDs, and barrier methods (but only in multigravid women).[232] The mechanisms and biologic plausibility for this impact are certainly a puzzle.

Cancer of the Cervix

Studies have indicated that the risk for dysplasia and carcinoma in situ of the uterine cervix increases with the use of oral contraception for more than 1 year.[233–238] Invasive cervical cancer may be increased after 5 years of use, reaching a 2-fold increase after 10 years. It is well recognized, however, that the number of partners a woman has had and age at first coitus are the most important risk factors for cervical neoplasia. Other

confounding factors include exposure to human papillomavirus, the use of barrier contraception (protective), and smoking. These are difficult factors to control, and, therefore, the conclusions regarding cervical cancer are not definitive. An excellent study from the Centers for Disease Control and Prevention (CDC) concluded there is no increased risk of invasive cervical cancer in users of oral contraception, and an apparent increased risk of carcinoma in situ is due to enhanced detection of disease (because oral contraceptive users have more frequent Pap smears).[236] In the World Health Organization Study of Neoplasia and Steroid Contraceptives, a Pap smear screening bias was identified, nevertheless the evidence still suggested an increased risk of cervical carcinoma in situ with long-term oral contraceptive use.[237]

A case-control study of patients in Panama, Costa Rica, Colombia, and Mexico concluded that there was a significantly increased risk for invasive adenocarcinoma.[239] Similar results were obtained in a case-control study in Los Angeles and in the World Health Organization Collaborative Study.[240, 241] In Los Angeles, the relative risk of adenocarcinoma of the cervix increased from 2.1 with ever use to 4.4 with 12 or more years of oral contraceptive use.[240] Because the incidence of adenocarcinoma of the cervix (10% of all cervical cancers) has increased in young women over the last 20 years, there is concern that this increase reflects the use of oral contraception.[242] Oral contraceptives increase cervical ectopia, but whether this increases the risk of cervical adenocarcinoma is unclear.

A large meta-analysis concluded that the relative risk of cervical cancer increased with increasing duration of use (for in situ and invasive cancer and both squamous cancer and adenocarcinoma); however, the risk was confined to the cases who tested positively for human papillomavirus (HPV).[243] A pooled analysis of case-control studies concluded that the risk of cervical cancer in women with HPV increases about 3-fold but not until after 5 years of use.[244] This obviously is an important reason for annual Pap smear surveillance. The liquid-based methods along with HPV DNA testing will provide even better identification of at-risk women. Fortunately, steroid contraception does not mask abnormal cervical changes, and the necessity for prescription renewals offers the opportunity for improved screening for cervical disease. It is reasonable to perform Pap smears every 6 months in women using oral contraception for 5 or more years who are also at higher risk because of their sexual behavior (multiple partners, history of sexually transmitted infections). Oral contraceptive use is appropriate for women with a history of cervical intraepithelial neoplasia (CIN), including those who have been surgically treated.

Liver Cancer

Oral contraception has been linked to the development of hepatocellular carcinoma.[245, 246] However, the very small number of cases, and, thus, the limited statistical power, requires great caution in interpretation. The largest study on this question, the WHO Collaborative Study of Neoplasia and Steroid Contraceptives, found no association between oral contraception and liver cancer.[247] Even case-control analysis of oral contraceptives containing cyproterone acetate (known to be toxic to the liver in high doses) could detect no evidence of an increased risk of liver cancer.[248] In the United States, Japan, Sweden, England, and Wales, the death rates from liver cancer did not change despite introduction and use of oral contraception.[249, 250] More recently, there has been an increase in liver cancer incidence and mortality in the United States, but this is believed to be due to infection with hepatitis C and hepatitis B.[251]

Breast Cancer

Because of breast cancer's prevalence and its long latent phase, concern over the relationship between oral contraception and breast cancer continues to be an issue in the minds of both patients and clinicians. Worth emphasizing is the protective effect of higher dose oral contraception on benign breast disease, an effect that became apparent after 2 years of use.[252–254] After 2 years there was a progressive reduction (about 40%) in the incidence of fibrocystic changes in the breast. Women who used oral contraception were one-fourth as likely to develop benign breast disease as nonusers, but this protection was limited to current and recent users. It is still uncertain whether this same protection is provided by the lower dose products. A French case-control study indicated a reduction of nonproliferative benign breast disease associated with low-dose oral contraceptives used before a first full-term pregnancy, but no effect on proliferative disease or with use after a pregnancy.[255] A Canadian cohort study that almost certainly reflected the use of modern low-dose oral contraceptives concluded that oral contraceptives do protect against proliferative benign disease, with an increasing reduction in risk with increasing duration of use.[256]

The Royal College of General Practitioners,[257] Oxford Family Planning Association,[258, 259] the Nurses' Health Study,[260] and Walnut Creek[261] cohort studies indicated no significant differences in breast cancer rates between users and nonusers. However, patients were enrolled in these studies at a time when oral contraception was used primarily by married couples spacing out their children. Beginning in the 1980s, oral contraception was primarily being used by women early in life, for longer durations, and to delay an initial pregnancy (remember, a full-term pregnancy early in life protects against breast cancer).

Case-control studies have focused on the use of oral contraception early in life, for long duration, and to delay a first, full-term pregnancy. Because the women who have used oral contraception in this fashion are just now beginning to reach the ages of postmenopausal breast cancer, many studies have had to focus on the risk of breast cancer diagnosed before age 45 (only 13% of all breast cancer). The results of these studies have not been clear-cut. Some studies have indicated an overall increased relative risk of early, premenopausal breast cancer,[262–270] whereas others indicated no increase in overall risk.[271–273] The most impressive finding indicates a link in most studies,[274–279] but not all,[280–284] of early breast cancer before age 40 with women who used oral contraception for long durations of time.

A collaborative group re-analyzed data from 54 studies in 26 countries, a total of 53,287 women with breast cancer and 100,239 without breast cancer, to assess the relationship between the risk of breast cancer and the use of oral contraceptives.[285, 286] Oral contraceptives were grouped into 3 categories: low, medium, and high dose (which correlated with less than 50 μg, 50 μg, and more than 50 μg of estrogen, respectively). At the time of diagnosis, 9% of the women with breast cancer were under age 35, 25% were 35–44, 33% were 45–54, and 33% were age 55 and older. A similar percentage of women with breast cancer (41%) and women without breast cancer (40%) had used combined oral contraceptives at some time in their lives. Overall, the relative risk (RR) of breast cancer in ever users of oral contraceptives was very slightly elevated and statistically significant: RR = 1.07; CI = 1.03–1.10.

The relative risk analyzed by duration of use was barely elevated and not statistically significant (even when long-term use, virtually continuous, was analyzed). Women who had begun use as teenagers had about a 20% statistically significant increased relative risk. In other words, recent users who began use before age 20 had a higher relative risk compared with recent users who began at later ages. The evidence was strong for a relationship with time since last use, an elevated risk being significant for current users and in women who had stopped use 1–4 years before (recent use). No influence on this risk was observed with the following: a family history of breast cancer, age of menarche, country of origin, ethnic groups, body weight, alcohol use, years of education, and the design of the study. There was no variation according to specific type of estrogen or progestin in the various products. Importantly, there was no statistically significant effect of low-, medium-, or high-dose preparations. Ten or more years after stopping use, there was no increased risk of breast cancer. Indeed, the risk of metastatic disease compared with localized tumors was reduced: RR = 0.88; CI = 0.81–0.95.

Oral Contraceptives and the Risk of Breast Cancer Re-analysis of the World's Data[252]

Current users	RR = 1.24, 95% CI = 1.15–1.33
1–4 years after stopping	RR = 1.16, 95% CI = 1.08–1.23
5–9 years after stopping	RR = 1.07, 95% CI = 1.02–1.13

Data were limited for progestin-only methods. The reanalysis indicated that the results were similar to those with combined oral contraceptives, but a close look at the numbers reveals that not one relative risk reached statistical significance.

Overall, this massive statistical exercise yielded good news. No major adverse impact of oral contraceptives emerged. ***Even though the data indicated that young women who begin use before age 20 have higher relative risks of breast cancer during current use and in the 5 years after stopping, this is a time period when breast cancer is very rare; and, thus, there would be little impact on the actual number of breast cancers.*** The difference between localized disease and metastatic disease was statistically greater and should be observable. Thus many years after stopping oral contraceptive use, the main effect may be protection against metastatic disease. Breast cancer is more common in older years, and 10 or more years after stopping, the risk was not increased.

What other explanation could account for an increased risk associated only with current or recent use, no increase with duration of use, and a return to normal 10 years after exposure? The slightly increased risk could be influenced by detection/surveillance bias (more interaction with the health care system by oral contraceptive users). It is also possible that this situation is analogous to that of pregnancy. Recent studies indicate that pregnancy transiently increases the risk of breast cancer (for a period of several years) after a woman's first childbirth, and this is followed by a lifetime reduction in risk.[287] And some have found that a concurrent or recent pregnancy adversely affects survival.[288, 289] It is argued that breast cells that have already begun malignant transformation are adversely affected by the hormones of pregnancy, while normal stem cells become more resistant because of a pregnancy. It is possible that early and recent use of oral contraceptives also affects the growth of a preexisting malignancy, explaining the limitation of the finding to current and recent use and the increase in localized disease. With the accumulation of greater numbers of older women previously exposed to oral contraceptives, a protective effect may become evident. In a case-control study of women

in Toronto, Canada, age 40–69 years, those women who had used oral contraceptives for 5 or more years, 15 or more years previously, had a 50% reduced risk of breast cancer.[290] However, a case-control study from Sweden could detect neither a beneficial nor an adverse effect of previous use of oral contraceptives (mainly 50 μg estrogen products) on the risk of breast cancer in women age 50–74 years.[291]

The largest case-control study included 4,575 American women with breast cancer, and most importantly, the women were 35 to 64 years old.[292] The risk of breast cancer was not increased in current users or past users of oral contraception. There was no adverse effect of increasing duration of use or higher doses of estrogen, with no differences in current or recent users. Initiation at a younger age had no impact, and there was no increase in risk in women with a family history of breast cancer. This large American study had consistently negative results. An analysis of the large database in the Women's Health Initiative concluded that postmenopausal women who were past users of oral contraceptives did not have an increased risk of breast cancer.[293]

A cohort study from Minnesota concluded that women with a first-degree relative with breast cancer had an increased risk of breast cancer with oral contraception; however, this association was present only with oral contraceptives used prior to 1976 (high-dose formulations), and the confidence intervals were wide because of small numbers (13 ever users).[294] In a study of women with BRCA1 and BRCA2 mutations, an elevated risk of breast cancer associated with oral contraception was based on only a few cases and did not achieve statistical significance.[295] A larger case-control study concluded that BRCA1 mutation carriers had small increases in the risk of breast cancer in users for at least 5 years (OR = 1.33, CI = 1.11–1.60), in users before age 30 (OR = 1.29, CI = 1.09–1.52), and in those who developed breast cancer before age 40 (OR = 1.38, CI = 1.11–1.72).[296]

Conclusion

Adding up the benefits of oral contraception, the possible slight increase in risk of breast cancer in young current users is far outweighed by positive effects on our public health. But the impact on public health is of little concern during the private clinician–patient interchange in the office. Here personal risk receives highest priority; fear of cancer is a motivating force, and compliance with effective contraception requires accurate information. For these reasons, we provide the following summary of our assessment of the impact of oral contraceptives on the risk of breast cancer.

SUMMARY: Oral Contraceptives and the Risk of Breast Cancer

- Current and recent use of oral contraceptives may be associated with about a 20% increased risk of early (under age 35) premenopausal breast cancer, essentially limited to localized disease and a very small increase in the actual number of cases (so small, there would be no major impact on incidence figures). This finding may be due to detection/surveillance bias and accelerated growth of already present malignancies, a situation similar to the effects of pregnancy and postmenopausal hormone therapy on the risk of breast cancer. Further comfort can be derived from the fact that the increase in breast cancer in American women was greater in older women from 1973 to 1994, those who did not have the opportunity to use oral contraception.[297] In women under 50 years of age, there was only a slight increase during this same time period. The large American case-control study of women age 35–64 years was totally negative and very reassuring.

- There is no effect of past use or duration of oral contraceptive use (up to 15 years of continuous use) on the risk of breast cancer, and there is no evidence indicating that higher dose oral contraceptives increased the risk of breast cancer.

- Previous oral contraceptive use may be associated with a reduced risk of metastatic breast cancer later in life and possibly with a reduced risk of postmenopausal breast cancer.

- Oral contraceptive use does not further increase the risk of breast cancer in women with positive family histories of breast cancer or in women with proven benign breast disease.

- The clinician should not fail to take every opportunity to direct attention to all factors that affect breast cancer. Breastfeeding and control of alcohol intake are good examples and are components of preventive health care. Especially important is this added motivation to encourage breastfeeding. The protective effect of breast feeding is exerted mainly on premenopausal breast cancer, the cancer of concern to younger women using oral contraception.

Other Cancers

The Walnut Creek study suggested that melanoma was linked to oral contraception; however, the major risk factor for melanoma is exposure to sunlight. More recent and accurate evaluation utilizing both the Royal College General Practitioners and Oxford Family Planning Association prospective cohorts and accounting for exposure to sunlight did not indicate a significant difference in the risk of melanoma comparing users to nonusers.[298,299] There is no evidence linking oral contraceptive use to kidney cancer, gallbladder cancer, or pituitary tumors.[300] Long-term oral contraceptive use may slightly increase the risk of molar pregnancy.[301-303] A case-control study concluded that oral contraceptives reduce the risk of salivary gland cancer.[304] Although previous studies have not been in agreement, the Nurses' Health Study reported about a 40% reduced risk of colorectal cancer associated with 8 years of previous use of oral contraceptives (most likely higher dose products).[305] A meta-analysis of published studies concluded that there is about a 20% reduction in risk of colorectal cancer in users of oral contraception, with a stronger effect in recent users.[306]

Endocrine Effects

Adrenal Gland

Estrogen increases the cortisol-binding globulin (CBG). It had been thought that the increase in plasma cortisol while on oral contraception was due to increased binding by this globulin and not an increase in free active cortisol. Now it is apparent that free and active cortisol levels are also elevated but only slightly.[307] Estrogen decreases the ability of the liver to metabolize cortisol, and in addition, progesterone and related compounds can displace cortisol from transcortin, and thus contribute to the elevation of unbound cortisol. The effects of these elevated levels over prolonged periods of time are unknown, but no obvious impact has become apparent. To put this into perspective, the increase is not as great as that which occurs in pregnancy, and, in fact, it is within the normal range for nonpregnant women.

The adrenal gland responds to adrenocorticotropic hormone (ACTH) normally in women on oral contraceptives; therefore, there is no suppression of the adrenal gland itself. Initial studies indicated that the response to metyrapone (an 11β-hydroxylase blocker) was abnormal, suggesting that the pituitary was suppressed. However, estrogen accelerates the conjugation of metyrapone by the liver; and, therefore, the drug has less effect, thus explaining the subnormal responses initially reported. The pituitary-adrenal reaction to stress is normal in women on oral contraceptive pills.

Thyroid

Estrogen increases the synthesis and circulating levels of thyroxine-binding globulin, Prior to the introduction of new methods for measuring free thyroxine levels, evaluation of thyroid function was a problem. Measurement of TSH (thyroid-stimulating hormone) and the free thyroxine level in a woman on oral contraception provide an accurate assessment of a patient's thyroid state. Oral contraception affects the total thyroxine level in the blood as well as the amount of binding globulin, but the free thyroxine level is unchanged.[307]

Oral Contraception and Reproduction

The impact of oral contraceptives on the reproductive system is less than initially thought. Early studies that indicated adverse effects have not stood the test of time and the scrutiny of multiple, careful studies. There are two major areas that warrant review: (1) inadvertent use of oral contraceptives during the cycle of conception and during early pregnancy, and (2) reproduction after discontinuing oral contraception.

Inadvertent Use during the Cycle of Conception and during Early Pregnancy

One of the reasons, if not the major reason, why a lack of withdrawal bleeding while using oral contraceptives is such a problem is the anxiety produced in both patient and clinician. The patient is anxious because of the uncertainty regarding pregnancy, and the clinician is anxious because of the concerns stemming from the retrospective studies that indicated an increased risk of congenital malformations among the offspring of women who were pregnant and using oral contraception. Organogenesis does not occur in the first 2 embryonic weeks (first 4 weeks since last menstrual period); however, teratogenic effects are possible between the third and eighth embryonic weeks (5 to 10 weeks since last menstrual period).

Initial positive reports linking the use of contraceptive steroids to congenital malformations have not been substantiated. Many suspect a strong component of recall bias in the few positive studies due to a tendency of patients with malformed infants to recall details better than those with normal children. Other confounding problems have included a failure to consider the reasons for the administration of hormones (e.g., bleeding in an already abnormal pregnancy) and a failure to delineate the exact timing of the treatment (e.g., treatment was sometimes confined to a period of time during which the heart could not have been affected).

An association with cardiac anomalies was first claimed in the 1970s.[308, 309] This link received considerable support with a report from the U.S. Collaborative Perinatal Project; however, subsequent analysis of these data

uncovered several methodologic shortcomings.[310] Simpson and Phillips, in a very thorough and critical review in 1990, concluded that there was no reliable evidence implicating sex steroids as cardiac teratogens.[311] In fact, in their review, Simpson and Phillips found no relationship between oral contraception and the following problems: hypospadias, limb reduction anomalies, neural tube defects, and mutagenic effects that would be responsible for chromosomally abnormal fetuses. Even virilization is not a practical consideration because the doses required (e.g., 20–40 mg norethindrone per day) are in excess of anything currently used. These conclusions reflect use of combined oral contraceptives as well as progestins alone.

In the past there was a concern regarding the VACTERL complex. VACTERL refers to a complex of vertebral, anal, cardiac, tracheoesophageal, renal, and limb anomalies. While case-control studies indicated a relationship with oral contraception, prospective studies have failed to observe any connection between sex steroids and the VACTERL complex.[312] Meta-analyses of the studies of the risk of birth defects with oral contraceptive ingestion during pregnancy concluded that there was no increase in risk for major malformations, congenital heart defects, or limb reduction defects.[313, 314]

Women who become pregnant while taking oral contraceptives or women who inadvertently take birth control pills early in pregnancy should be advised that the risk of a significant congenital anomaly is no greater than the general rate of 2–3%. This recommendation can be extended to those pregnant woman who have been exposed to a progestational agent such as medroxyprogesterone acetate or 17-hydroxyprogesterone caproate.[315, 316]

Reproduction after Discontinuing Oral Contraception

Fertility

The early reports from the British prospective studies indicated that former users of oral contraception had a delay in achieving pregnancy. In the Oxford Family Planning Association study, former use had an effect on fertility for up to 42 months in nulligravida women and for up to 30 months in multigravida women.[317] Presumably, the delay is due to lingering suppression of the hypothalamic-pituitary reproductive system.

A later analysis of the Oxford data indicated that the delay was concentrated in women age 30–34 who had never given birth.[318] At 48 months, 82% of these women had given birth compared with 89% of users of other contraceptive methods, not a big difference. No effect was observed in women younger than 30 or in women who had previously given birth. Childless women age 25–29 experienced some delay in return to fertility, but by 48 months, 91% had given birth compared with 92% in users of

other methods. After 72 months the proportions of women who remained undelivered were the same in both groups of women.

This delay has been observed in the United States as well. In the Boston area, the interval from cessation of contraception to conception was 13 months or greater for 24.8% of prior oral contraceptive users compared with 10.6% for former users of all other methods (12.4% for intrauterine device, IUD, users, 8.5% for diaphragm uses, and 11.9% for other methods).[319] Oral contraceptive users had a lower monthly percentage of conceptions for the first 3 months, and somewhat lower percentage from 4 to 10 months. It took 24 months for 90% of previous oral contraceptive users to become pregnant, 14 months for IUD users, and 10 months for diaphragm users. Similar findings in Connecticut indicate that this delay lasts at least a year, and the effect is greater with higher dose preparations.[320] Despite this delay, there is no evidence that infertility is increased by the use of oral contraception. In fact, in young women, previous oral contraceptive use is associated with a lower risk of primary infertility.[321] Furthermore, the studies indicating a delay in conception are influenced by older, higher dose products. In a prospective study from the United Kingdom reflecting modern, low-dose oral contraceptives, no delay to conception was found and long-term use was actually associated with greater fertility.[322]

Spontaneous Miscarriage

There is no increase in the incidence of spontaneous miscarriage in pregnancies after the cessation of oral contraception. Indeed, the rate of spontaneous miscarriages and stillbirths is slightly less in former pill users, about 1% less for spontaneous miscarriages and 0.3% less for stillbirths.[323] A protective effect of previous oral contraceptive use against spontaneous miscarriage has been observed to be more apparent in women who become pregnant after age 30.[324]

Pregnancy Outcome

There is no evidence that oral contraceptives cause changes in individual germ cells that would yield an abnormal child at a later time.[311] There is no increase in the number of abnormal children born to former oral contraceptive users, and there is no change in the sex ratio (a sign of sex-linked recessive mutations).[323,325] These observations are not altered when analyzed for duration of use. Initial observations that women who had previously used oral contraception had an increase in chromosomally abnormal fetuses have not been confirmed. Furthermore, as noted above, there is no increase in the miscarriage rate after discontinuation, something one would expect if oral contraceptives induce chromosomal abnormalities because these are the principal cause of spontaneous miscarriage.

In a 3-year follow-up of children whose mothers used oral contraceptives prior to conception, no differences could be detected in weight, anemia, intelligence, or development.[326] Former pill users have no increased risks for the following: perinatal morbidity or mortality, prematurity, and low birth weight.[327,328] Dizygous twinning has been observed to be nearly 2-fold (1.6% versus 1.0%) increased in women who conceive soon after cessation of oral contraception.[323] This effect was greater with longer duration of use.

The only reason (and it is a good one) to recommend that women defer attempts to conceive for a month or two after stopping the pill is to improve the accuracy of gestational dating by allowing accurate identification of the last menstrual period.

Breastfeeding

Oral contraception has been demonstrated to diminish the quantity and quality of lactation in postpartum women. Also of concern is the potential hazard of transfer of contraceptive steroids to the infant (a significant amount of the progestational component is transferred into breast milk);[329] however, no adverse effects have thus far been identified. Women who use oral contraception have a lower incidence of breastfeeding after the sixth postpartum month, regardless of whether oral contraception is started at the first, second, or third postpartum month.[330–332]

In adequately nourished breastfeeding women, no impairment of infant growth can be detected; presumably, compensation is achieved either through supplementary feedings or increased suckling.[333–335] In an 8-year follow-up study of children breastfed by mothers using oral contraceptives, no effect could be detected on diseases, intelligence, or psychological behavior.[336] This study also found that mothers on birth control pills lactated a significantly shorter period of time than controls, a mean of 3.7 months versus 4.6 months in controls.

Because the above considerations indicate that oral contraception shortens the duration of breastfeeding, it is worthwhile to consider the contraceptive effectiveness of lactation. The contraceptive effectiveness of lactation, i.e., the length of the interval between births, depends on the level of nutrition of the mother (if low, the longer the contraceptive interval), the intensity of suckling, and the extent to which supplemental food is added to the infant diet. If suckling intensity and/or frequency is diminished, contraceptive effect is reduced. Only amenorrheic women who exclusively breastfeed (full breastfeeding) at regular intervals, including nighttime, during the first 6 months have the contraceptive protection equivalent to that provided by oral contraception (98% efficacy); with menstruation or after 6 months, the chance of ovulation

increases.[337, 338] With full or nearly full breastfeeding, approximately 70% of women remain amenorrheic through 6 months and only 37% through 1 year; nevertheless with exclusive breastfeeding, the contraceptive efficacy at 1 year is high, at 92%.[338] Fully breastfeeding women commonly have some vaginal bleeding or spotting in the first 8 postpartum weeks, but this bleeding is not due to ovulation.[339]

Supplemental feeding increases the chance of ovulation (and pregnancy) even in amenorrheic women.[340] Total protection is achieved by the exclusively breastfeeding woman for a duration of only 10 weeks.[339] Half of women studied who are not fully breastfeeding ovulate before the 6th week, the time of the traditional postpartum visit; a visit during the 3rd postpartum week is strongly recommended for contraceptive counseling.

It is apparent that although lactation provides a contraceptive effect, it is variable and not reliable for every woman. Furthermore, because frequent suckling is required to maintain full milk production, women who use oral contraception and who breastfeed less frequently (e.g., because they work outside their home) have two reasons for decreased milk volume. This combination can make it especially difficult to continue nursing.

Initiation of Oral Contraception in the Postpartum Period

The individual woman is in need of contraception early in the postpartum period. In a careful study of 22 postpartum, nonbreastfeeding women, the mean time from delivery to the first menses was 45 ± 10.1 days, and no woman ovulated before 25 days after delivery.[341] A high proportion of the first cycles (81.8%) and the subsequent cycles (37%) were not normal; however, this is certainly not predictable in individual women. Others have documented a mean delay of 7 weeks before resumption of ovulation, but half of the women studied ovulated before the sixth week, the time of the traditional postpartum visit. The obstetrical tradition of scheduling the postpartum visit at 6 weeks should be changed. A 3-week visit would be more productive in avoiding postpartum surprises.

The Rule of 3's:

In the presence of FULL breastfeeding, a contraceptive method should be used beginning in the *3rd postpartum month.*

With PARTIAL breastfeeding or NO breastfeeding, a contraceptive method should begin during the *3rd postpartum week.*

After the termination of a pregnancy of less than 12 weeks, oral contraception can be started immediately. After a pregnancy of 12 or more weeks, oral contraception has traditionally been started 2 weeks after delivery to avoid an increased risk of thrombosis during the initial postpartum period. We believe that oral contraception can be started immediately after a second-trimester abortion or premature delivery.

Because of the concerns regarding the impact of oral contraceptives on breastfeeding, a useful alternative is to combine the contraceptive effect of lactation with the progestin-only minipill. This low dose of progestin has no negative impact on breast milk, and some studies document an increase in milk quantity and nutritional quality.[342] Highly effective (near total) protection can be achieved with the combination of lactation and the minipill. Because of the slight positive impact on lactation, the minipill can be started immediately after delivery.[343] Use of the progestin-only minipill has been reported to be associated with a 3-fold increased risk of diabetes mellitus in overweight, lactating, Latina women with recent gestational diabetes.[176] Women who have experienced gestational diabetes should consider other methods of contraception.

Other Considerations

Prolactin-Secreting Adenomas

Because estrogen is known to stimulate prolactin secretion and to cause hypertrophy of the pituitary lactotrophs, it is appropriate to be concerned over a possible relationship between oral contraception and prolactin-secreting adenomas. Case-control studies have uniformly concluded that no such relationship exists.[344, 345] Data from both the Royal College of General Practitioners and the Oxford Family Planning Association studies indicated no increase in the incidence of pituitary adenomas.[300, 346] Previous use of oral contraceptives is not related to the size of prolactinomas at presentation and diagnosis.[346, 347] Oral contraception can be prescribed to patients with pituitary microadenomas without fear of subsequent tumor growth.[348, 349] ***We have routinely prescribed oral contraception to patients with pituitary microadenomas and have never observed evidence of tumor growth.***

Postpill Amenorrhea

The approximate incidence of "postpill amenorrhea" is 0.7–0.8%, which is equal to the incidence of spontaneous secondary amenorrhea,[328, 350, 351] and there is no evidence to support the idea that oral contraception causes secondary amenorrhea. If a cause-and-effect relationship exists between oral contraception and subsequent amenorrhea, one would expect the incidence of infertility to be increased after a given population discontinues use of oral contraception. In those women who discontinue oral contra-

ception in order to get pregnant, 50% conceive by 3 months, and after 2 years, a maximum of 15% of nulliparous women and 7% of parous women fail to conceive,[328] rates comparable with those quoted for the prevalence of spontaneous infertility. Attempts to document a cause-and-effect relationship between oral contraceptive use and secondary amenorrhea have failed.[352] Although patients with this problem come more quickly to our attention because of previous oral contraceptive use and follow-up, there is no cause-and-effect relationship. Women who have not resumed menstrual function within 12 months should be evaluated as any other patient with secondary amenorrhea.

Use During Puberty

Should oral contraception be advised for a young woman with irregular menses and oligo-ovulation or anovulation? The fear of subsequent infertility should not be a deterrent to providing appropriate contraception. Women who have irregular menstrual periods are more likely to develop secondary amenorrhea whether they use oral contraception or not. The possibility of subsequent secondary amenorrhea is less of a risk and a less urgent problem for a young woman than leaving her unprotected. The need for contraception takes precedence.

There is no evidence that the use of oral contraceptives in the pubertal, sexually active girl impairs growth and development of the reproductive system.[321] Again, the most important concern is and should be the prevention of an unwanted pregnancy. For most teenagers, oral contraception, dispensed in the 28-day package for better compliance, is the contraceptive method of choice; however, even better compliance can be achieved with the vaginal and transdermal methods of estrogen-progestin contraception (Chapter 4).

Eye and Ear Diseases

In the 1960s and 1970s, there were numerous anecdotal reports of eye disorders in women using oral contraception. An analysis of the two large British cohort studies (the Royal College of General Practitioners' Study and the Oxford Family Planning Association Study) could find no increase in risk for the following conditions: conjunctivitis, keratitis, iritis, lacrimal disease, strabismus, cataract, glaucoma, and retinal detachment.[353] Retinal vascular lesions were slightly more common in recent users of oral contraception, but this finding did not reach statistical significance. Contact lens may be less well tolerated, requiring more frequent use of wetting solutions.

The Oxford Family Planning Association Study could detect no evidence of any adverse effects of oral contraception on ear disorders.[354]

Multiple Sclerosis

There is no evidence in two cohort studies (the Royal College of General Practitioners' Study and the Oxford Family Planning Association Study) that there is any effect of oral contraceptive use on the risk or course of multiple sclerosis.[355, 356]

Infections and Oral Contraception

Viral STIs

The viral sexually transmitted infections (STIs) include human immunodeficiency virus (HIV), human papillomavirus (HPV), herpes simplex virus (HSV), and hepatitis B (HBV). At the present time, no known associations exist between oral contraception and the viral STIs. Of course, significant prevention includes barrier methods of contraception. Thus far, most studies have found no association between oral contraceptive use and HIV seropositivity, and some have indicated a protective effect.[357-359] Antiretroviral drugs may decrease oral contraceptive efficacy by affecting drug metabolism or causing diarrhea and vomiting. The degree of clinical impact, if any, is not established. ***For women not in a stable, monogamous relationship, a dual approach is recommended, combining the contraceptive efficacy and protection against pelvic inflammatory disease (PID) offered by estrogen-progestin contraception with the use of a barrier method for prevention of viral STIs.***

Bacterial STIs

Sexually transmitted infections (STIs) are one of the most common public health problems in the United States. Pelvic inflammatory disease is usually a consequence of STIs. The best estimate of subsequent tubal infertility is derived from an excellent Swedish report; approximately 12% after one episode of PID, 23% after 2 episodes, and 54% after 3 episodes.[360] Because pelvic infection is the single greatest threat to the reproductive future of a young woman, the now recognized protection offered by oral contraception against PID is highly important.[361-363] ***The risk of hospitalization for PID is reduced by approximately 50–60%, but at least 12 months of use are necessary, and the protection is limited to current users.***[361, 364] Furthermore, if a patient does get a pelvic infection, the severity of the salpingitis found at laparoscopy is decreased.[365, 366] The mechanism of this protection remains unknown. Speculation includes thickening of the cervical mucus to prevent movement of pathogens and bacteria-laden sperm into the uterus and tubes and decreased menstrual bleeding, reducing movement of pathogens into the tubes as well as a reduction in "culture medium." This protection probably accounts for the greater fertility rate observed in previous users of oral contraception.[321, 322]

The argument has been made that this protection is limited to gonococcal disease, and chlamydial infections may even be enhanced. Fifteen of 17 published studies by 1985 reported a positive association of oral contraceptives with lower genital tract chlamydial cervicitis.[367] Because lower genital tract infections caused by *Chlamydia* are on the rise (now the most prevalent bacterial STI in the United States) and the rate of hospitalization for PID is also increased, it is worthwhile for both patients and clinicians to be alert for symptoms of cervicitis or salpingitis in women on oral contraception who are at high risk of STI (multiple sexual partners, a history of STI, or cervical discharge). The mechanism for the association between chlamydial cervicitis and oral contraceptives may be the well-recognized extension of the columnar epithelium from the endocervix out over the cervix (ectopia) that occurs with oral contraceptive use.[368] This ectropion may allow a more effective collection of cervical specimens for culture, thus introducing detection bias into the epidemiologic studies. However, large, prospective cohort studies have found no association between oral contraceptive use and either chlamydial or gonorrheal infection, and cervical ectopy did not influence the risk of infection.[369, 370] If the impact of oral contraceptives on the risk of chlamydial infection is real, it is a modest one.

Despite this potential relationship between oral contraception and chlamydial infections, it should be emphasized that there is no evidence for an impact of oral contraceptives increasing the incidence of tubal infertility.[371] In fact, a case-control study indicated that oral contraceptive users with *Chlamydia* infection are protected against symptomatic PID.[372] A case-control study has suggested that oral contraceptive users are more likely to harbor unrecognized endometritis, and that this would explain the discrepancy between the observed rates between lower and upper tract infection.[373] However, this would not explain the lack of an association between oral contraceptive use and tubal infertility. Thus, the influence of oral contraception on the upper reproductive tract may be different than on the lower tract. These observations on fertility are derived mostly, if not totally, from women using oral contraceptives containing 50 μg of estrogen. The continued progestin dominance of the lower dose formulations, however, should produce the same protective impact. Early evidence indicated protection with low-dose oral contraceptives, but a later study failed to find a reduction in upper genital tract disease with either oral contraceptives or barrier methods.[364, 374]

Other Infections

In the British prospective studies of high-dose oral contraceptives, urinary tract infections were increased in users of oral contraception by 20%, and a correlation was noted with estrogen dose. An increased incidence of

cervicitis was also reported, an effect related to the progestin dose. The incidence of cervicitis increased with the length of time the pill was used, from no higher after 6 months to 3 times higher by the sixth year of use. A significant increase in a variety of viral diseases, e.g., chickenpox, was observed, suggesting steroid effects on the immune system. The prevalence of these effects with low-dose oral contraception is unknown.

Oral contraception appears to protect against bacterial vaginosis and infections with *Trichomonas*.[375-377] Evidence is lacking to convincingly implicate oral contraception with vaginal infections with *Candida* species;[375] however, clinical experience is sometimes impressive when recurrence and cure repeatedly follow use and discontinuation of oral contraception.

Patient Management

Absolute Contraindications to the Use of Oral Contraception

1. Thrombophlebitis, thromboembolic disorders (including a close family history, parent or sibling, suggestive of an inherited susceptibility for venous thrombosis), cerebral vascular disease, coronary occlusion, or a past history of these conditions, or conditions predisposing to these problems.

2. Markedly impaired liver function. Steroid hormones are contraindicated in patients with hepatitis until liver function tests return to normal.

3. Known or suspected breast cancer.

4. Undiagnosed abnormal vaginal bleeding.

5. Known or suspected pregnancy.

6. Smokers over the age of 35.

7. Severe hypercholesterolemia or hypertriglyceridemia.

8. Elevated blood pressure.

Relative Contraindications Requiring Clinical Judgment and Informed Consent

1. Migraine headaches.
2. Hypertension.
3. Uterine leiomyoma.
4. Gestational diabetes.
5. Diabetes mellitus.
6. Elective surgery.
7. Seizure disorders.
8. Obstructive jaundice in pregnancy.
9. Sickle cell disease or sickle C disease.
10. Gallbladder disease.
11. Mitral valve prolapse.
12. Systemic lupus erythematosus.
13. Hyperlipidemia.
14. Smoking.
15. Hepatic disease.

Clinical Decisions

Surveillance

Many women can be prescribed hormonal contraception without a clinical breast and pelvic examination.[378] Problems requiring further evaluation can be identified with a careful medical history and measurement of blood pressure. Subsequently, in view of the increased safety of low-dose preparations for healthy young women with no risk factors, patients need be seen only every 12 months for exclusion of problems by history, measurement of the blood pressure, urinalysis, breast examination, palpation of the liver, and pelvic examination with Pap smear. Women with risk factors should be seen every 6 months by appropriately trained personnel for screening of problems by history and blood pressure measurement. Breast and pelvic examinations are necessary only yearly. It is worth emphasizing that better continuation is achieved by reassessing new users within 1–2 months. It is at this time that subtle fears and unvoiced concerns need to be confronted and resolved.

Oral contraception is safer than most people think it is, and the low-dose preparations are extremely safe. Health care providers should make a significant effort to get this message to our patients (and our colleagues). We must make sure our patients receive adequate counseling, either from ourselves or our professional staff. The major reason why patients discontinue oral contraception is fear of side effects.[379] Let's take time to put the risks into proper perspective and to emphasize the benefits as well as the risks.

Laboratory surveillance should be used only when indicated. Routine biochemical measurements fail to yield sufficient information to warrant the expense. Assessing the cholesterol-lipoprotein profile and carbohydrate metabolism should follow the same guidelines applied to all patients, users and nonusers of contraception. The following is a useful guide as to who should be monitored with blood screening tests for glucose, lipids, and lipoproteins:

Young women, at least once.
Women 35 years or older.
Women with a strong family history of heart disease, diabetes mellitus, or hypertension.
Women with gestational diabetes mellitus.
Women with xanthomatosis.
Obese women.
Diabetic women.

Choice of Pill

The therapeutic principle remains: utilize the formulations that give effective contraception and the greatest margin of safety. You and your patients are urged to choose a low-dose preparation containing less than 50 μg of estrogen, combined with low doses of new or old progestins. Current data support the view that there is greater safety with preparations containing less than 50 μg of estrogen. The arguments in this chapter indicate that all patients should begin oral contraception with low-dose products, and that patients on higher dose oral contraception should be changed to the low-dose preparations. Stepping down to a lower dose can be accomplished immediately with no adverse reactions such as increased bleeding or failure of contraception.

The multiphasic preparations do have a reduced progestin dosage compared with some of the existing monophasic products; however, based on currently available information there is little difference between the low-dose monophasics and the multiphasics.

The pharmacologic effects in animals of various formulations have been used as a basis for therapeutic recommendations in selecting the optimal oral contraceptive pill. *These recommendations (tailor-making the pill to the patient) have not been supported by appropriately controlled clinical trials. All too often this leads to the prescribing of a pill of excessive dosage with its attendant increased risk of serious side effects.* It is worth repeating our earlier comments on potency. Oral contraceptive potency (specifically progestin potency) is no longer a consideration when it comes to prescribing birth control pills. The potency of the various progestins has been accounted for by appropriate adjustments of dose. Clinical advice based on potency is an artificial exercise that has not stood the test of time. The biologic effect of

the various progestational components in current low-dose oral contraceptives is approximately the same. Our progress in lowering the doses of the steroids contained in oral contraceptives has yielded products with little serious differences.

Pill Taking

Effective contraception is present during the first cycle of pill use, provided the pills are started no later than the fifth day of the cycle and no pills are missed. Thus, starting oral contraception on the first day of menses ensures immediate protection. In the United States, most clinicians and patients prefer the Sunday start packages, beginning on the first Sunday following menstruation. This can be easier to remember, and it usually avoids menstrual bleeding on weekends. It is probable, but not totally certain, that even if a dominant follicle should emerge in occasional patients after a Sunday start, an LH surge and ovulation would still be prevented.[380] Some clinicians prefer to advise patients to use added protection in the first week of use.

The conventional approach to starting oral contraceptives, either with menses or on Sunday, carries with it a delay in achieving contraception for many women. Many clinicians advocate an immediate start on the day the patient receives her prescription, regardless of the patient's day in her cycle.[381] Combined with a backup method for the first week, preferably condoms, an immediate start may avoid unwanted pregnancies occurring during the delay before initiating oral contraception with the conventional methods. In some instances, a sensitive pregnancy test would be a wise precaution. Women who use the immediate start method do not experience an increase in breakthrough bleeding.[382]

Occasionally patients would like to postpone a menstrual period, e.g., for a wedding, holiday, or vacation. This can be easily achieved by omitting the 7-day hormone-free interval. Simply start a new package of pills the next day after finishing the series of 21 pills in the previous package. Remember, when using a 28-pill package, the patient would start a new package after using the 21 active pills.

There is no rationale for recommending a pill-free interval "to rest." The serious side effects are not eliminated by pill-free intervals. This practice all too often results in unwanted pregnancies.

How important is it to take the oral contraceptive at the same time every day? Although not well studied, there is reason to believe precise pill taking minimizes breakthrough bleeding. In addition, compliance is improved by a fixed schedule that is habit-forming.

Avoiding Menstrual Bleeding

More and more women are embracing the idea that fewer menstrual periods provide a welcome relief from bleeding and menstrual symptoms. A regimen (Seasonale) is available that supplies a package containing the number of pills required for 84 days of daily administration, a reduction of menstrual frequency to 4 per year.[383] However, clinicians for years have prescribed unlimited daily oral contraceptives to treat conditions such as endometriosis, bleeding disorders, menstrual seizures, and menstrual migraine headaches, even to avoid bleeding in athletes and busy individuals. Many women do not require the periodic experience of vaginal bleeding to assure themselves they are not pregnant. And of course, modern society is long past the notion that menstrual bleeding is a cleansing event, a detoxification. It is not necessary for women using oral contraceptives to experience any withdrawal bleeding. Monthly bleeding, periodic bleeding, or no bleeding—this is an individual woman's choice. Any combination oral contraceptive can be used on a daily basis; even the lowest estrogen dose formulations provide excellent bleeding and side-effect profiles in a continuous regimen.[384, 385] A further benefit of continuous use is simplification of the pill-taking schedule with the potential of better compliance and a lower failure rate. When breakthrough bleeding occurs, patients can be reassured that it is almost always temporary. When breakthrough bleeding is persistent, a 3–4 day interruption without pill taking has been reported to be helpful.[386]

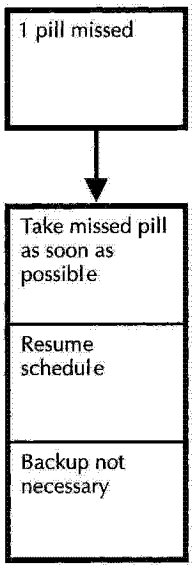
What To Do When Pills Are Missed

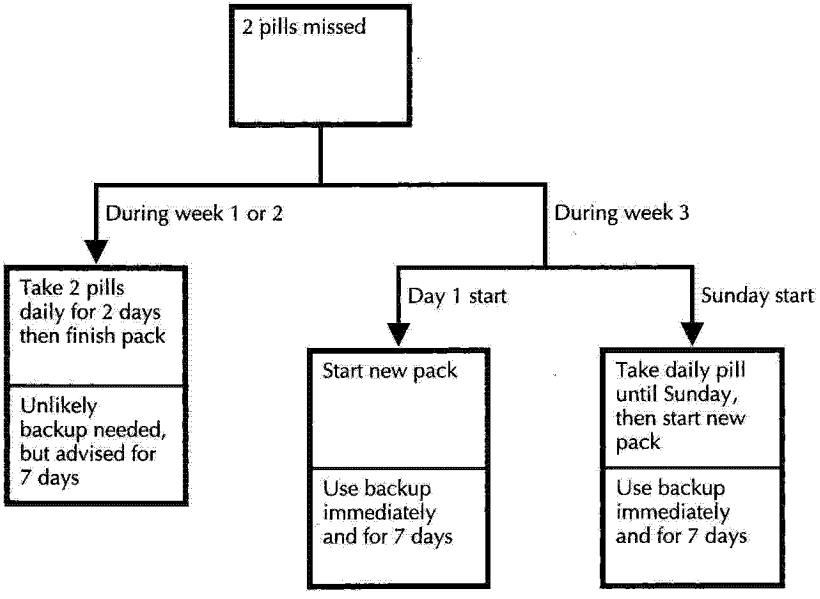
Irregular pill taking is a common occurrence. Using an electronic monitoring device to measure compliance, it was apparent that consistency of pill taking is even worse than what patients report; only 33% of women were documented to have missed no pills in cycle 1, and by cycle 3, about one-third of the women missed 3 or more pills with many episodes of consecutive days of missed pills.[387] These data indicate that women become less careful over time, emphasizing the importance of repeatedly reviewing with patients what to do when pills are missed.

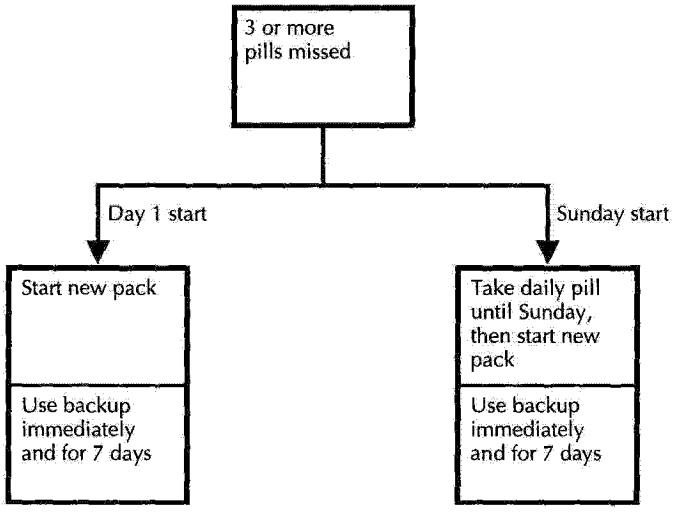
If a woman misses 1 pill, she should take that pill as soon as she remembers and take the next pill as usual. No backup method is needed.

If she misses 2 pills in the first 2 weeks, she should take 2 pills on each of the next 2 days; it is unlikely that a backup method is needed, but the official consensus is to recommend backup for the next 7 days.

If 2 pills are missed in the third week, or if more than 2 active pills are missed at any time, another form of contraception should be used as backup immediately and for 7 days; if a Sunday starter, keep taking a pill every day until Sunday, and on Sunday start a new package; if a non-Sunday starter, start a new package the same day.


1 pill missed
Take missed pill as soon as possible
Resume schedule
Backup not necessary


2 pills missed
During week 1 or 2
During week 3
Take 2 pills daily for 2 days then finish pack
Unlikely backup needed, but advised for 7 days
Day 1 start
Sunday start
Start new pack
Use backup immediately and for 7 days
Take daily pill until Sunday, then start new pack
Use backup immediately and for 7 days



Studies have questioned whether missing pills has an impact on contraception. One study demonstrated that skipping 4 consecutive pills at varying times in the cycle did not result in ovulation.[380] Studies in which women deliberately lengthen their pill-fee interval up to 11 days have failed to show signs of ovulation.[388, 389] So far there is no evidence that moving to lower doses has had an impact on the margin of error. Despite greater follicular activity with the lowest-dose oral contraceptives, ovulation is still effectively prevented.[390]

The studies have involved small numbers of women, and given the large individual variation, it still is possible that some women might be at risk with a small increase in the pill-free interval. However, the progestational effects on endometrium and cervical mucus serve to ensure good contraceptive efficacy.[26] We may well prove that current recommendations are too conservative and that a woman's chance of getting pregnant with missing pills is nearly zero. Nevertheless, this conservative advice is the safest message to convey.

The most prevalent problems that can be identified associated with apparent oral contraceptive failures are vomiting and diarrhea.[30, 31] ***Even if no pills have been missed, patients should be instructed to use a backup method for at least 7 days after an episode of gastroenteritis.***

Clinical Problems

Breakthrough Bleeding

A major continuation problem is breakthrough bleeding. Breakthrough bleeding gives rise to fears and concerns; it is aggravating and even embarrassing. Therefore, on starting oral contraception, patients need to be fully informed about breakthrough bleeding.

There are two characteristic breakthrough bleeding problems: irregular bleeding in the first few months after starting oral contraception and unexpected bleeding after many months of use. Effort should be made to manage the bleeding problem in a way that allows the patient to remain on low-dose oral contraception. ***There is no evidence that the onset of bleeding is associated with decreased efficacy, no matter what oral contraceptive formulation is used, even the lowest dose products.*** Indeed, in a careful study, breakthrough bleeding did not correlate with changes in the blood levels of the contraceptive steroids.[391]

The most frequently encountered breakthrough bleeding occurs in the first few months of use. The incidence is greatest in the first 3 months, ranging from 10–30% in the first month to less than 10% in the third. Breakthrough bleeding rates are higher with the lowest dose oral contraceptives but not dramatically.[392, 393] Breakthrough bleeding are higher in women who smoke and in smokers who use formulations with 20 μg ethinyl estradiol.[394] However, the differences among the various formulations currently available are of minimal clinical significance. The basic pattern is the same, highest in the first month and a greater prevalence in smokers, especially in later cycles.

Breakthrough bleeding is best managed by encouragement and reassurance. This bleeding usually disappears by the third cycle in the majority of women. If necessary, even this early pattern of breakthrough bleeding can be treated as outlined below. It is helpful to explain to the patient that this bleeding represents tissue breakdown as the endometrium adjusts from its usual thick state to the relatively thin state allowed by the hormones in oral contraceptives.

Breakthrough bleeding that occurs after many months of oral contraceptive use is a consequence of the progestin-induced decidualization. This endometrium and the blood vessels within the endometrium tend to be fragile and prone to breakdown and asynchronous bleeding.

There are two recognized factors (both preventable) that are associated with a greater incidence of breakthrough bleeding. Consistency of use and smoking increase spotting and bleeding, but inconsistency of pill taking is

more important and has a greater effect in later cycles, whereas smoking exerts a general effect at any time.[395] Reinforcement of consistent pill taking can help minimize breakthrough bleeding. Cervical infection can be another cause of breakthrough bleeding; the prevalence of cervical chlamydial infections is higher among oral contraceptive users who report breakthrough bleeding.[396]

If bleeding occurs just before the end of the pill cycle, it can be managed by having the patient stop the pills, wait 7 days, and start a new cycle. If breakthrough bleeding is prolonged or if it is aggravating for the patient, regardless of the point in the pill cycle, control of the bleeding can be achieved with a short course of exogenous estrogen. Conjugated estrogen, 1.25 mg, or estradiol, 2 mg, is administered daily for 7 days when the bleeding is present, no matter where the patient is in her pill cycle. The patient continues to adhere to the schedule of pill taking. Usually, one course of estrogen solves the problem, and recurrence of bleeding is unusual (but if it does recur, another 7-day course of estrogen is effective).

Responding to irregular bleeding by having the patient take 2 or 3 pills is not effective. The progestin component of the pill always dominates; hence, doubling the number of pills also doubles the progestational impact and its decidualizing, atrophic effect on the endometrium and its destabilizing effect on endometrial blood vessels. The addition of extra estrogen while keeping the progestin dose unchanged is logical and effective. This allows the patient to remain on the low-dose formulation with its advantage of greater safety. Breakthrough bleeding, in our view, is not sufficient reason to expose patients to the increased risks associated with higher dose oral contraceptives. Any bleeding that is not handled by this routine requires investigation for the presence of pathology.

There is no evidence that any oral contraceptive formulations that are approximately equivalent in estrogen and progestin dosage are significantly different in the rates of breakthrough bleeding. Clinicians often become impressed that switching to another product effectively stops the breakthrough bleeding. It is more likely that the passage of time is the responsible factor, and bleeding would have stopped regardless of switching and regardless of product.

Amenorrhea

With low-dose pills, the estrogen content is not sufficient in some women to stimulate endometrial growth. The progestational effect dominates to such a degree that a shallow atrophic endometrium is produced, lacking sufficient tissue to yield withdrawal bleeding. It should be emphasized that permanent atrophy of the endometrium does not occur, and resumption

of normal ovarian function restores endometrial growth and development. Indeed, there is no harmful, permanent consequence of amenorrhea while on oral contraception.

The major problem with amenorrhea while on oral contraception is the anxiety produced in both patient and clinician because the lack of bleeding may be a sign of pregnancy. The patient is anxious because of the uncertainty regarding pregnancy, and the clinician is anxious because of the medicolegal concerns stemming from the old studies, which indicated an increased risk of congenital abnormalities among the offspring of women who inadvertently used oral contraception in early pregnancy. We reviewed this problem earlier, and emphatically stated that there is no association between oral contraception and an increased risk of congenital malformation, and there is no increased risk of having abnormal children.

The incidence of amenorrhea in the first year of use with low-dose oral contraception is less than 2%. This incidence increases with duration, reaching perhaps 5% after several years of use. It is important to alert patients upon starting oral contraception that diminished bleeding and possibly no bleeding may ensue.

Amenorrhea is a difficult management problem. A pregnancy test allows reliable assessment for pregnancy even at this early stage. However, routine, repeated use of such testing is expensive and annoying and may lead to discontinuation of oral contraception. ***A simple test for pregnancy is to assess the basal body temperature during the END of the pill-free week; a basal body temperature less than 98 degrees (36.7°C) is not consistent with pregnancy, and oral contraception can be continued.***

Many women are reassured with an understanding of why there is no bleeding and are able to continue on the pill despite the amenorrhea. Some women cannot reconcile themselves to a lack of bleeding, and this is an indication for trying other formulations (a practice unsupported by any clinical trials, and, therefore, the expectations are uncertain). But again, this problem does not warrant exposing patients to the greater risks of major side effects associated with higher dose products.

Some clinicians have observed that the addition of extra estrogen for 1 month (1.25 mg conjugated estrogens or 2 mg estradiol daily throughout the 21 days while taking the oral contraceptive) rejuvenates the endometrium, and withdrawal bleeding resumes, persisting for many months.

Weight Gain

The complaint of weight gain is frequently cited as a major problem with compliance. Yet, studies of the low-dose preparations fail to demonstrate a significant weight gain with oral contraception, and no major differences among the various products.[193-196, 199, 201] This is obviously a problem of perception, a conclusion supported by finding the weight gain identical in treated and placebo groups. The clinician has to carefully reinforce the lack of association between low-dose oral contraceptives and weight gain and focus the patient on the real culprit: diet and level of exercise. Most women gain a moderate amount of weight as they age, whether they take oral contraceptives or not.

Acne

Low-dose oral contraceptives improve acne regardless of which product is used.[167, 191, 192, 200, 397-400] The low progestin doses (including levonorgestrel formulations) currently used are insufficient to stimulate an androgenic response and provide effective treatment for acne and hirsutism.

Ovarian Cysts

Anecdotal reports suggested that functional ovarian cysts are encountered more frequently and suppress less easily with multiphasic formulations. This observation failed to withstand careful scrutiny.[401, 402] Functional ovarian cysts occurred less frequently in women on higher dose oral contraception.[403] This protection is reduced with the current lower dose products to the point where little effect can be measured.[402, 404-407] Thus, the risk of such cysts is not eliminated; and, therefore, clinicians can encounter such cysts in patients taking any of the oral contraceptive formulations.

Drugs That Affect Efficacy

There are many anecdotal reports of patients who conceived on oral contraceptives while taking antibiotics. There is little evidence, however, that antibiotics such as ampicillin, metronidazole, quinolone, and tetracycline, which reduce the bacterial flora of the gastrointestinal tract, affect oral contraceptive efficacy. Studies indicate that while antibiotics can alter the excretion of contraceptive steroids, plasma levels are unchanged, and there is no evidence of ovulation.[408-411] A review of a large number of patients derived from dermatology practices failed to find an increased rate of pregnancy in women on oral contraceptives and being treated with antibiotics (tetracyclines, penicillins, cephalosporins).[412]

There is good reason to believe that drugs that stimulate the liver's metabolic capacity can affect oral contraceptive efficacy. St. John's wort must be added to this list.[413] On the other hand, a search of a large database

failed to discover any evidence that lower dose oral contraceptives are more likely to fail or to have more drug interaction problems when other drugs are used.[414]

To be cautious, patients on medications that affect liver metabolism should choose an alternative contraceptive. A list, which may not be complete, includes the following:

Carbamazepine (Tegretol).
Felbamate.
Nevirapine.
Oxcarbazepine.
Phenobarbital.
Phenytoin (Dilantin).
Primidone (Mysoline).
Rifabutin.
Rifampicin (Rifampin).
St. John's Wort.
Topiramate.
Vigabatrin.
Possibly ethosuximide, griseofulvin, and troglitazone.

Other Drug Interactions

Although not extensively documented, there is reason to believe that oral contraceptives potentiate the action of diazepam (Valium), chlordiazepoxide (Librium), tricyclic antidepressants, and theophylline.[415] Thus, lower doses of these agents may be effective in oral contraceptive users. Because of an influence on clearance rates, oral contraceptive users may require larger doses of acetaminophen and aspirin.[416]

Migraine Headaches

True migraine headaches are more common in women, while tension headaches (90% of all headaches) occur equally in men and women. There have been no well-done studies to determine the impact of oral contraception on migraine headaches. Patients may report that their headaches are worse or better.

Migraine headaches, especially with aura, are a risk factor for stroke.[417] The risk is greater in women with hypertension, in smokers, with a family history of migraine, and in women with a long history of migraine or with more than 12 attacks per year of migraine with aura.[418, 419] Studies with high-dose pills indicated that migraine headaches were linked to a risk of stroke. More recent studies reflecting the use of low-dose formulations yield mixed results. One failed to find a further increase in stroke in

patients with migraine who use oral contraception, another concluded that the use of oral contraception by migraineurs was associated with a 4-fold increase of the already increased risk of ischemic stroke.[420, 421] The World Health Organization case-control study indicated an increased risk in oral contraceptive users who smoked.[418] Because 20–30% of women experience migraine headaches, one would expect the populations in the most recent studies of thrombosis to have included substantial numbers of migraineurs. An adverse effect of low-dose oral contraceptives on stroke risk in migraineurs should have manifested itself in the data. The lack of an increased risk of stroke in these studies is reassuring. Nevertheless, it is believed that migraineurs on oral contraceptives have an increased risk of stroke; the absolute risk in a 20-year-old woman is estimated to be 10 per 100,000 and for a 40-year-old woman, 100 per 100,000.[422]

There are two categories of migraine headaches: common migraine, which is migraine without aura and classic migraine, which is migraine with aura (essentially migraine headaches with visual aura or other neurologic symptoms, occurring in 30% of migraine sufferers). Because of the seriousness of this potential complication, the onset of visual symptoms or severe headaches requires a response. If the patient is at a higher dose, a move to a low-dose formulation may relieve the headaches. Switching to a different brand is worthwhile, if only to evoke a placebo response. True vascular headaches (migraine with aura) are an indication to avoid or discontinue oral contraception. Oral contraceptives should be avoided in women who have migraine with complex or prolonged aura, or if additional stroke factors are present (older age, smoking, hypertension, diabetes mellitus, obesity, family history of arterial disease at a young age).[422] Oral contraceptives can be considered in women under age 35, who have migraine without aura, and who are otherwise healthy and not smokers.

Clues to Migraine with Aura:

- Scotomata or blurred vision.
- Episodes of blindness.
- Numbness, paresthesias.
- Speech difficulties.
- Unilateral symptoms, such as weakness.

In some women, a relationship exists between their fluctuating hormone levels during a menstrual cycle and migraine headaches, with the onset of headaches characteristically coinciding with menses (also seen during the pill-free week of oral contraception). We have had personal success (anecdotal to be sure) alleviating headaches by eliminating the menstrual cycle, either with the use of daily oral contraceptives or the daily administration of a progestational agent (such as 10 mg medroxyprogesterone acetate) or

the use of depot-medroxyprogesterone acetate. Some women with migraine headaches have extremely gratifying responses. Women who experience an exacerbation of their headaches with oral contraception should consider one of the progestin-only methods.

Summary: Oral Contraceptive Use and Medical Problems

Migraine Headaches. Some women report an improvement in their headaches with oral contraceptives. Low-dose oral contraception (the lowest estrogen dose formulation) can be tried with careful surveillance in women with migraine headaches without aura. Daily administration can prevent menstrual migraine headaches. Oral contraception is best avoided in women with migraine headaches with aura or if additional stroke risk factors are present (especially older age, smoking, and hypertension).

Hypertension. Low-dose oral contraception can be used in women less than age 35 with hypertension well controlled by medication, and who are otherwise healthy and do not smoke. We recommend the lowest estrogen dose formulations. Nevertheless, a cross-sectional study in Brazil reported worse control of hypertension in users of oral contraceptives.[161] Certainly a woman with controlled hypertension who has additional medical problems or who smokes should not use estrogen-progestin contraceptives (including the transdermal and vaginal methods). In a young woman with controlled hypertension who is otherwise healthy, very frequent and close monitoring of the blood pressure is essential. Myocardial infarction and stroke become more common after age 35, and we believe that combined estrogen-progestin contraception should not be used by women with controlled hypertension after age 35. Progestin-only methods are acceptable.

Pregnancy-Induced Hypertension. Women with pregnancy-induced hypertension can use oral contraception as soon as the blood pressure is normal in the postpartum period.

Uterine Leiomyoma. This is not a contraindication for low-dose oral contraceptives. There is evidence that the risk of leiomyomas was decreased by 31% in women who used higher dose oral contraception for 10 years.[423] However, case-control studies with lower dose oral contraceptives have found neither a decrease nor an increase in risk, although the Nurses' Health Study reported a slightly increased risk when oral contraceptives were first used in early teenage years.[424–426] One case-control study indicated a decreasing risk of uterine fibroids with increasing duration of oral contraceptive use.[427] The administration of low-dose oral contraceptives to women with leiomyomas does not stimulate fibroid growth and is associated with a reduction in menstrual bleeding.[428]

Gestational Diabetes. Low-dose formulations do not produce a diabetic glucose tolerance response in women with previous gestational diabetes, and there is no evidence that combined oral contraceptives increase the incidence of overt diabetes mellitus.[175, 176] We believe that women with previous gestational diabetes can use oral contraception with annual assessment of the fasting glucose level. There is a concern with breastfeeding women using the progestin-only minipill (discussed in Chapter 3).

Diabetes Mellitus. Oral contraception can be used by diabetic women less than 35 years old who do not smoke and are otherwise healthy (especially an absence of diabetic vascular complications). A case-control study could find no evidence that oral contraceptive use by young women with insulin-dependent diabetes mellitus increased the development of retinopathy or nephropathy.[178] In a 1-year study of women with insulin-dependent diabetes mellitus who were using a low-dose oral contraceptive, no deterioration could be documented in lipoprotein or hemostatic biochemical markers for cardiovascular risk.[179] And finally, no effect of oral contraceptives on cardiovascular mortality could be detected in a group of women with diabetes mellitus.[180] Women with diabetes and vascular disease or major cardiovascular risk factors should avoid pharmacologic doses of exogenous estrogen.

Elective surgery. The recommendation that oral contraception should be discontinued 4 weeks before elective major surgery to avoid an increased risk of postoperative thrombosis is based on data derived from high-dose pills. If possible, it is safer to follow this recommendation when a period of immobilization is to be expected. With major surgery and immobilization, prophylactic treatment should be considered for a current or recent user of oral contraceptives. It is prudent to maintain contraception right up to the performance of a sterilization procedure, and this short, outpatient operation carries very minimal, if any, risk.

Seizure Disorders. Oral contraceptives do not exacerbate epilepsy, and in some women, improvement in seizure control has occurred.[429, 430] Antiepileptic drugs that affect liver metabolism, however, may decrease the effectiveness of oral contraception. Some clinicians advocate the use of higher dose (50 μg estrogen) products; however, no studies have been performed to demonstrate that this higher dose is necessary. Another problem is that moving to a higher dose product increases the estrogen dose (and the risk of side effects) but does not significantly change the progestin dose, the component that inhibits ovulation. A wiser course is to consider intrauterine contraception with an IUD, long-acting methods, barrier methods, or sterilization.

Obstructive Jaundice in Pregnancy. Not all patients with this history develop jaundice on oral contraception, especially with the low-dose formulations.

Sickle Cell Disease. Patients with sickle cell trait can use oral contraception. The risk of thrombosis in women with sickle cell disease or sickle C diseases is theoretical (and medicolegal). We believe effective protection against pregnancy in these patients warrants the use of low-dose oral contraception. In the only long-term (10 years) follow-up report of women with sickle cell disease and using oral contraceptives, no apparent adverse effects were observed (at a time when higher dose products were prevalent).[431] A study of erythrocyte deformability in women with sickle cell anemia could detect no adverse effects of contraceptive steroids.[432] Keep in mind that depot-medroxyprogesterone acetate used for contraception is associated with inhibition of sickling and improvement in anemia in patients with sickle cell disease.[433]

Gallbladder Disease. Oral contraception use may precipitate a symptomatic attack in women known to have stones or a positive history for gallbladder disease and, therefore, should either be used very cautiously or not at all.

Mitral Valve Prolapse. Oral contraception use is limited to nonsmoking patients who are asymptomatic (no clinical evidence of regurgitation). There is a small subset of patients with mitral valve prolapse who are at increased risk of thromboembolism. Patients with atrial fibrillation, migraine headaches, or clotting factor abnormalities should consider progestin-only methods or the IUD (prophylactic antibiotics should cover IUD insertion if mitral regurgitation is present).

Systemic Lupus Erythematosus. Oral contraceptive use can exacerbate systemic lupus erythematous, and the vascular disease associated with lupus, when present, represents a contraindication to estrogen-containing contraceptives.[434] The progestin-only methods are a good choice. However, in patients with stable or inactive disease, without renal involvement and high antiphospholipid antibodies, low-dose oral contraception can be considered.[435]

Hyperlipidemia. Because low-dose oral contraceptives have negligible impact on the lipoprotein profile, hyperlipidemia is not an absolute contraindication, with the exception of very high levels of triglycerides (which can be made worse by estrogen). In women with triglyceride levels greater than 250 mg/dL, estrogen should be provided with great caution. If vascular disease is already present, oral contraception should be avoided. If other risk factors are present, especially smoking, oral contraception is

not recommended. Dyslipidemic patients who begin oral contraception should have their lipoprotein profiles monitored monthly for a few visits to ensure no adverse impact. If the lipid abnormality cannot be held in control, an alternative method of contraception should be used.[436] Oral contraceptives containing desogestrel, noregestimate, or gestodene can increase HDL levels, but it is not known if this change is clinically significant. If hypertriglyceridemia is the only concern, keep in mind that the triglyceride response to estrogen is rapid. A repeat level should be obtained in 2–4 weeks. A level greater than 750 mg/dL represents an absolute contraindication to estrogen treatment because of the risk of pancreatitis.

Smoking. Oral contraception is absolutely contraindicated in smokers over the age of 35. In patients 35 years old and younger, heavy smoking (15 or more cigarettes per day) is a relative contraindication. The relative risk of cardiovascular events is increased for women of all ages who smoke and use oral contraceptives; however, because the actual incidence of cardiovascular events is so low at a young age, the real risk is very low for young women, although it increases with age. An ex-smoker (for at least 1 year) should be regarded as a nonsmoker. Risk is only linked to active smoking. Is there room for judgment? Given the right circumstances, low-dose oral contraceptives might be appropriate for a light smoker or the user of a nicotine patch. A 20 μg estrogen formulation may be a better choice for smoking women, regardless of age (because this dose of estrogen has no impact on clotting factors and platelet activation).[54, 55]

Hepatic Disease. Oral contraception can be utilized when liver function tests return to normal. Follow-up liver function tests should be obtained after 2–3 months of use.

Hemorrhagic Disorders. Women with hemorrhagic disorders and women taking anticoagulants can use oral contraception. Inhibition of ovulation can avoid the real problem of a hemorrhagic corpus luteum in these patients. A reduction in menstrual blood loss is another benefit of importance.

Obesity. An obese woman who is otherwise healthy can use low-dose oral contraception. However, there are special considerations associated with obesity:

- Obesity is an independent risk factor for venous thrombosis, and case-control studies have indicated this risk adds to that associated with oral contraceptives.[75, 87, 437]

- There is modest evidence that hormonal contraceptive failure is increased in overweight women (over 155 pounds).[438–440] Clinical trials have excluded women with high body weight,

and for this reason, the effect of body weight on contraception was not well studied. Selecting a 50 μg estrogen product for over weight women might overcome the failure rate, but this would add the risks associated with a higher dose of estrogen to those already linked with obesity. Keep in mind that the conclusions regarding failure rates and weight were based on differences of only 2 to 4 pregnancies per 100 women per year. Efficacy in overweight women is still greater than that with barrier methods.

Benign Breast Disease. Benign breast disease is not a contraindication for oral contraception; with 2 years of use, the condition may improve.

Congenital Heart Disease or Valvular Heart Disease. Oral contraception is contraindicated only if there is marginal cardiac reserve or a condition that predisposes to thrombosis.

Depression. Low-dose oral contraceptives have minimal, if any, impact on mood.

Polycystic Ovaries and Insulin Resistance. Because older, high-dose oral contraceptives increased insulin resistance, it has been suggested that this treatment should be avoided in anovulatory, overweight women. However, low-dose oral contraceptives have minimal effects on carbohydrate metabolism, and the majority of hyperinsulinemic, hyperandrogenic women can be expected to respond favorably to treatment with oral contraceptives.[441] Insulin and glucose changes with low-dose (less than 50 μg ethinyl estradiol) oral contraceptives are so minimal that it is now believed that they are of no clinical significance.[169] Long-term follow-up studies have failed to detect any increase in the incidence of diabetes mellitus or impaired glucose tolerance (even in past and current users of high-dose pills).[171, 173] Furthermore, there is no evidence of an increase in risk of cardiovascular disease among past users of oral contraceptives.[59, 60] In addition, low-dose oral contraceptives have been administered to women with recent gestational diabetes without an adverse impact, and in women with insulin-dependent diabetes mellitus, low-dose oral contraceptives have not produced deterioration of lipid and biochemical markers for cardiovascular disease or increased the development of retinopathy or nephropathy.[175, 176, 178, 179] The administration of a low-dose oral contraceptive to women with extreme obesity and very severe insulin resistance resulted in only a mild deterioration of glucose tolerance.[442] Impressively, in a follow-up study (about 10 years) of women with polycystic ovaries and hyperinsulinism, comparing oral contraceptive users with nonusers, the metabolic parameters not only did not worsen in the users, but they actually improved, including body weight, glucose tolerance, insulin levels, and

HDL-cholesterol levels, which was in striking contrast to the metabolic worsening observed in the nonusers.[443] This experience supports the safety of estrogen-progestin contraceptive treatment for anovulatory, hyperandrogenic, hyperinsulinemic women.

Eating Disorders. In patients with eating disorders, bone density correlates with body weight. The response to hormone therapy impaired as long as an abnormal weight is maintained.[444] The failure to respond to estrogen treatment with an increase in bone density may be due to the adverse bone effects of the hypercortisolism associated with stress disorders. Furthermore, because the pubertal gain in bone density is so significant, individuals who fail to experience this adolescent increase may continue to have a deficit in bone mass despite hormone treatment. Reduced menstrual function for any reason early in life (even beyond adolescence) may leave a residual deficit in bone density that cannot be totally retrieved with resumption of menses or with hormone treatment.[445, 446]

Pituitary Prolactin-Secreting Adenomas. Low-dose oral contraception can be used in the presence of microadenomas.

Infectious Mononucleosis. Oral contraception can be used as long as liver function tests are normal.

Ulcerative Colitis. There is no association between oral contraception and ulcerative colitis. Women with this problem can use oral contraceptives.[203] Oral contraceptives are absorbed mainly in the small bowel.

Regional Enteritis (Crohn's Disease). In a prospective cohort of women with Crohn's disease, no adverse impact of oral contraceptives could be detected on the clinical course, specifically on flare-ups.[447]

An Alternative Route of Administration

Occasionally, a situation may be encountered when an alternative to oral administration of contraceptive pills is required. For example, patients receiving chemotherapy can either have significant nausea and vomiting, or mucositis, both of which would prevent oral drug administration. The low-dose oral contraceptives can be administered vaginally. Initially, it was claimed that two pills must be placed high in the vagina daily to produce contraceptive steroid blood levels comparable with the oral administration of one pill.[448] However, a large clinical trial has demonstrated typical contraceptive efficacy with one pill administered vaginally per day.[449] In a comparative study, a major reduction in side effects was associated with vaginal administration.[450] Of course, the vaginal and transdermal methods discussed in Chapter 4 should also be considered.

Athletes and Oral Contraception

Because athletes are often amenorrheic and hypoestrogenic, oral contraceptives provide not only confidence against the risk of an unwanted pregnancy but also estrogen support against bone loss. This is a situation where bone density measurements are worthwhile. A low bone density can help motivate an athlete to take hormone therapy, and a subsequent bone density measurement that reveals a failure of response to estrogen can indicate the presence of a hidden eating disorder. The amenorrheic exerciser should be made aware that the hypoestrogenic state is associated with a greater risk of stress fractures.

Competing athletes are often concerned that oral contraceptives could reduce exercise performance. A rationale for the concern can be traced to the physiologic increase in ventilation during pregnancy, mediated by progesterone. Thus, progestin enhancement of ventilatory response could consume energy otherwise available for athletic performance. Indeed, reports have generated conflicting data as measured by laboratory testing. However, experimental studies that simulate athletic events can find no adverse effects on oxygen uptake, respiratory rate, endurance, or isometric exercises.[451, 452] One study documented decreased soreness, both perceived and with palpation, after exercise in women using oral contraceptives.[453] Oral contraceptive use has no effect on prevalence or severity of low back pain, a common problem among female athletes.[454]

Estrogen-progestin contraceptives have a lot to offer with no serious drawbacks for athletes. In athletes who wish to avoid menstrual bleeding, oral contraceptives can be administered on a daily basis, with no breaks, preventing withdrawal bleeding. Continuous administration is also a good choice for women in the military. The vaginal and transdermal methods (Chapter 4) can be used in a similar fashion.

The Noncontraceptive Benefits of Oral Contraception

The noncontraceptive benefits of low-dose oral contraception can be grouped into two main categories: benefits that incidentally accrue when oral contraception is specifically utilized for contraceptive purposes and benefits that result from the use of oral contraceptives to treat problems and disorders.

The noncontraceptive incidental benefits can be listed as follows:

Effective Contraception:
- **Less need for induced abortion.**
- **Less need for surgical sterilization.**

Less Endometrial Cancer.
Less Ovarian Cancer.
Fewer Ectopic Pregnancies.
More Regular Menses:
- **Less flow.**
- **Less dysmenorrhea.**
- **Less anemia.**

Less Salpingitis.
Increased Bone Density.
Probably Less Endometriosis.
Possibly Less Benign Breast Disease.
Possibly Less Rheumatoid Arthritis.
Possibly Protection against Atherosclerosis.
Possibly Fewer Fibroids.
Possibly Fewer Ovarian Cysts.

Many of these benefits have been previously discussed. Protection against PID is especially noteworthy and a major contribution to not only preservation of fertility but to lower health care costs. Also important is the prevention of ectopic pregnancies. Ectopic pregnancies have increased in incidence (partly due to an increase in STIs) and represent a major cost for our society and a threat to both fertility and life for individual patients. Of course, prevention of benign and malignant neoplasia is an outstanding feature of oral contraception. High-dose oral contraceptive use decreased the incidence of benign breast disease diagnosed clinically as well as fibrocystic disease and fibroadenomas diagnosed by biopsy; hopefully, the same impact becomes evident with current lower dose formulations. A 40% reduction in ovarian cancer and a 50% reduction in endometrial cancer represent substantial protection.

Studies with higher dose formulations documented in long-term users a 31% reduction in uterine leiomyomas and, in current users, a 78% reduction in corpus luteum cysts and a 49% reduction in functional ovarian cysts.[403] Two case-control studies with low-dose oral contraceptives have found no impact on the risk of uterine fibroids, neither increased nor decreased,[424, 425] and one indicated a decreasing risk with increasing duration of use, reaching a 50% reduction after 7 or more years of use (the effect was limited to current users).[427] Epidemiologic studies have indicated that a progressive decline in the incidence of ovarian cysts is proportional to the steroid doses in oral contraceptives.[404, 405] Current low-

dose monophasic and multiphasic formulations provide no protection against functional ovarian cysts.[404–407] This apparent weaker protection afforded by the current low-dose formulations makes it very likely that clinicians will encounter such cysts in their patients on oral contraceptives.

The low-dose contraceptives are as effective as higher dose preparations in reducing menstrual flow and the prevalence and severity of dysmenorrhea.[455–457] The use of oral contraception is associated with a lower incidence of endometriosis, although the protective effect is probably limited to current or recent use.[458–460] These benefits involving two common gynecologic problems have an important, positive impact on compliance.

An Austrian study concluded that osteoporosis occurs later and is less frequent in women who have used long-term oral contraception.[461] Most studies indicate that prior use of oral contraception is associated with higher levels of bone density and that the degree of protection is related to duration of exposure.[462–468] However, other studies reflecting modern use of low-dose products indicate little impact of oral contraceptive use on bone.[469–471] These measurements of bone density are not as important as the clinical outcome: fractures. The available evidence fails to provide a clear-cut picture. Retrospective studies indicated a reduction in fractures in postmenopausal women who had previously used oral contraceptives.[472–475] In the Royal College of General Practitioners Study, the overall risk of fractures in long-time users of oral contraceptives was actually slightly increased.[476] Similar results have been observed in the Oxford Family Planning Association Study.[477] It is likely that the increased risk reflects lifestyle effects among oral contraceptive users, but there was no evidence of a protective effect against fractures. In contrast, a case-control study from Sweden found a reduction in the risk of postmenopausal hip fractures when oral contraceptives (mostly older high-dose products) were used after age 40 by women who were not overweight, with an increasing benefit with increasing duration of use.[478] Previous oral contraceptive users are just now becoming elderly and reaching the age of greatest fracture prevalence. Future studies of postmenopausal women should eventually reveal the accurate relationship between oral contraceptive use and osteoporotic fractures.

The literature on rheumatoid arthritis has been controversial, with studies in Europe finding evidence of protection and studies in North America failing to demonstrate such an effect. An excellent Danish case-control study was designed to answer criticisms of shortcomings in the previous literature.[479] Long-time use of oral contraception reduced the relative risk of rheumatoid arthritis by 60%, and the strongest protection was present in women with a positive family history. One meta-analysis concluded that the evidence consistently indicated a protective effect, but that rather than preventing the development of rheumatoid arthritis, oral contraception

may modify the course of disease, inhibiting the progression from mild to severe disease, whereas a later meta-analysis concluded there was no evidence of a protective effect.[480, 481]

Oral contraceptives are frequently utilized to manage the following problems and disorders:

Definitely Beneficial:
- **Dysfunctional uterine bleeding.**
- **Dysmenorrhea.**
- **Mittelschmerz.**
- **Endometriosis prophylaxis.**
- **Acne and hirsutism.**
- **Hormone therapy for hypothalamic amenorrhea.**
- **Prevention of menstrual porphyria.**
- **Control of bleeding (dyscrasias, anovulation).**

Possibly Beneficial:
- **Functional ovarian cysts.**
- **Premenstrual syndrome.**

Oral contraceptives have been a cornerstone for the treatment of anovulatory, dysfunctional uterine bleeding; the only randomized, placebo-controlled trial documented the beneficial impact long recognized by clinicians.[457] For patients who need effective contraception, oral contraceptives are a good choice to provide hormone therapy for amenorrheic patients, as well as to treat dysmenorrhea. Oral contraceptives are also a good choice to provide prophylaxis against the recurrence of endometriosis in a woman who has already undergone more vigorous treatment with surgery or the gonadotropin-releasing hormone (GnRH) analogues. To protect against endometriosis, oral contraceptives should be taken daily, with no break and no withdrawal bleeding. In a prospective series, women with endometriosis who had persistent dysmenorrhea despite cyclic oral contraceptive treatment experienced a significant decrease in symptoms with daily, continuous use.[482] Endometriosis may be associated with a slight increase in the risk of ovarian cancer, and another benefit of treatment with estrogen-progestin contraception is a reduction in this risk comparable to that in women without endometriosis.[483]

The low-dose oral contraceptives are effective in treating acne and hirsutism. Suppression of free testosterone levels is comparable with that achieved with higher dosage.[397, 484] The beneficial clinical effect is the same with low-dose preparations containing levonorgestrel, previously recognized to cause acne at high dosage.[397, 485] Formulations with desogestrel, gestodene, and norgestimate are associated with greater increases in sex

hormone-binding globulin and significant decreases in free testosterone levels. Comparison studies with oral contraceptives containing these progestins can detect no differences in effects on various androgen measurements among the various products or compared with older products.[15, 399, 486] Theoretically, these products would be more effective in the treatment of acne and hirsutism; however, this has not been documented by clinical studies. It is likely that all low-dose formulations, through the combined effects of an increase in sex hormone-binding globulin and a decrease in testosterone production, produce an overall similar clinical response, especially over time (a year or more).

Oral contraceptives have long been used to speed the resolution of ovarian cysts, but the efficacy of this treatment has not been established. Randomized trials have been performed with women who develop ovarian cysts after induction of ovulation.[487–489] No advantage for the contraceptive treatment could be demonstrated. The cysts resolved completely and equally fast in both treated and nontreated groups. Of course, these were functional cysts secondary to ovulation induction, and this experience may not apply to spontaneously appearing cysts. Two short-term (5 and 6 weeks) randomized studies could document no greater effect of oral contraceptive treatment on resolution of spontaneous ovarian cysts when compared with expectant management.[490, 491] Clinical experience (untested by studies) leads us to believe that oral contraception does provide protection in women against the recurrent formation of ovarian cysts.

A case-control study indicated a reduced risk for benign ovarian tumors; however, the results did not achieve statistical significance.[492] The impact was limited to endometrioid lesions, an expected result.

Continuation: Failure or Success?

Despite the fact that oral contraception is highly effective, hundreds of thousands of unintended pregnancies (close to 1 million) occur each year in the United States because of the failure of oral contraception. Worldwide, millions of unintended pregnancies result from poor compliance. In general, unmarried, poor, and minority women are more likely to have failures, reaching rates of 10–20%.[493, 494] Overall, the failure rate with actual use is as high as 8%. This difference between the theoretical efficacy and actual use reflects compliance and noncompliance. Noncompliance includes a wide variety of behavior: failure to fill the initial prescription, failure to continue on the medication, and incorrectly taking oral contraception. Compliance (continuation) is an area in which personal behavior, biology, and pharmacology come together. Oral contraceptive continuation reflects the interaction of these influences. Unfortunately, women who discontinue oral contraception often utilize a less effective method or, worse, fail to substitute another method.

There are 3 major factors that affect continuation:

1. The experience of side effects, such as breakthrough bleeding and amenorrhea, and perceived experience of "minor" problems, such as headaches, nausea, breast tenderness, and weight gain. Multiple side effects dramatically and progressively increase the likelihood of discontinuation.[495, 496] Because these complaints respond well even to placebo treatment,[497] it is reasonable to expect a favorable response to sensitive and attentive counseling, as well as changing to a different product.

2. Fears and concerns regarding cancer, cardiovascular disease, and the impact of oral contraception on future fertility.

3. Nonmedical issues, such as inadequate instructions on pill taking, complicated pill packaging, and difficulties arising from the patient package insert.

The information in this chapter is the foundation for good continuation, but the clinician must go beyond the presentation of information and develop an effective means of communicating that information. We recommend the following approach to the clinician–patient encounter as one way to improve continuation with oral contraception.

1. Explain how oral contraception works.

2. Review briefly the risks and benefits of oral contraception, but be careful to put the risks in proper perspective, and to emphasize the safety and noncontraceptive benefits of low-dose oral contraceptives.

3. Show and demonstrate to the patient the package of pills she will use.

4. Explain how to take the pills:
   - When to start.
   - The importance of developing a daily routine to avoid missing pills.
   - What to do if pills are missed (identify a backup method).

5. Review the side effects that can affect continuation: amenorrhea, breakthrough bleeding, headaches, weight gain, nausea, etc., and what to do if one or more occurs.

6. Explain the warning signs of potential problems: abdominal or chest pain, trouble breathing, severe headaches, visual problems, leg pain or swelling.

7. Ask the patient to be sure to call if another clinician prescribes other medications.

8. Ask the patient to repeat critical information to make sure she understands what has been said. Ask if the patient has any questions.

9. Schedule a return appointment in 1–2 months to review understanding and address fears and concerns; a visit at 3 months is too late because most questions and side effects occur early.[496] Inconsistent use of oral contraceptives is more common in women who are new starters.[494]

10. Make sure a line of communication is open to clinician or office personnel. Ask the patient to call for any problem or concern before she stops taking the oral contraceptives.

Concluding Thoughts

In the 1970s, as epidemiologic data first became available, we emphasized in our teaching and in our communication with patients the risks and dangers associated with oral contraceptives. In the 1990s, with better patient screening and epidemiologic data documenting the effects of low-dose products, we appropriately emphasized the benefits and safety of modern oral contraceptives. In the new millennium, we can with confidence promote the idea that the use of oral contraceptives yields an overall improvement in individual health, and from a public health point of view, the collection of effects associated with oral contraceptives leads to a decrease in the cost of health care.

Contraceptive advice is a component of good preventive health care, and the clinician's approach is a key factor. This is an era of informed choice by the patient. Patients deserve to know the facts and need help in dealing with the state of the art and those issues clouded by uncertainty. But there is no doubt that patients are influenced in their choices by their clinician's advice and attitude. Although the role of a clinician is to provide the education necessary for the patient to make proper choices, one should not

lose sight of the powerful influence exerted by the clinician in the choices ultimately made. Emphasizing the safety and benefits of oral contraceptives, and the contribution of oral contraceptives to individual and public health, allows a clinician to present oral contraception with a very positive attitude, an approach that makes an important contribution to a patient's ability to make appropriate health choices.

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