# A CLINICAL GUIDE FOR CONTRACEPTION

## THIRD EDITION

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## Dedication

This book is dedicated to o
As Sherlock Holmes said: "Yo

D. Darney.—3rd ed.

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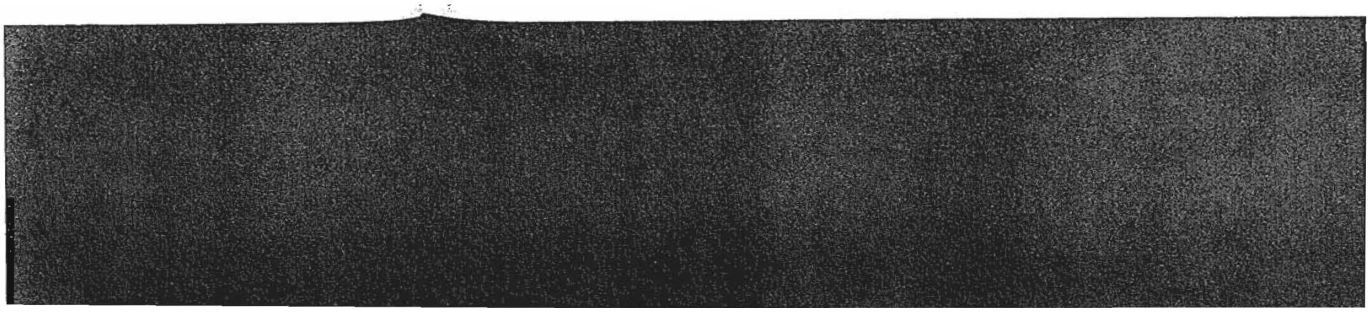
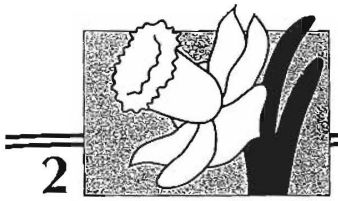
## Dedication

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



# Contents



# 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 hormonal contraception with synthetic sex steroids that is recent.

## History[1-3]

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 announciated 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, it required the ovaries from 2500 pregnant pigs 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. The plant ingredient in Beth's root was diosgenin, and it is unlikely that it exerted any therapeutic effect. The rhizome in Beth's root was too small to provide sufficient amounts for commercial use, and Marker's search for an appropriate plant then 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

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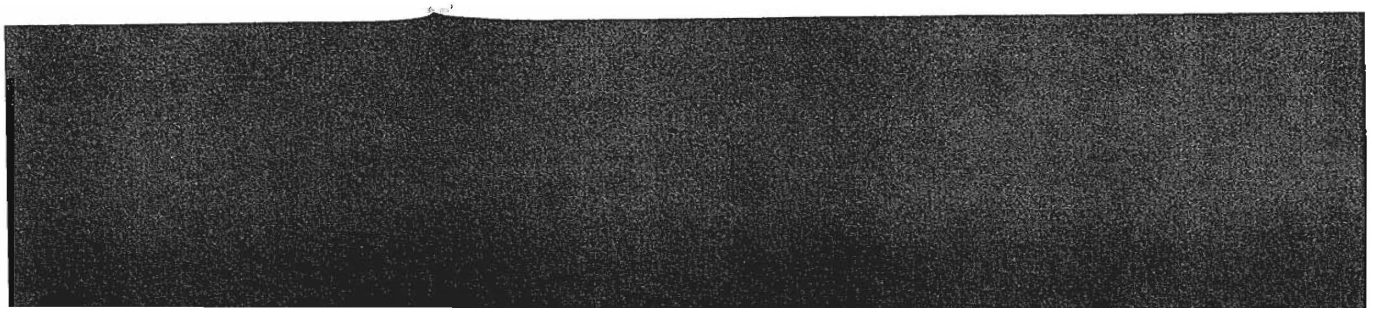
Marker managed to get one bag of tubers back to Pennsylvania State University and isolated diosgenin. Unable to obtain support from the pharmaceutical industry, Marker used his life savings, and in 1942, he returned to Veracruz, collected the roots of the Mexican yam, and prepared a syrup from the roots. 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 two 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 one 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, sold, eventually reaching ownership by 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 recognized 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[4]

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 graduare 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 tional agent to receive a patent G.D. Searle & Company.

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

### Gregory Pincus

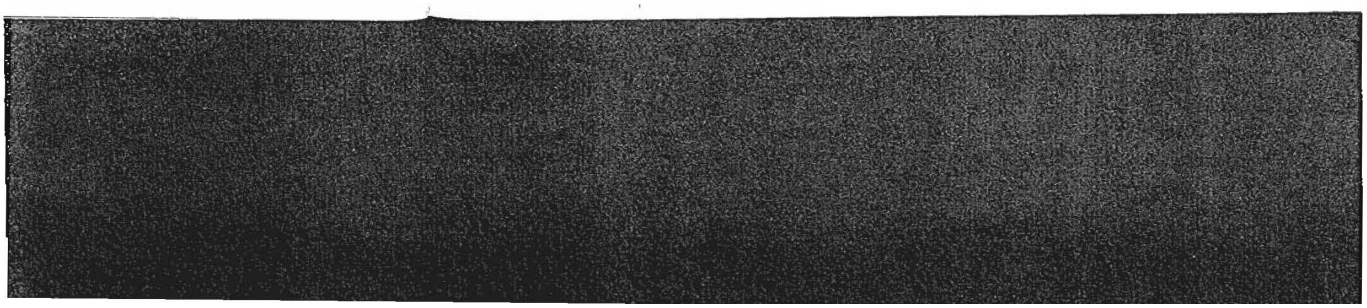
Gregory Goodwin (Goody) Pincus was born in 1903 in New Jersey, the son of Russian Jewish immigrants who lived on a farm colony founded by a German-Jewish philanthropic organization. Pincus was the oldest of 6 children and grew up in a home of intellectual curiosity and energy, but even his family regarded 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. degree 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, 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 3 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 3000 scientific papers were published.

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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.

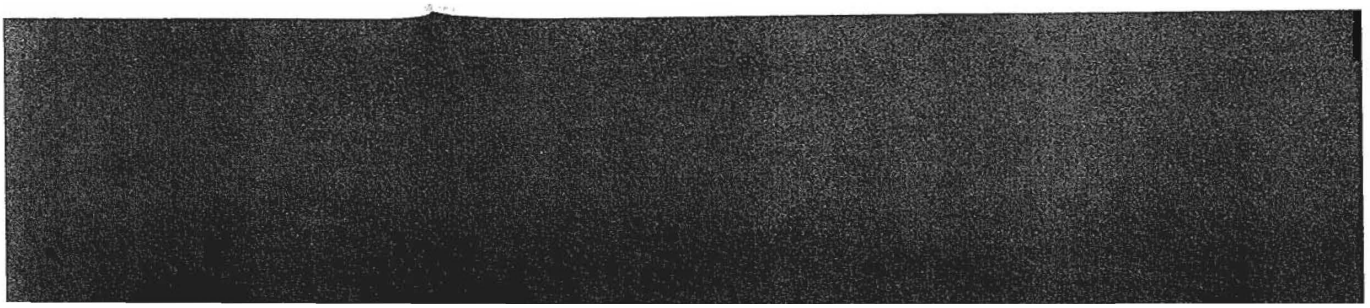
The initial discoveries that led to an oral contraceptive can be attributed to M-C Chang (also the first to describe the capacitation process of sperm). In 1951, he confirmed the work of Makepeace (in 1937) demonstrating that progesterone could inhibit ovulation in rabbits. When norethindrone and norethynodrel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

Katherine Dexter McCormick 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, so she established the Neuroendocrine Research Foundation at Harvard to study the disease. 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."[5]

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, probably 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
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> in almost every Europ
> American country. We ha
> lation in country after
> demographic future, asses
> efficient fertility control.
> heartening experience; s
> continuing poverty and
> dedicated colleagues and
> handicap of excess fertilit
> tive function. Among th
> found devoted students."

Syntex, a wholesale drug suppli
organization. By the time Syntex
a sales outlet, Searle marketed E
mg norethynodrel). Ortho-No

Using oocytes from oophorectomies, they
944, probably the first demonstration of
vitro. Rock was interested in the work
r contraception however, but because he
d be used to overcome infertility.

ome convincing that Rock's Catholicism
were eventually won over because of his
literally transformed his personal values
the problems secondary to uncontrolled
igi Mastroianni, the first administration
was to Rock's patients in 1954. Of the
mg of synthetic progestin (a dose extrap-
20 days each month, all failed to ovulate
to begin referring to the medication as
came pregnant after discontinuing the
l along was motivated to treat infertility).

lounce their findings at the International
Tokyo, in the fall of 1955. Rock refused
iat Pincus and Chang were moving too
hich apparently was spirited and strong),
ıtation generated worldwide publicity.

ırcia and Edris Rice-Wray, working in
al was performed. The initial progestin
ı about 1% mestranol. In the amounts
500 µg of mestranol, a sufficient amount
y itself. When efforts to provide a more
gen content and yielded breakthrough
the estrogen for cycle control, thus estab-
combined estrogen-progestin oral
were conducted by J.W. Goldzieher in
s Angeles.

Searle, picked the Searle compound for
rt, convinced Searle that the commercial
warranted the risk of possible negative
rinced Rock, and together they pushed
istration for acceptance of oral contra-
proved for the treatment of miscarriages
1960, for contraception. Neither Pincus
got rich on the pill; alas, there was no

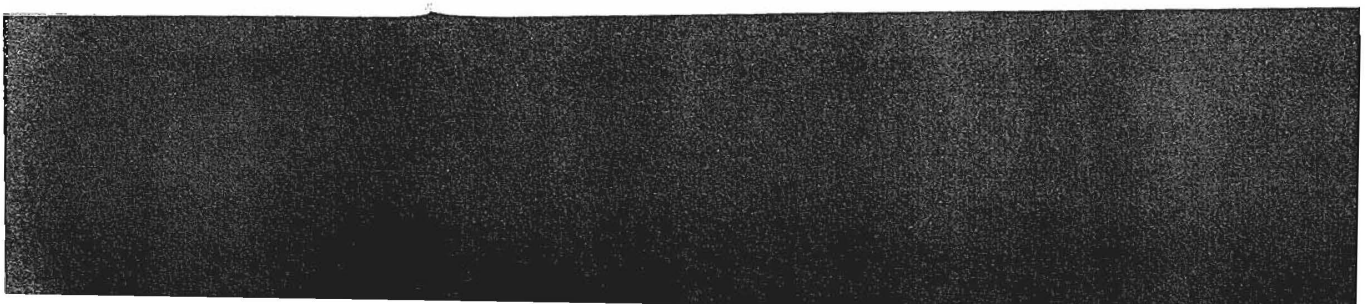
The Pill did bring Pincus fame and travel. There is no doubt that he was very much aware of the accomplishment and its implications. As he traveled and lectured in 1957, he said: "How a few precious facts obscurely come to in the laboratory may resonate into the lives of men everywhere, bring order to 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."[5]

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, and Chang, in 1991, was buried at the age of 82, 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."[5]

> "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."[5]

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,

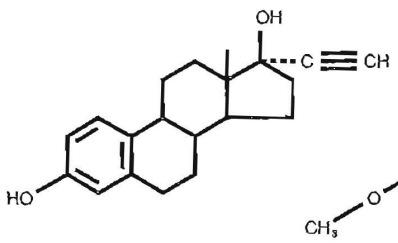


appeared in 1962. Wyeth Laboratories introduced norgestrel in 1968, the same year in which the first reliable prospective studies were initiated. It was not until the late 1970s that a dose-response relationship between problems and the amount of steroids in the pill was appreciated. As a result, health 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 with acceptable side effects.

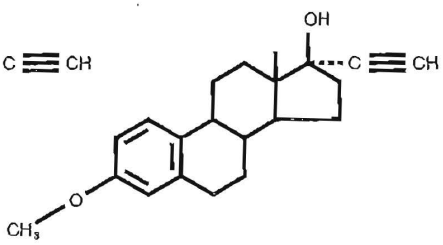
## Pharmacology of Steroid Contraception

### 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 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 will 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 estr
levels) varies significantly from
population to another.[6] There is
sampling times within the same
that the same dose can cause sic
another.

The estrogen content (dosage) o
Thrombosis is one of the most se
role in the increased risk of death
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an oral contraceptive.

### The Progestin Component o

The discovery of ethinyl substitu
the 1930s) to the preparation of
testosterone. In 1951, it was dem
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and most importantly, it change
an androgen to that of a progest
tional derivatives of testosteron
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### Combination Oral Contraceptives

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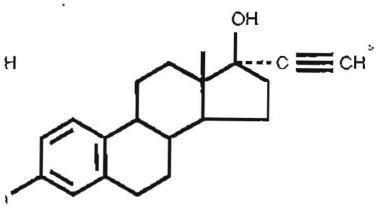


Mestranol

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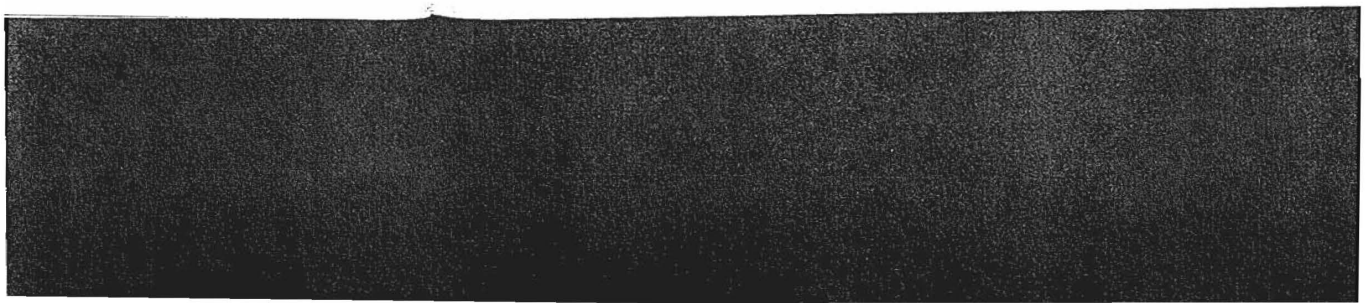
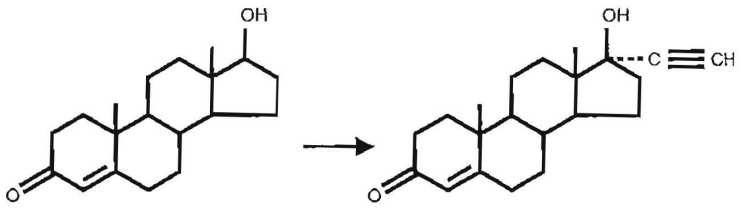
The metabolism of ethinyl estradiol (particularly as reflected in blood levels) varies significantly from individual to individual, and from one population to another.[6] There is even a range of variability at different sampling times within the same individual. Therefore, it is not surprising that the same dose can cause side effects in one individual and none 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.

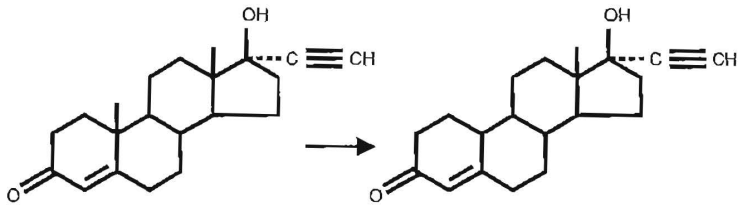
### The Progestin Component of Combination Oral Contraceptives

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



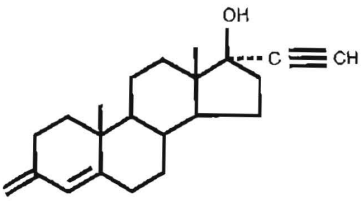

Ethisterone Norethindrone

The "impurity" of 19-norrestosterone, 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.[7] 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.[8] Clinically, androgenic and estrogenic activities of the progestin component are, therefore, 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 is now limited to the low-dose products.

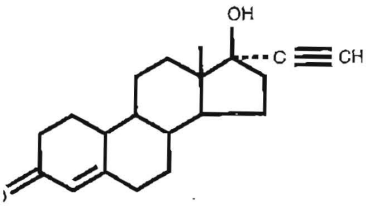
The norethindrone family cc
progestins: norethindrone, nore
diol diacetate, lynestrenol, n
gestodene. Dienogest is a 19-nc
ethinyl group.

Most of the progestins closely
the parent compound. Thus th
acetate, ethynodiol diacetate, an
norethindrone.

Norgestrel is a racemic equal mi
the levorotatory enantiomer. Th
other and rotate the plane of p
dextrorotatory form is known as
l-norgestrel (known as levonorg
of norgestrel.




Ethisterone




Norethindrone

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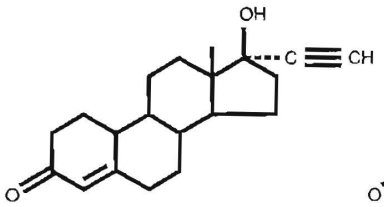
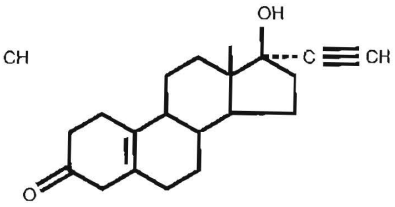
The norethindrone family contains the following 19-nortestosterone progestins: norethindrone, norethynodrel, norethindrone acetate, ethynodiol diacetate, lynestrenol, norgestrel, norgestimate, desogestrel, and gestodene. Dienogest is a 19-nortestosterone, but it does not have a 17α-ethinyl group.

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.

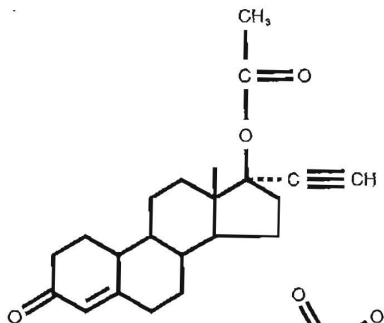
Norgestrel is a racemic equal mixture of the dextrorotatory enantiomer and the levorotatory enantiomer. These enantiomers are mirror images of each other and rotate the plane of polarized light in opposite directions. The dextrorotatory form is known as d-norgestrel, and the levorotatory form is l-norgestrel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



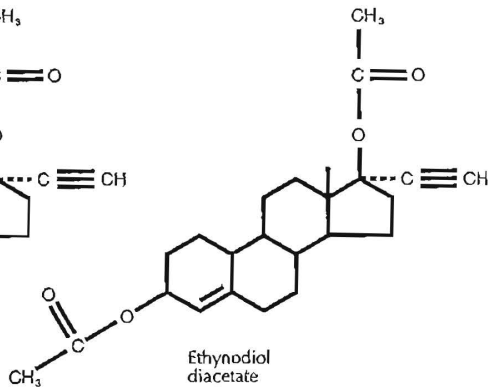

Norethindrone



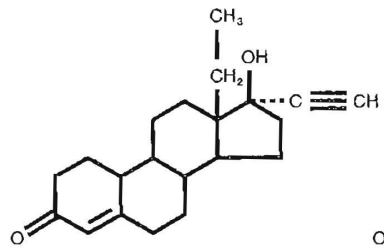

Norethynodrel



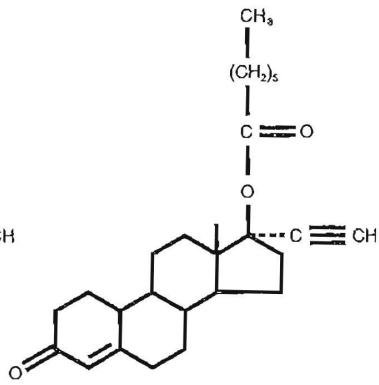

Norethindrone acetate




Ethynodiol diacetate




Levonorgestrel



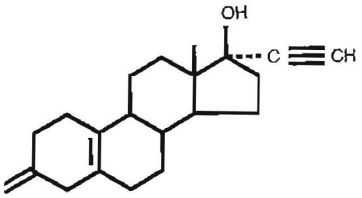

Norethindrone enanthate

Desogestrel undergoes two metal
ity is expressed in its active meta
This metabolite differs from leve
the 11 position. Gestodene differ
double bond between carbons 1
metabolized into many derivati
levonorgestrel. Several metaboliti
mate, including 17-deacetylated
levonorgestrel. Although norgest
gists have included it in the oral
because its activity is believed
levonorgestrel metabolites, althou

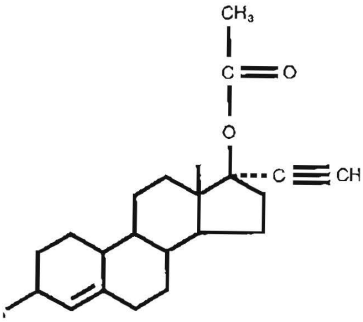
Definitions used in Epidemiolo

Low-Dose Oral Contracep
- Products con
ethinyl estrac
First Generation Oral Co
- Products con
ethinyl estrac
Second Generation Oral
- Products con
norgestimate
norethindron
ethinyl estrac
Third Generation Oral C
- Products con
with 20 or 3

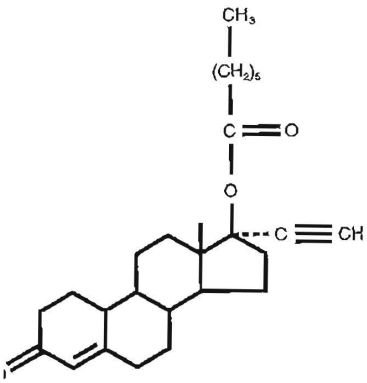
A second group of progestins
discovered that acetylation of th
gesterone produced an orally ac
the 6 position is necessary to gi
human use, probably by inhibiti
one with substituents at the 17
medroxyprogesterone acetate.




Norethynodrel




Ethynodiol diacetate




Norethindrone enanthate

Desogestrel undergoes two metabolic steps before the progestational activity is expressed in its active metabolite, 3-keto-desogestrel (etonorgestrel). 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 $\Delta^{15}$ gestodene. It is metabolized into many derivatives with progestational activity, but not levonorgestrel. Several metabolites contribute to the activity of norgestimate, including 17-deacetylated norgestimate, 3-keto norgestimate, and levonorgestrel. Although norgestimate is a "new" progestin, epidemiologists have included it in the oral contraceptive second generation family because its activity is believed to be largely due to levonorgestrel and levonorgestrel metabolites, although this may not be totally accurate.[9,10]

Definitions used in Epidemiologic Studies:

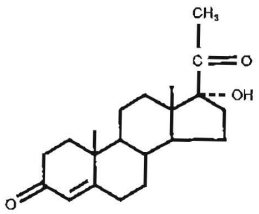
Low-Dose Oral Contraceptives
- Products containing less than 50 µg ethinyl estradiol

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

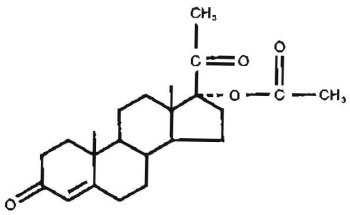
Second Generation Oral Contraceptives
- Products containing levonorgestrel, norgestimate, and other members of the norethindrone family and 30 or 35 µg ethinyl estradiol

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

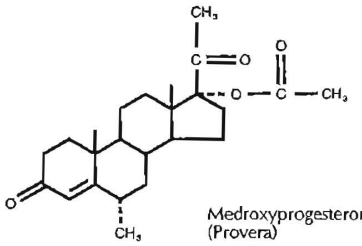
A second group of progestins became available for use when it was discovered that acetylation of the 17-hydroxy group of 17-hydroxyprogesterone produced an orally active but weak progestin. An addition at the 6 position is necessary to give sufficient progestational strength for human use, probably by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



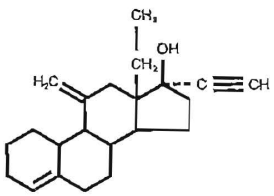
17α-Hydroxyprogesterone



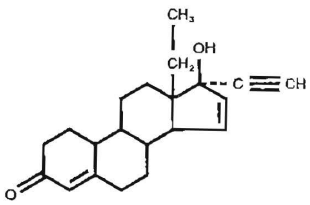
17-Acetoxy progesterone



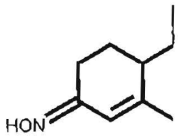
Medroxyprogesterone acetate (Provera)



Desogestrel

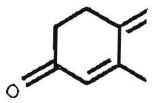


Gestodene



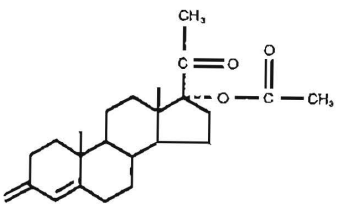
Norgestin

Dienogest is a progestin that cc
nortestosterone family and the
antiandrogenic activity and is use
estradiol as an oral contraceptive.

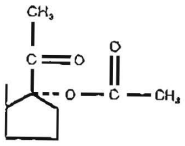


Dienoges

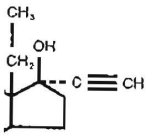
**Potency.** For many years, clinic
the pharmaceutical industry atte
ous progestational component
assessment, however, has been
Progestins act on numerous targ
glands, and the liver), and poten
and end point being studied.
Clauberg test (endometrial cha
prostate assay, were used to dete
were considered acceptable meth
steroid hormone action and m
and human responses differ, hav
from human studies.

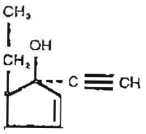


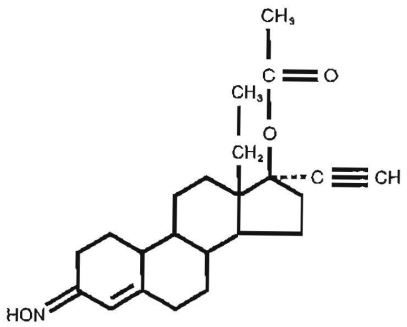
17-Acetoxy progesterone



Medroxyprogesterone acetate
(Provera)

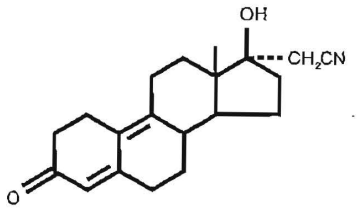






Norgestimate

Dienogest is a progestin that combines the properties of both the 19-nortestosterone family and the derivatives of progesterone.[1] It exerts antiandrogenic activity and is used in a 2 mg dose combined with ethinyl estradiol as an oral contraceptive.



Dienogest

**Potency.** For many years, clinicians, scientists, medical writers, and even the pharmaceutical industry 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 upon 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. Potency is no longer an important clinical issue.

**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.[12] 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 may be of greater clinical value in the treatment of acne and hirsutism, but appropriate comparative clinical studies to document a better response have not been performed.

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## New Formulations

The multiphasic preparation alter
progestin components periodically
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out sacrificing efficacy. Metab
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Reduction of the pill-free interval
pill omission with low-dose oral c
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usual 7 days) is associated with
approach adds estrogen for 5 of th
approaches have failure rates and
comparable to the standard regime
alterations can be established.

An estrophasic approach (Estrostep
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yielding a low rate of side effects s
results in a marked increase in
produces a very low androgenic s
circulating free androgens.

## Mechanism of Action

The combination pill, consisting o
given daily for 3 of every 4 weeks.
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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 may even promote 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.

## 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 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.

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.[13] Another approach adds estrogen for 5 of the usual 7 pill-free days. 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.

An estrophasic approach (Estrostep®) combines a continuous low dose of a progestin with a low, but gradually increasing dose of estrogen.[14] 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.

## 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.[15-17] 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 selection and 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 will always take 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.[18]

## Efficacy

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 in order 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 as being associated with apparent oral contraceptive failures are vomiting and diarrhea.[19,20] *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
multiphasic formulations, and lo
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higher dose monophasic combin
monitored studies with motivate
0.1%, typical usage is associated
year of use. A new estimate for
year of use is now available, usin
of Family Growth and correctin
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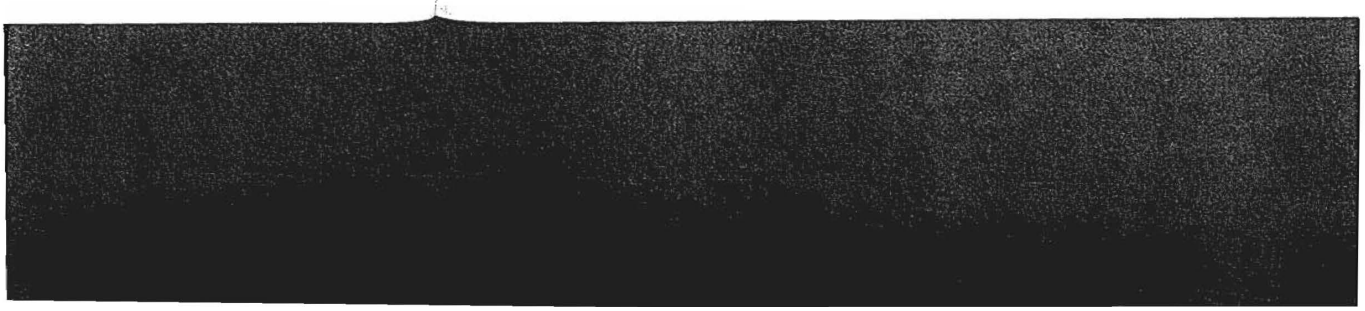
*sed later).*

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.[18] 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. A new estimate for contraceptive failure rates during the first year of use is now available, using the data from the 1995 National Survey of Family Growth and correcting for the underreporting of induced abortion.[21] Previous estimates overestimated effectiveness because contraceptive failures that result in induced abortions are significantly underreported.



Failure Rates During the First Year of Use, United States [21,22]

| Method | Percent of Women with Pregnancy Lowest Expected | Typical |
|---|---|---|
| No method | 85.0% | 85.0% |
| Combination pill | 0.1 | 7.6 |
| Progestin-only pill | 0.5 | 3.0 |
| IUDs | | |
| Progesterone IUD | 1.5 | 2.0 |
| Levonorgestrel IUD | 0.1 | 0.1 |
| Copper T 380A | 0.6 | 0.8 |
| Implant | 0.05 | 0.2 |
| Injectable | 0.3 | 3.1 |
| Female sterilization | 0.05 | 0.05 |
| 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 Contra

### Cardiovascular Disease

In October, 1995, the Unite
Medicines sent a letter to all U.I
women taking oral contracepti
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The controversy involving new p
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desogestrel and gestodene have
with oral contraceptives contair
divided into two major categori
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sis and pulmonary embolism
myocardial infarction and stroke

**The Coagulation System.** Tl
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generated from prothrombin b
calcium, and phospholipids. T
factors VII, IX, and X, as well as
the body's natural anticoagular
and factors IXa, Xa, and XIa. Pr
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and its helper, protein S, inhibit
Tissue plasminogen activator (t-
released when a clot forms. Both
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degrading the fibrin. Deficienc
protein S are inherited in an aut
10–15% of familial thrombosis
venous thromboembolism are
distantly by a mutation in the p

Year of Use, United States [21,22]

| Percent of Women with Pregnancy | |
|---|---|
| Lowest Expected | Typical |
| 85.0% | 85.0% |
| 0.1 | 7.6 |
| 0.5 | 3.0 |
| 1.5 | 2.0 |
| 0.1 | 0.1 |
| 0.6 | 0.8 |
| 0.05 | 0.2 |
| 0.3 | 3.1 |
| 0.05 | 0.05 |
| 0.1 | 0.15 |
| 6.0 | 25.7 |
| | 20.5 |
| 9.0 | |
| 3.0 | |
| 2.0 | |
| 1.0 | |
| 4.0 | 23.6 |
| 20.0 | 40.0 |
| 9.0 | 20.0 |
| 20.0 | 40.0 |
| 9.0 | 20.0 |
| 6.0 | 12.1 |
| 3.0 | 13.9 |
| 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 two-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.[23,24]

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.[25]

Coagulation and Fibrinolysis Factors:

- 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)
  - Factors that favor 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.[26,27] The factor V Leiden mutation is found in approximately 30% of individuals who develop venous thromboembolism.[28] Activated protein C inhibits coagulation by degrading factors V and VIII. One of the 3 cleavages 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).[28] 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 8-fold increased risk of venous thrombosis, and homozygotes, an 80-fold increased risk, and this risk appears to be further enhanced by oral contraceptive use. 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.[29] The mutation is believed to have arisen in a single ancestor approximately 21,000 to 34,000 years ago.[30] 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.[25,31] The prevalence of this abnormality in the white

population is estimated to range
use has been reported to markedl
in carriers of the prothrombin mu

The administration of pharmacol
oral contraceptives causes an incre
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are offset by increased fibrinolyti
tions containing 30 and 35 µg of
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these changes are essentially all
significance is unknown.

Smoking produces a shift to hype
lation has been reported to have
smokers.[40,41] One study comparin
found similar mild pro-coagulant
was a trend toward increased fibri

There is no evidence of an increas
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Royal College of General Practiti
contraceptives was not associated
Part of the concern for a possible
was based on a presumed advers
which would then be added to
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### Venous Thromboembolism –

Older epidemiologic evaluations
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tinuation.[48,49] Thromboembolic d
the pharmacologic administratio
believed to be related to the estr

actors:

clotting when increased

VIII, X
clotting when decreased
n III

clotting when increased

activator inhibitor-1 (PAI-1)
clotting when decreased

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ited disorder (after the factor V Leiden ine to adenine change, in the gene encod- alence of this abnormality in the white population is estimated to range from 0.7% to 4%.[32] Oral contraceptive use has been reported to markedly increase the risk of venous thrombosis in carriers of the prothrombin mutation.[33]

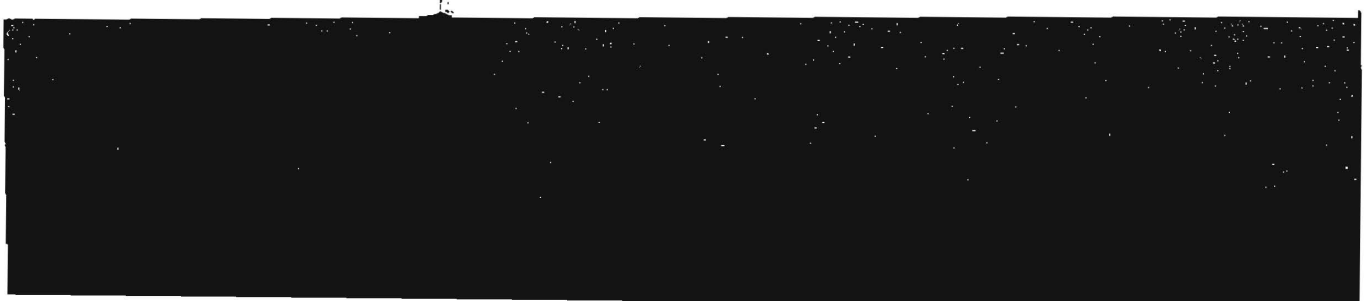
The administration of pharmacologic amounts of estrogen as in high-dose oral contraceptives causes an increase in the production of clotting factors such as factor VII, factor VIII, factor X, factor XII, protein C, and fibrinogen, and a decrease in antithrombin III and protein S.[34,35] Progestins given alone have no effect on the clotting system and when combined with estrogen can attenuate estrogen-induced activity.[36] 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.[37,38] 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.[39] However, these changes are essentially all within normal ranges and their clinical significance is unknown.

Smoking produces a shift to hypercoagulability.[40] A 20 µg estrogen formulation has been reported to have no effect on clotting parameters, even in smokers.[40,41] One study comparing a 20 µg product with a 30 µg product found similar mild pro-coagulant and fibrinolytic activity, although there was a trend toward increased fibrinolytic activity with the lower dose.[42]

There is no evidence of an increase in risk of cardiovascular disease among past users of oral contraception.[43-45] In the Nurses' Health Study and the Royal College of General Practitioners' Study, long-term past use of oral contraceptives was not associated with an increase in overall mortality.[46,47] 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.[48,49] 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.[50-52] Smoking was documented



to produce an additive increase in the risk of arterial thrombosis,[53-55] but had no effect on the risk of venous thromboembolism.[56,57]

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.[58] 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.[59] 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.[60] 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 µg 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).[61] There were only 9 cases and 3 controls using combined oral contraceptives with other progestins, precluding precise analysis. The users of the levonorgestrel formulation 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 second case-control study (f
gists and called *The Transnation*
*Health of Young Women*) analy
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## Venous Thromboembolism

The publication of the 4 reports
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### – The Controversial Studies

*ion (WHO) Collaborative Study of*
*id Hormone Contraception* was a hospi-
subjects collected from 21 centers in 17
e, and Latin America.[60] As part of this
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hinyl estradiol and levonorgestrel (doses
was compared with the risk with prepara-
hinyl estradiol and either desogestrel or
in 9 countries).[61] There were only 9 cases
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users of the levonorgestrel formulation
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ed with nonusers. Current users of a
ased risk of 9.1 compared with nonusers,
tio was also 9.1. Thus, the increased risk
is 2.6 times that of levonorgestrel, when
ight. Also of note, the increased risk for
aining 20 µg ethinyl estradiol was 38.2, a
liable because it was based upon only 8
ice interval (CI) of 4.5–325 reflected this
ised risks were lower than those estimated
higher dose oral contraceptives.

The second case-control study (from an international team of epidemiologists and called *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.[62] 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.

The third 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 U.K.[63] 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 users. 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.

Similar results were reported when women with deep vein thrombosis in the *Leiden Thrombophilia Study* in the Netherlands were re-analyzed for their use of oral contraceptives.[64] 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.

Smoking, well recognized as a risk factor for arterial thrombosis, did not affect the risk estimates in these studies. This is not a new observation; older studies of venous thromboembolism also failed to identify smoking as a risk factor.[56,57]

### Venous Thromboembolism — Subsequent Studies

The publication of the 4 reports in late 1995 and early 1996 was followed by a flood of letters to editors, as well as reviews and editorials, highlighting confounding and bias problems in these studies.[65-67] Some prominent figures were convinced the reports of increased risks with desogestrel and gestodene were real;[68,69] others were skeptical, pointing out possible

confounding biases. Subsequently, re-analysis and new studies revealed confounders and biases in the initial studies. Thus, a consistent picture gradually emerged with consideration of proper analysis of the generated data, and the adjustment for confounding biases not initially apparent.

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).[70] 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.

A case-control study using 83 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 below).[71] *In this study, matching cases and controls by exact 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.[72] Thus, in these two studies, more precise adjustments for age eliminated a confounding bias.

A re-analysis of the Transnational Case-Control Study considered the duration and patterns of oral contraceptive use.[73,74] This re-analysis focused on first-time users of second and third generation oral contraceptives. *Statistical analysis with adjustment for duration of use and for first-time users could find no differences between second and third generation products.* Similarly, a re-analysis of the U.K. General Practice Database (the MediPlus database) could demonstrate do difference between different oral contraceptive formulations.[75]

## Evaluation of the Studies

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Former users discontinue oral contr
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## 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. Furthermore, progestational agents, and desogestrel and gestodene in particular, have no significant impact on clotting parameters.[12,35] 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.[76,77] Other laboratories, however, could not replicate Kuhl's findings.[78-80]

Former users discontinue oral contraceptives for a variety of reasons, and often are switched to what clinicians perceive to be "safer" products (*"preferential prescribing"*).[81-83] 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 will be 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.[66] *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.[81,82] 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.[73,74] It is unlikely that the "healthy user effect" will be 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. Examples are the protective effect of oral contraceptives on the risk of ovarian cancer, and the benefits of postmenopausal estrogen therapy on cardiovascular disease. 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 will produce consistent conclusions.*

*The apparent differences associated with the new progestins, it is now apparent, were due to two major factors: (1). The marketing and preferential prescribing of new products, and (2). The characteristics of the patients for whom the new products were prescribed. Most impressive and important is the fact that there is no evidence of an increase in mortality due to venous thromboembolism since the introduction of new progestin oral contraceptives.*[63,84]

## Venous Thromboembolism and the Factor V Leiden Mutation

The new studies indicate that 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.[51-64,85] 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[86,87]

| 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 | 30 | 120-150 |
| Leiden mutation – homozygous | 80 | 320-400 |

An inherited resistance to activate
tion, is the most common inherit
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reported to have a 30-fold increas
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thrombosis.[91]

An increase in the risk of venous
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woman with an inherited clotting
ting factor is responsible.

Should screening for the factor V
clotting disorders) be routine p
carrier frequencies of the Leiden n
percentages are similar in men an

- Caucasian Americans –
- Hispanic Americans –
- Native Americans –
- Black Americans –
- Asian Americans –

These estimates are consistent w
that this is a trait carried in pe
States, of the approximately 10 m
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However, because the incidence i
(4–5 per 100,000 young wom
required to be screened to prev
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present tests.[92]

Furthermore, because only a sma
mutation (less than 1 in 1000) h
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### n and the Factor V Leiden Mutation

it a risk of idiopathic venous thrombosis ontraceptives, at a level of approximately tmal, general incidence.[61-64,85] However, an d protein C, the factor V Leiden mutation, t portion of the patients who experience g oral contraceptives.

### Actual Incidence of mboembolism[86,87]

| Relative Risk | Incidence |
|---|---|
| 1 | 4-5 per 100,000 per year |
| 12 | 48-60 |
| 6-10 | 24-50 |
| 3-4 | 12-20 |
| 6-8 | 24-40 |
| 30 | 120-150 |
| 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.[56,88] Heterozygotes have a 6- 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.[89,90] There is no known association between the factor V Leiden mutation and arterial thrombosis.[91]

An increase in the risk of venous thrombosis associated with oral contraceptive use has been observed in carriers of the prothrombin mutation.[33] It is probable that oral contraceptive use further increases the risk in any woman with an inherited clotting disorder no matter which specific clotting factor is responsible.

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:[87]

| | | |
|---|---|---|
| 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),[86,87] 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.[92]

Furthermore, because only a small number of women even with the Leiden mutation (less than 1 in 1000) have a clinical event (99.85% of the women 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 idiopathic venous thromboembolism or a close positive family history (parent or sibling) of venous thrombosis.*

This aspect of the oral contraceptive venous thromboembolism controversy received a transfusion of energy with the publication of a report from the Netherlands, utilizing a laboratory test for resistance to activated protein C to compare differences in oral contraceptive non-users, users of second generation oral contraceptives, and users of third generation oral contraceptives.[93] Women who used any oral contraceptive had a decreased sensitivity to activated protein C compared with nonusers, and women who used third generation oral contraceptives were even less sensitive, and less than users of second generation products. This was presented as an explanation for the epidemiologic data indicating greater risks of venous thromboembolism associated with desogestrel and gestodene, and an editorial in the April 19, 1997, issue of Lancet concluded that this report was the "nail in the coffin" confirming the epidemiologic evidence.[59]

Subsequent epidemiologic reports not only removed the nails from the coffin, but returned the coffin to its maker. A closer look at the report from the Netherlands finds considerable overlap in the results among all the groups tested, and many of the oral contraceptive users had results comparable with the nonusers. In a subsequent report from these investigators, the study design, a cross-over trial, was an improvement over the cross-sectional design of the first report.[94] Although once again oral contraceptives containing desogestrel were associated with a greater resistance to activated protein C compared with levonorgestrel-containing products, there was still considerable overlap comparing the two progestins, and with baseline levels as well. It is always prudent to avoid making clinically meaningful conclusions from acquired changes in a single laboratory test (especially when the clinical meaning of a laboratory test is uncertain). Furthermore, the results could not be corroborated by another laboratory, and in a case-control study of women with venous thromboembolism, no association could be detected with measurements of acquired activated protein C resistance.[95,96]

## Arterial Thrombosis

Because the incidence of cerebral thrombotic attacks (thrombotic strokes and transient ischemic attacks) among young women is slightly higher than venous thromboembolism and myocardial infarction, and death and disability are more likely, stroke is the most important possible side effect. A very low incidence of stroke in young women means there would be little increase in absolute risk associated with oral contraceptives. However, because the incidence of cerebral thrombotic attacks is higher in women over age 35, we should do our best, as the following paragraphs will indi-

cate, to make sure oral contracep
and without significant risk fact
hypertension, migraine with aura
and smoking). The estrogen dose
infarction and thrombotic strokes
dose estrogen oral contraceptives

### Arterial Thrombosis — Myoc

A population-based, case-control
infarction in users of low-do
Permanente Medical Care Progra
*increase in the odds ratio for myocar
users compared with past or never*
reported by a community-base
Scotland, and Wales.[100]

In the Transnational case-control
from 16 centers in Austria, Franc
Kingdom, the results were as foll

| | Cases | Co |
|---|---|---|
| Any OC use | 57 | |
| 50 µg estrogen OCs | 14 | |
| Old progestin OCs | 28 | |
| New progestin OCs | 7 | |

These data were interpreted as in
infarction associated with oral c
gestodene. However, the *reduced*
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thrombotic attacks (thrombotic strokes mong young women is slightly higher id myocardial infarction, and death and the most important possible side effect. ı young women means there would be iated with oral contraceptives. However, thrombotic attacks is higher in women r, as the following paragraphs will indi-

cate, to make sure oral contraceptive users over age 35 are in good health and without significant risk factors for cardiovascular disease (especially hypertension, migraine with aura, diabetes mellitus with vascular disease, and smoking). The estrogen dose is important for the risk of myocardial infarction and thrombotic strokes.[97,98] 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.[99] *There was no statistically significant increase in the odds ratio for myocardial infarction in current oral contraceptive users compared with past or never users.* A similar negative outcome was reported by a community-based case-control study from England, Scotland, and Wales.[100]

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:[101,102]

| | 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 prod-

ucts, and, in our view, the power is too limited to make any conclusion regarding the new progestin oral contraceptives. This is a good example of a conclusion that may be statistically significant, but clinically not real.

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.*[101] In addition, there was an indication that patient screening is important in minimizing the impact of hypertension on the risk of myocardial infarction.

In the WHO multicenter study, there were 368 cases of acute myocardial infarction.[103] 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. However, 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.* Similarly, the Oxford-Family Planning Association cohort study could detect no increased risk of myocardial infarction in nonsmokers or in light smokers (less than 15 cigarettes daily).[104]

*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.*[98] 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.

## Incidence of Myocardial Infarction

| |
|---|
| Overall incidence[105] |
| Women less than age 35 |
| Nonsmokers |
| Nonsmokers & OCs |
| Smokers |
| Smokers & OCs |
| Women 35-years-old and older |
| Nonsmokers |
| Nonsmokers & OCs |
| Smokers |
| Smokers & OCs |

NOTE: The above incidences are
use paired with cardiovascular risk
lation. Effective screening wou
increased risks in the smokers and
tected cardiovascular factors, espe

### Arterial Thrombosis — Stroke

Older case-control and cohort stuc
bral thrombosis among current use
However, thrombotic stroke did r
nonsmoking women with the use
than 50 µg ethinyl estradiol.[107,108] A
by the Royal College of General P
concluded that current users were a
ing effect in former users); howev
smokers and to formulations with
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ers or in light smokers (less than 15 ciga-

*of acute myocardial infarction in young*
*increase in risk was noted only in current*
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oked, (accounting for 80% of the acute
women), increasing body mass index,
pertension in pregnancy, diabetes melli-
graine, and family history of myocardial
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ated with oral contraceptives; no influ-
as apparent with diabetes, hypertension,
es could be demonstrated according to

**Incidence of Myocardial Infarction in Reproductive Age Women**[103]

| | |
|---|---|
| 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 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.[106-108] 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.[107,108] 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.[108] A case-control study of all 794 women in Denmark who suffered a cerebral thromboembolic attack during 1985–1989 was a lone contrast, concluding that there was an almost two-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.[55]

More recent studies have emphasized the safety of low-dose oral contraceptives. 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.[109] 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). A pooled analysis of two case-control studies from U.S. concluded that there is no increased risk of ischemic or hemorrhagic stroke in current users of low-dose oral contraceptives.[110]

The Transnational study also analyzed their data for ischemic stroke in a case-control study of 220 ischemic strokes in the United Kingdom, Germany, France, Switzerland, and Austria.[111] 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 similar analysis of the General Practice Research Database could also detect no difference in stroke risk comparing progestin components.[112]

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.[113,114] In addition, an analysis focusing on specific progestins could detect no differences comparing oral contraceptives containing desogestrel or gestodene with formulations containing levonorgestrel.[115]

The WHO 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.[113] 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 o
case in developing countries. I
impact, and past users did nc
more cigarettes daily exerted
increasing the risk of ischemi
tension and oral contraceptiv
and older; however, this, too,
tension. *Thus, the conclusion c*
*is extremely low, concentrated i*
*have hypertension.*

In the WHO study on hemorr
use of oral contraceptives wa
hemorrhagic stroke only in de
reflects the lack of screening fo
risk (about 10- to 15-fold) wa
tives who had a history of h
increased the risk in oral cor
hypertension. For hemorrhagi
risk, and neither did duratic
*concluded that the risk of her*
*increased only slightly in older v*
*risk factors such as hypertension.*

A second Danish case-control
sitory cerebral ischemic
thromboembolic attacks.[97] In
1995 included 146 cases of c
ischemic attacks. Only use
(levonorgestrel, norgestrel, an
increased risk (about 2.5-fol
with estrogen in the dose rang
although the number of 20 µ
cient to establish a lower risk
reduced risk associated with d
ratio did not achieve statistica
ing, treated hypertension, di
family history of myocardial i
history of venous thromboem