

Hormonal Contraception Forty Years After Approval of “The Pill”

In May of 1960, the U.S. Food and Drug Administration (FDA) approved the first hormonal method of contraception for women in the U.S.: a daily oral dose of the synthetic hormones estrogen and progesterone. Commonly referred to as “the Pill,” this birth control option offered American women a new way to control their fertility. Because the Pill is easy to use, highly effective, and quickly reversible, it is often said to have transformed America’s relationship with sex — and possibly ushered in a new sexual era. Dozens of oral contraceptive products have been approved over the last forty years, and a range of alternative hormonal birth control methods have come onto the market in just the last decade. While still relying on synthetic hormones, these contraceptive options — multi-year IUDs and implants, quarterly and monthly shots, multi-week vaginal rings, and weekly skin patches — do not require taking a pill every day.

Today, a woman in the U.S. is more likely to rely on a hormonal birth control method than any other reversible means of preventing pregnancy (surgical sterilization is actually the most common method overall). Oral contraceptives, in particular, are the single most popular reversible birth control choice. Approximately ten million U.S. women — about 25 percent of women aged 15-44 who are at risk for unintended pregnancy¹ — were using the Pill in 1995, the most recent year for which data are available.² Teens and young adults are most likely to rely on oral contraceptives: Among women at risk for unintended pregnancy, 48 percent aged 20-24 and 37 percent aged 25-29 use this method, as do 35 percent of sexually active women aged 15-19.²

Oral contraceptives have been extensively studied. More than forty years of research have brought “safer” pills to market by reducing the amount of estrogen used and creating progesterone-only versions. Studies also show that using oral contraceptives may have benefits beyond pregnancy prevention, including protection from pelvic inflammatory disease, reduced ovarian cancer risk, less irregularity in menstrual bleeding, and fewer ectopic pregnancies. At the same time, extensive experience with oral contraceptives has also confirmed that the Pill can still increase the risk of cardiovascular disease for certain groups of women — namely smokers, older women, and those who are obese or have a history of certain illnesses such as high blood pressure, diabetes, or elevated cholesterol. Oral contraceptives require a prescription in the U.S., although several other countries have weighed the Pill’s risks and benefits and decided that it can be safely sold “over the counter,” or without a prescription.³

The widespread use of the Pill in the U.S. suggests that women find this birth control method to be convenient and effective. Yet, it has also sparked continuing debate over the possible link between hormonal contraceptives and various health problems, including stroke, cervical cancer, and breast cancer. These concerns remain in some quarters, even though women who use hormonal contraception in the U.S. are encouraged to have a regular Pap test to detect any cervical changes and to discuss breast self-examination, clinical breast exams, and routine mammograms with their health care providers.

Since 2000, the FDA has approved four new hormonal birth control methods — more than were brought to market in the U.S. during the entire previous decade. The arrival of these new contraceptives — and others in the pipeline for approval — will likely encourage continued evaluation of the risks and benefits of hormonal contraceptives. This issue update reviews the research to date on the Pill — the oldest hormonal contraceptive option — as well as current medical recommendations concerning what women should know to make an informed choice about which method to use.

The Pill: Four Decades of Preventing Pregnancy

The Pill is considered an excellent method of birth control, even though it does not offer protection from HIV or other STDs.² Today, the most widely used oral contraceptives (OCs) are called “combined” pills, so named because they contain two hormones (an estrogen and a progestin) similar to those the ovary produces naturally. A second, less commonly used, pill contains only progesterone.

Over the years, the formulations of OCs have changed, largely in response to research linking high levels of estrogen in early combined pills to uncommon but serious side effects such as blood clots, heart attacks, and strokes. In response, new versions of combined pills containing less estrogen were developed, and the progesterone levels in these OCs were reduced. Researchers also developed a progestin-only OC, known as the “minipill.”

As a result, women taking the Pill today receive lower doses of both estrogen and progesterone than women in many of the studies that were conducted to assess the risks of using OCs. Most women can prevent pregnancy using combined pills with less than 35 micrograms (mcg) of estrogen, compared to the 80 to 100 mcg of estrogen that women using older versions of the pill may have taken.² In fact, the FDA now urges physicians who are starting patients on combined pills to use OCs with no more than 50 mcg of estrogen and, if possible, to consider one of the newer

“low-dose” combined pills that contain only 30 or 35 mcg of estrogen.⁴

How Pills Prevent Pregnancy

When estrogen occurs naturally in a woman’s body, it stimulates the growth and development of the uterus at puberty, triggers changes in breast tissue at puberty and childbirth, and thickens the inner lining of the uterus (endometrium) during the first half of the menstrual cycle. Progesterone, which the body produces during the second half of the menstrual cycle, is often called the “pregnancy-supporting” hormone because it prepares the endometrium to receive the fertilized egg. Once pregnancy occurs, the continued presence of progesterone prevents the release of any additional eggs (ovulation).

Combined oral contraceptives which contain both estrogen and progestin prevent pregnancy by inhibiting ovulation. These pill types as well as progestin-only pills also discourage sperm from entering the uterus by making the cervical mucus thick and make it difficult for a fertilized egg to implant by causing changes in the fallopian tubes and the uterine lining.

Combined OCs, taken consistently and correctly, have a 0.1% pregnancy rate among users, which means that just one in 1,000 women will become pregnant during their first year of use. When progestin-only pills are used consistently and correctly, one in 200 women — or 0.5% — will become pregnant. Used “typically,” meaning that some women will occasionally miss a pill, about five percent of women will experience an unintended pregnancy within the first year of typical use of either type of oral contraceptive. Side effects, when they occur, are generally mild, and can include nausea, breast tenderness, headaches, or weight gain.² Fertility is restored once a woman discontinues her pills, although the resumption of regular ovulation may take several months.⁴

Beyond Birth Control: Benefits and Risks of the Pill

Ovarian Cancer Prevention⁵

Most studies to date show an association between use of combined oral contraceptives and a reduced risk for ovarian cancer. In fact, authors of the Centers for Disease Control and Prevention’s Cancer and Steroid Hormone Study estimate that OC use averts more than 1,700 cases of ovarian cancer each year in the U.S. This research, along with other studies conducted over the past 13 to 18 years, showed that the longer a woman used OCs, the lower her risk of ovarian cancer.

Compared with women who have never used pills, women who have taken OCs for four years or less are 30 percent less likely to develop ovarian cancer; women who take them for five to eleven years are 60 percent less likely; and those who have taken them for 12 or more years are 80 percent less likely.² Moreover, this lowered risk persisted long after OC use ceased. The most recent report from the CDC study found that the protective effect was seen in women who

had used OCs for as little as 3 to 6 months, and it continued for 15 years after use ended.

Several hypotheses have been offered to explain how combined OCs might protect against ovarian cancer, but the exact mechanism is still not known. One explanation may be that the Pill inhibits ovulation, a process that has been linked to a woman’s risk of ovarian cancer. However, new research indicates that the progestin contained in combined pills may play a dominant role in the chemical prevention of the disease.⁶ In fact, oral contraceptives with higher levels of progestin are associated with a greater reduction of ovarian cancer risk of than those with a lower dose of progestin.

Endometrial Cancer Reduction⁷

As with ovarian cancer risk, researchers have found that use of oral contraceptives may protect against cancers of the endometrium. Results of the Cancer and Steroid Hormone Study found that women who used combination OCs for at least one year had about half the risk of developing endometrial cancer seen among women who never took birth control pills. Additionally, the beneficial effect of OC use appeared to persist at least 15 years after women had stopped taking birth control pills. Other studies have found that the longer the OC use, the greater the reduction in risk. However, taking combination pills for less than a year appears to provide no protection against endometrial cancer.

Bone Density Improvement

Oral contraceptives have a positive effect on bone mineral density. Estrogen deficiency is known to contribute to bone loss in postmenopausal women, and combined OCs deliver consistent doses of estrogen. Studies of women who have not yet gone through menopause as well as young women with low estrogen levels indicate that, compared with nonusers, users of combined OCs have higher bone mineral density.⁸ Combined OC use during the reproductive years is believed to promote attainment of higher peak bone mass, so that women using these pills will enter menopause with stronger bones.⁹

Menstrual Regulation

Some women take oral contraceptives to reduce menstrual bleeding irregularities because pills can decrease the severity of menstrual cramps and pain. OCs may also decrease the number of bleeding days and amount of blood loss during menstruation by 60 percent or more.² These uses have led researchers to explore the use of oral contraceptives for longer than the standard 28-day cycle (21 days of hormones followed by 7 “pill-free” days during which a woman takes a placebo or nothing). They believe that, if still effective at preventing pregnancy, decreasing the number of “pill-free” weeks in a year might prevent or suppress menstrual migraines and estrogen withdrawal symptoms, which include bleeding, pain, headaches, and endometriosis. It would also reduce a woman’s annual expenditure on menstrual hygiene products. One recent, small study found that extending the standard cycle to 49 days continued to prevent pregnancy without increasing episodes of spotting or bleeding.¹⁰

There are currently no products approved or packaged for extended OC use in the U.S. However, some physicians are offering longer OC regimens to their patients using a common practice that allows use of an approved product in a manner supported by clinical evidence but not indicated on the label. One product in development, known as Seasonale, is designed to result in just four menstrual periods annually by using an 84-day dosing regimen. The FDA is currently reviewing it.

Acne Management

Research indicates that oral contraceptives with low androgen-to-progestin activity can help women manage problematic acne. To date, the FDA has approved two combined oral contraceptives — Ortho-Tricyclen (Ortho-McNeil) and Estrostep (Parke-Davis) — for treatment of acne.¹¹ Other pills containing low-androgen progestins may be equally effective for acne management,¹² and the recently approved low-dose combined pill, Yasmin, may also have the capacity to improve acne.¹³

Cardiovascular Problems

Low-dose oral contraceptive formulations have been found to pose little increased risk for a stroke or myocardial infarction (MI) — commonly called a heart attack — when used in appropriately selected women. Among healthy non-smoking women who use combined OCs with less than 50 mcg of estrogen, studies have found no increased risk for MI or stroke.¹⁴ However, increased risk for MI associated with combined OCs has occurred in women who smoke — and the risk appears to increase with age (particularly for women over age 35), with the dose of estrogen in the formulation, and the number of cigarettes smoked. As a result, most data suggest that women smokers who are older than 35 years should not use combined OCs.¹⁵

The other main cardiovascular risk found to be associated with combined OCs is venous thromboembolism (VTE), whose symptoms include swelling, warmth, and pain to the touch on the lower leg. Studies have consistently shown a 3- to 6-fold increased risk of VTE in combined OC users.¹⁶ Most data indicate that the primary contributing factor to VTE is estrogen (because it can alter blood-clotting mechanisms) and that progestins pose little risk, although there are some conflicting data about the VTE risk of the current “third-generation” progestins. Combined oral contraceptives may also increase blood pressure in a small percentage of women, and the probability of developing hypertension increases with age and the duration of pill use. When an increase in blood pressure occurs, it is usually mild to moderate and reversible within 1 to 3 months after discontinuing use of combined OCs.¹⁷

Risk of Liver Tumors

A non-cancerous tumor of the liver called hepatic adenoma has been found to occur, rarely, among women who use the Pill. They occur in about 1 in 33,000 pill users per year, mostly in women who have taken OCs for 5 years or longer. These tumors do not spread, but they may rupture and cause internal bleeding. There is also some evidence

that oral contraceptives may increase the risk of certain malignant liver tumors. However, the risk is difficult to evaluate because of the different patterns of women’s use of oral contraceptives and because these tumors are very rare in American women (the incidence is less than 1 case per 100,000 white women).¹⁸

Cervical Cancer Risk

A study conducted by scientists at the National Cancer Institute and other cancer centers support a direct relationship between extended use of the pill (5 or more years) and a slightly increased risk of cervical cancer. However, the exact nature of the association between OC use and the development of cervical cancer is unclear.¹⁹ One study found that long-term use of oral contraceptives increases the risk of cancer of the cervix up to four-fold in women infected with the human papillomavirus (HPV).²⁰ The labels on oral contraceptives warn of the possible risk of cervical cancer, advising users to have a yearly Pap test to monitor for possible cellular changes in the cervix.

Breast Cancer Risk and Hormones Still Being Studied

Researchers now understand that a woman’s risk of developing breast cancer is influenced by certain “hormonally related” factors, such as age at the beginning of menstrual function (menses), age at first live birth, and age at menopause. However, the actual association between hormones and breast cancer remains subject to debate.²¹

To date, nearly all studies of oral contraceptives indicate that they do not increase the risk of breast cancer in women over 45 years of age. More recently, some studies have shown an increase in risk in relation to OC use in women diagnosed with breast cancer before age 45. Even so, it is still unclear what factors may be contributing to the elevation in risk for younger women. Some studies suggest that OCs may promote tumor growth. Others suggest that the responsible factors are long-term pill use or starting OCs at an early age.

Four recent studies (two in the United States, one in England, and one in the Netherlands) suggest that OCs especially increase the risk of breast cancers occurring before age 35. Again, researchers are uncertain whether OCs themselves predispose women to suffer these early, very rare breast cancers or whether the way OCs have been used in recent times may be responsible. And, because the majority of breast cancers occur in women after 50 years of age, it remains to be seen whether the increased risk that has been seen among these women will persist as they age.

Given the strong interest in breast cancer prevention and treatment, additional research over the next several years will help to clarify what relationship, if any, exists between the Pill and breast cancer risk.²²

Pill May Not Be Good Choice for Some Women

While most women can successfully use oral contraceptives, there are some women for whom this birth control method is contraindicated. They include women who: are pregnant or breastfeeding; women; have unexplained vaginal bleeding, current breast cancer, liver tumors, active hepatitis, or severe cirrhosis; are aged 35 or older; smoke heavily (20 cigarettes/day or more); or are at greatly increased risk of cardio-vascular conditions.²³

The Pill and Drug Interactions

Some medications can diminish the Pill's effectiveness, including certain antibiotics (rifampin, and possibly ampicillin and tetracycline); epilepsy drugs (Dilantin); anti-inflammatory or antiarthritic drugs (phenylbutazone); and barbiturates (phenobarbital).²⁴ A review of studies of the impact of antibiotic treatment on oral contraceptive effectiveness conducted by the American Medical Association's Council on Scientific Affairs found that women who use combined OCs and antibiotics at the same time could be at risk for pregnancy because some women using both drugs had significant decreases in the concentration of the contraceptive hormone ethinyl estradiol (a synthetic form of estrogen) in their blood and appeared to ovulate. The researchers warned health care providers to be cautious in prescribing combined OCs to women using antibiotics and to advise women uncomfortable with the potential risk to use another — nonhormonal — method of contraception. The World Health Organization advises only that women taking specific antibiotics that increase the rate of hepatic drug metabolism, such as rifampicin and griseofulvin, avoid using combined OCs.²⁵

The effectiveness of oral contraceptives may also be influenced by the use of non-prescription herbal supplements, such as St. John's Wort — a product sometimes used to help fight mild depression. Officials in Sweden and the United Kingdom have started suggesting that women taking oral contraceptives not take St. John's Wort in the wake of reports that several women in both countries became pregnant unintentionally while taking birth control pills in conjunction with the herbal supplement.²⁶

Conclusion

Four decades after the first Pill was approved in the U.S., hormonal methods of contraception continue to be the first choice for many American women. Over the years, studies have shown that oral contraceptives are highly effective in preventing pregnancy (but not STDs) — and have a number of additional health benefits. Yet there are still some concerns about certain risks of the Pill, and there are not yet definitive answers about the long-term effects of using this and other hormonal contraceptive methods.

It remains to be seen whether the recent approval of new contraceptive methods will increase the overall number of women who rely on hormonal methods or merely shift the balance away from use of the Pill specifically. As more women take advantage of alternatives to oral

contraceptives, researchers will be able to track the impact these methods have on women's health.

In the coming years, researchers will continue to consider the outstanding questions about benefits and risks of using the Pill and other hormonal birth control options. Pharmaceutical companies are also expected to explore additional contraceptive options, bringing new types of OCs to market while also seeking alternative ways to deliver pregnancy-preventing hormones — potentially allowing birth control methods to be more easily tailored to women's varied lifestyles and contraceptive needs.

New Methods of Hormonal Contraception

In addition to different formulations of "the Pill," hormonal contraception has been available to women in the U.S. for a number of years by injection or through an implant. In the last two years, however, a record four new alternative delivery systems for hormonal contraception were approved by the FDA.

Lunelle is a monthly intramuscular injection (shot) of a combination of estrogen and progestin, which is more than 99 percent effective when administered as recommended. It works in ways similar to combined oral contraceptives by preventing a woman from ovulating, building up cervical mucus to prevent sperm from entering a woman's uterus, and altering the endometrial lining of her uterus. Side effects are similar to those experienced with combination oral contraceptives. After Lunelle is discontinued, it takes about two to three months to return to fertility. Lunelle does not protect against sexually transmitted diseases. For more information, go to: <http://www.lunelle.com>

Mirena is a small, T-shaped device that is inserted into a woman's uterus by a health care provider. Each day, it releases a low dose of progestin. Mirena can be used to prevent pregnancy for up to five years, with a failure rate of less than 1 percent. It protects against pregnancy by inhibiting ovulation or sperm mobility, thickening a woman's cervical mucus, and thinning the endometrial lining of the uterus. Side effects, which are reportedly minimal, are similar to those experienced by some users of progestin-only oral contraceptives and intrauterine systems; some women may also experience a change in their menstrual bleeding patterns. After removal of Mirena, return to menstruation and fertility is rapid—about 8 out of 10 women trying to become pregnant will do so within the first year. Like other intrauterine devices, Mirena does not protect against sexually transmitted diseases. For more information, go to: <http://www.mirena.com>

NuvaRing is a flexible vaginal ring that contains estrogen and progestin. A woman inserts the ring into the back of her vagina, much like a diaphragm, and leaves it in place for three weeks, followed by one ring-free week. NuvaRing releases a low, daily dose of hormones to prevent pregnancy. It is more than 98 percent effective in preventing pregnancy for one month when it is used correctly. NuvaRing works in ways similar to combined oral contraceptives and the side effects are also similar to those experienced with combination oral contraceptives. It does not protect against sexually transmitted diseases. For more information, go to: www.nuvaring.com

Ortho Evra is a small, thin, adhesive skin patch that contains estrogen and progestin. The patch is worn continuously on the buttocks, abdomen, upper outer arm, or upper torso (excluding the breasts), for one week (seven days) and then replaced the same day with a new patch. The patch is worn for three weeks, followed by one patch-free week. Ortho Evra releases a continuous dose of hormones through the skin and into the bloodstream to prevent pregnancy. It is 99 percent effective in preventing pregnancy when used correctly. Ortho Evra works in ways similar to combined oral contraceptives and the side effects are also similar. After Ortho Evra is discontinued, there can be some delay in returning to regular menstruation and fertility. Like other hormonal methods, it does not protect against sexually transmitted diseases. For more information, go to: www.orthoevra.com

References

- ¹ Women are not considered to be at risk for pregnancy if they have not had intercourse within the last three months; they are pregnant, trying to become pregnant, have given birth within the previous two months; or are sterile.
- ² Hatcher RA et al., *Contraceptive Technology*, 17th revised edition, NY: Ardent Media, 1998.
- ¹ Trussell J et al., Should oral contraceptives be available without a prescription? *American Journal of Public Health*, 1993; 83:1094-1099.
- ⁴ Sulak PJ. Oral contraceptives: therapeutic uses and quality-of-life benefits -- case presentations. *Contraception*. 1999;59(1 suppl):35S-38S and Hatcher RA, Trussell J, Stewart F, et al., *Contraceptive Technology*, 17th revised edition, NY: Ardent Media, 1998.
- ⁵ Unless otherwise noted, data in this section is drawn from The Center for Disease Control: Oral contraceptive use and the risk of ovarian cancer: The Centers for Disease Control Cancer and Steroid Hormone Study. *Journal of the American Medical Association* 249:1596-1599, 1983; The Centers for Disease Control and the National Institute of Child Health and Human Development: The reduction in risk of ovarian cancer associated with oral contraceptive use: The Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development. *New England Journal of Medicine* 316:650-655, 1987
- ⁶ Schildkraut JM et al., *Journal of the National Cancer Institute* 2002 94:32-38, *Contraceptive Technology Update* March 2002, p. 28
- ⁷ The Centers for Disease Control: Oral Contraceptive use and the risk of endometrial cancer: The Centers for Disease Control Cancer and Steroid Hormone Study. *Journal of the American Medical Association* 249:1600-1604, 1983.
- ⁸ Hergenroeder AC, Smith EO, Shypailo R, et al. Bone mineral changes in young women with hypothalamic amenorrhea treated with oral contraceptives, medroxyprogesterone, or placebo over 12 months. *Am J Obstet Gynecol*. 1997;176:1017-25 and Kuohung W, Borgatta L, Stubblefield P, et al. Low-dose oral contraceptives and bone mineral density: an evidence-based analysis. *Contraception*. 2000;61:77-82.
- ⁹ Kuohung W, Borgatta L, Stubblefield P, et al. Low-dose oral contraceptives and bone mineral density: an evidence-based analysis. *Contraception*. 2000;61:77-82.
- ¹⁰ Miller L and KM Notter, Menstrual reduction with extended use of combination oral contraceptive pills: Randomized controlled trial, *Journal of Obstetrics and Gynecology*, 2001, 98:771-778.
- ¹¹ Redmond GP. Effectiveness of oral contraceptives in the treatment of acne. *Contraception*. 1998;58(3 suppl):29S-33S
- ¹² Mansour D. Yasmin -- a new oral contraceptive, a new progestogen: the reasons why. *Eur J Contracept Reprod Health Care*. 2000;5(suppl 3):9-16 and Redmond GP. Effectiveness of oral contraceptives in the treatment of acne. *Contraception*. 1998;58(3 suppl):29S-33.
- ¹³ Foidart JM. The contraceptive profile of a new oral contraceptive with antiminerlocorticoid and antiandrogenic effects. *Eur J Contracept Reprod Health Care*. 2000;5(suppl 3):25-33.
- ¹⁴ Clinical Management Guidelines for Obstetrician-Gynecologists. The use of hormonal contraception in women with coexisting medical conditions. Washington, DC: American College of Obstetricians and Gynecologists; 2000. ACOG Practice Bulletin 18 and Venous thromboembolic disease and combined oral contraceptives: results of international multicentre case-control study. *World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception*. *Lancet*. 1995;346(8990):1575-82.
- ¹⁵ Goldbaum GM, Kendrick JS, Hogelin GC, et al. The relative impact of smoking and oral contraceptive use on women in the United States. *JAMA*. 1987;258:1339-42.
- ¹⁶ Cardiovascular Disease and Steroid Hormone Contraception. Report of a Scientific Group. Geneva, Switzerland: World Health Organization; 1998. WHO Technical Report Series, No. 877. Available at: www.who.int/hrp/progress/46/01.html and Lawrenson R, Farmer R. Venous thromboembolism and combined oral contraceptives: does the type of progestogen make a difference? *Contraception*. 2000(2 suppl):62:21S-28S.
- ¹⁷ Venous thromboembolic disease and combined oral contraceptives: results of international multicentre case-control study. *World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception*. *Lancet*. 1995;346(8990):1575-82.
- ¹⁸ Rooks JB, Ory HW, Ishak KG, et al: Epidemiology of hepatocellular adenoma: The role of oral contraceptive use. *Journal of the American Medical Association* 242:644-648, 1979; Tao, LC: Oral contraceptive-associated liver cell adenoma and hepatocellular carcinoma. *Cancer* 68: 341-347, 1991; Palmer J, Rosenberg L, Kaufman DW, et al: Oral contraceptive use and liver cancer. *American Journal of Epidemiology* 130:878-882, 1989
- ¹⁹ Brinton LA, Huggins GR, Lehman HF, et al: Long-term use of oral contraceptives and risk of invasive cervical cancer. *International Journal of Cancer* 38(3):399-44, 1986
- ²⁰ Moreno V et al., Effect of oral contraceptives on risk of cervical cancer in women with human papillomavirus infection: the IARC multicentric case-control study, *Lancet*, 2002; 359(9312).
- ²¹ Unless otherwise noted, data in this section is drawn from Brinton, LA, Daling, JR, Liff, JM, et al: Oral contraceptives and breast cancer risk among younger women. *Journal of the National Cancer Institute*, 87(13):827-835, 1995; The Centers for Disease Control and the National Institute of Child Health and Human Development: Oral contraceptive use and the risk of breast cancer: The Centers for Disease Control and the National Institute of Child Health and Human Development Cancer and Steroid Hormone Study. *New England Journal of Medicine* 315:405-411, 1986; Romiu I, Berlin JA, Colditz G: Oral contraceptives and breast cancer: Review and meta-analysis. *Cancer* 66:2253-2263, 1990; Rookus MA, and Van Leeuwen, FE: Oral contraceptives and risk of breast cancer in women aged 25-54 years. The Netherlands Oral Contraceptives and Breast Cancer Study Group. *Lancet* 344:844-851, 1994; Thomas DB: Oral contraceptives and breast cancer: Review of the epidemiologic literature. *Contraception* 43(6):597-642, 1991; White E, Malone KE, Weiss NS, et al: Breast cancer among young U.S. women in relation to oral contraceptive use. *Journal of the National Cancer Institute* 86: 505-514, 1994
- ²² Marchbanks PA et al., The NICHD Women's Contraceptive and Reproductive Experiences Study: Methods and Operational Results, *Annals of Epidemiology*, 2002, 12:213-221.
- ²³ FHI and WHO, Fact Sheet on Oral Contraceptives, 2001.
- ²⁴ Facts about oral contraceptives, Maureen B. Gardner, Office of Research Reporting, National Institute of Child Health and Human Development (NICHD).
- ²⁵ Family Health International, Network: Improving Reproductive Health Services, Vol. 21, No. 3, 2002.
- ²⁶ See www.reutershealth.com (Reuters Health), February 5, 2002.



The Henry J. Kaiser Family Foundation
2400 Sand Hill Road
Menlo Park, CA 94025
Phone: 650-854-9400 Fax: 650-854-4800

Washington Office:
1450 G Street N.W., Suite 250
Washington, DC 20005
Phone: 202-347-5270 Fax: 202-347-5274

www.kff.org

Additional copies of this publication (#3243) are available on the Kaiser Family Foundation's web site at www.kff.org or by calling the Foundation's Publication Request Line at 1-800-656-4533.