CHAPTER 2

REVIEW OF LITERATURE
REVIEW OF LITERATURE

Introductory Statement

Oral contraceptive pills are widely used and are generally safe and effective for many women. The world health organization has developed a risk classification system to help physicians to advise patient about the safety of oral contraceptive pills. The choice of pill formulation is influenced by clinical considerations. By choosing appropriately from the available pill formulations, family physicians can minimize negative side effects and maximize non contraceptive benefits. Additional monitoring and follow up are necessary in special populations, such as women over 35 years of age, smokers, perimenopausal women and adolescents. Third generation progestin’s are additional options for achieving non contraceptive benefits, but their use has raised new questions about thrombogenesis. The U.S. food and drug administration has labeled emergency postcoital contraception for use following unprotected coitus.

Oral contraceptive pills are combined formulations of a progestin and estrogen. These pills have been widely used in the United States for almost 40 years. Recent data indicate that oral contraceptive pills are used annually by approx. 10 million U.S. women. (JC, Adma et al. 1997: (19) 1-114)

History of contraception:

Long before condoms came in rainbow colors and exotic skins, legendary lover Casanova was sewing together strips of fine linen. Centuries before nonoxynol 9, young women in Constantinople snook the gritty and from sea sponges and dipped them in lemon juice before insertion. Contraception has a long and inventive history. Now there is a museum dedicated to one of human kind’s most persistent quests.
Located just outside Toronto, Canada, The History of contraception Museum is billed as one of a kind. With over 600 different I.U.Ds sponges, condoms and other contraceptive devices, the museum is certainly in a class by itself.

“We started collecting back in the 1960’s”, explains Walter Masonic, Director of public Affairs for ortho-MC Neil, Inc., the company that is responsible for the museum. “People weren’t collecting then so we had items taken from a few doctors’ offices. But then word spread and we started getting things from all over the world. Asia, Europe, South America, it’s an International museum now.” The museum is quick to remind visitors that contraception can trace its roots all the way back to the Bible. According to an ancient medical manuscript called the Ebers papyrus. (1550 BC), women were advised to grind together dates, acacia (a tree bark) and a touch of honey into a moist paste, dip seed wool into the sweet gel and place it in the value. As primitive as this sugary mix appears, it was usually effective. Acacia eventually ferments into lactic acid, well known spermicides.

Passaries made their appearance in the second century, according to the museum. They were made of many different substances including elephant and crocodile dung. The museum displays examples of each. “The elephant dung was especially hard to obtain,” Says Mr. Masonic “It was surprising.”

It’s even harder to imagine the difficulty of wearing other passaries such as the so-called block passary. This square block of wood was carved with concaved sides not unlike some door stops. The Victorians, according to some accounts, were especially fond of this method. It was finally condemned in the early 1930’s as an instrument of torture.

The museum’s most extensive wing however is left for I.U.Ds. Long before women were struggling with the Dalkon shield, inter-uterine
devices were being manufactured in a dizzying array of sizes, shapes and materials. The history of contraception Museum owns some 300 examples, including a handmade model from Morocco another that resembles a shepherd’s staff and another carved from a precious jewel in the shape of a crown. The vast majority of modern women, of course, no longer need rely on primitive methods of contraception. The pill alone changed all that. But visitors to the museum might be surprised to learn that the availability and use of oral contraception also stretches back to biblical times and further. Over 4,000 years ago, women in China drank mercury to prevent unwanted pregnancies, centuries later, women in India imbibed carrot seeds. In North America, the museum learned that women in New Brunswick made a kind of white lightening brewed with dried beaver testicles. (By William petreek)

Unlike other commonly prescribed drugs, oral contraceptive pills are taken by healthy women for long periods of time. Thus, it is important for family physicians to be familiar with the most recent information on the side effect profiles of oral contraceptive pills and their risk-to-benefit ratios. Armed with this information, family physicians should be able to help patients choose a primary method. (Health CB, patients choose appropriate contraception. Am fam physician 1993; 48:1115-24)

May 9th, 1960: US-FDA approved the first combined OCP: Less than two years after FDA approval of the first pill for therapeutic purposes, an unusually large number of American women mysteriously develop severe menstrual disorders and ask their doctors for the drug. By late 1959, over half a million American women were taking the drug shortly to become “The Pill”, presumably for the “off-label” contraceptive purposes. In 1960, the pill is approved for use as a contraceptive.
When the contraceptive pills were introduced in 1960, the contained high doses of norethynodrel (progestin) and mestranol (estrogen). Norethynodrel is one of the first-generation progestin called "estranes." This class includes the current agents norethindrone, norethindrone acetate and ethynodiol diacetate. Margaret Sanger died in September 1966 with a dream fulfilled of "Magic Pill".

Lowering the drug does

In 1970s Scientists found that smoking was major factor contributing to blood clotting in pill users, but that the lower doses of pill not only greatly reduce the risk of cloths but also reduce other side effects such as weight gain, headaches and nausea.

Levonorgestrel, a more potent, second-generation progestin, was developed in about 1970. Over the past several decades, the dose of the estrogen component of oral contraceptive pills has decreased from the original 150 µg to 50 µg and then to 35 to 20 µg. These changes were made to lower the risk of thromboembolic complications associated with the use of oral contraceptive pills.

Original, most combination oral contraceptive pill formulation were monophasic, with each active tablet containing a fixed dose of estrogen and progestin throughout the cycle.

Early 1980s The FDA reports that 10.7 million American women are on the Pill. Confidence in the safety of the pill has risen dramatically in the years since the pill hearings. Multiphasic preparations (biphasic and triphasic) were developed in the 1980s to reduce the total dosage of progestin throughout the cycle without increasing the risk of breakthrough bleeding.

1988 At the FDA's urging, drug companies remove the original high dose oral contraceptives from the market as a result of the side effects to the high dose pills.
Introduction of Low dose Pills

In 1990s, third-generation progestins from the gonane class were incorporated into oral contraceptive pill formulations to reduce the androgenic and metabolic side effects that occur with older agents. These new progestins include desogestrel, gestodene and norgestimate.

Low dose pills containing third-generation progestins reportedly have several benefits. Androgenicity associated with older progestins has been linked to adverse lipoprotein and carbohydrate changes, weight gain, acne, hirsutism, mood changes and anxiety. Thus, they are suitable to use in patients with lipid disorders or diabetes.

Third-generation progestins have also been shown to resolve or reduce acne and hirsutism. Furthermore, they do not adversely affect weight or blood pressure. In addition, fewer incidences of contraceptive discontinuation because of lack of cycle control (i.e., breakthrough bleeding, spotting and amenorrhea) have been reported with the newer progestins.

Products containing third-generation progestins are indicated for use in patients who are unable to tolerate other combination oral contraceptive pills.

Progestin-only pills, or minipills, contain no estrogen and also have a lower dose of progestin. These agents are recommended for women with contraindications to the use of combined oral contraceptives and women who are breast-feeding.

1990 According to the annual FDA consumer report, the Pill is considered safe and effective by the government, medical establishment and public.

The high dose OC pill was once the most popular form of reversible birth control. It has now been replaced with the Low Dose Pill (LDP).
**Oral contraceptive pill formulations**

The formulations of oral contraceptive pills have changed dramatically over the years. The first oral contraceptive pill, introduced in 1960, contained high doses of norethynodrel (Progestin) and mestranol (estrogen). Norethynodrel is one of the first generation progestin’s called “estranes”. This class includes the current agents norethindrone, norethindrone acetate and ethynodiol diacetate. Levonorgestrel, a more potent, second generation progestin, was developed in about 1970. Over the past several decades, the dose of the estrogen component of oral contraceptive pills has decreased from the original 150 mcg to 50 mcg and then 20 to 35 mcg. These changes were made to lower the risk of thromboembolic complications associated with the use of oral contraceptive pills.

Originally, most combination oral contraceptive pill formulations were monophasic, with each active tablet containing a fixed dose of estrogen and progestin throughout the cycle. Multiphasic preparations (Biphasic and triphasic) were developed in the 1980s to reduce the total dosage of progestin throughout the cycle without increasing the risk of break through bleeding.

Five years ago, third generation progestin’s from the gonane class were incorporated into oral contraceptive pill formulation to reduce the androgenic and metabolic side effects that occur with older agents. These new progestin’s ,included desogestrel, gestodene and norgestimate. Oral contraceptive pills containing third- generation progestin’s reportedly have several benefits. *(B. Kaplan 1995; 29: 736-42)*.

The third generation progestin’s have minimal impact on blood glucose levels, plasma insulin concentrations and the lipid profile. Thus, they are suitable to use in patients with lipid disorders or diabetes.
Third-generations progestins have also been shown to resolve or reduce acne and hirsutism. Furthermore, they do not adversely affect weight or blood pressure. In addition, fewer incidences of contraceptive discontinuation because of lack of cycle control (i.e. breakthrough bleeding, spotting and Amenorrhea) have been reported with the newer progestins. (B. Kaplan Ann pharmacotherapy 1995; 29: 736-42).

Although third- generations progestin’s may have a better side effect profile in selected patients, no evidence exists to show that these agents are clinically superior to first or second - generation progestin’s. Therefore, switching to third-generation progestins is not necessarily indicated and use of older oral contraceptive pill formulations can be continued. However, products containing third - generation progestin’s are indicated for use in patients who are unable to tolerate other combination oral contraceptive pills.

Progestin - only pills, or minipills, contain no estrogen and also have a lower dose of progestin. These oral contraceptive pills have been marketed in the United States for the past 30 years. Norethindrone (Norlutin) and norgestrel (ovrette) are currently available in India, but they account for only 0.2 percent of the total oral contraceptive pill market. These agents are recommended for women with contraindications to the use of combined oral contraceptives and women who are breast-feeding (IC Chi. Clin obstet gynecol 1995).

Androgenicity associated with older progestins has been linked to adverse lipoprotein and carbohydrate changes, weight gain, acne, hirsutism, mood changes and anxiety. (PD. Darney AM J Med 1995; 98 (Suppl 1A) 1A-104S.)
Efficacy Rates and patterns of oral contraceptive pill use

Efficacy data, or failure rates, for oral contraceptive use can be analyzed based on information about the “perfect” user and the “typical” user. The perfect user never misses taking a pill, takes the pill at the same time each day and never vomits or has diarrhea. They “typical” user’s behavior results in the failure rates reported for the general population. Whereas only one of 1,000 women who take oral contraceptive pills “perfectly” becomes pregnant with in years, 50 of 1,000 women who take the pills “typically” become pregnant with in one year. (Heather RA, et al. Contraceptive technology. 1998).

Benefits of oral contraceptive pills

High efficacy (with proper use), easy of use, separation of pill administration from coitus, reversibility and non contraceptive benefits are among the reasons women and their sexual partners may choose oral contraceptive pills over other forms of contraception.

Contraceptive methods such as the intrauterine device and subdermal contraceptive implants do not require daily administration. However, many women find swallowing a pill easier than manipulating a diaphragm. Likewise, the separation of administration from the coital act allows many oral contraceptive pill users to feel more spontaneous about sexual activity.

Reversibility data are clear. Despite a possible few month’s leg in the return of normal menstrual cycles, most women resume their previous level of fertility once they stop taking oral contraceptive pills.

The non contraceptive benefits (and favorable side effect profiles) of oral contraceptive pills are so important that some patients use the pills exclusively for those reasons. (Darney PD. Am J Med 1995; 98 (Suppl 1A): 1A-104S)
Four decades after introduction of the pill, more women than ever are using it. Today’s low-dose oral contraceptives are safer than and just as effective as earlier pills. Oral contraceptives have substantial benefits for women’s health.

Currently more than 100 million women rely on the pill. It is the top modern family planning method among married women in half of countries surveyed. The pill is most popular in western Europe, where half of married women use it. It is least used in China, India and Japan.

A great many women use the pill at some point in their lives. Outside India and China, half of married women who have ever used family planning have relied on the pill at some time. In the US 80% of all women, born since 1945 have used the pill. A method so widely used deserves continuing attention from health care programs, providers, and researchers.

The important benefit, of course, is highly effective protection against pregnancy, less pain and fewer cramps with periods, lighter periods that last fewer days, and regular periods. OCs also helps prevent ectopic pregnancy (pregnancy outside the uterus) and, by reducing menstrual blood loss, OCs lowers the risk of iron deficiency anemia. In addition, they help to protect women from epithelial ovarian cancer and endometrial cancer and also may reduce the risks of bone density loss, ovarian cysts, benign breast disease and colorectal cancer.

**Fertility-Related Benefits**

**Oral contraceptives can:**
- Effectively prevent unwanted pregnancy.
- Prevent ectopic pregnancy.
Preventing pregnancy

When taken correctly, OCs offers highly effective contraception. All types of pill-combined estrogen-progestin (including multiphasic) and progestin – only – are effective. The newer, lower-dose combined pills containing less than 50 μg of estrogen appear to be as effective as older formulations containing 50 μg of estrogen or more. They prevent ovulation in nearly all cycles. The few studies that have compared lower-dose formulations and higher dose formulations have found no significant difference in effectiveness between the two. A World Health Organization (WHO) study that compared six combined OCs containing 20 to 50 μg of estrogen no significant differences in effectiveness (533).

Generally among perfect users (women who miss no pills and follow instructions exactly), only 1 in every 1,000 women becomes pregnant in the first year of use (189). Some women forget pills or stop them for a time. This largely account for the gap in OC effectiveness between perfect users and typical users. Irregular pill-taking may explain why users of oral contraceptives sometimes experience higher pregnancy rates than users of injectables, IUDs, or implants.

According to Demographic and Health survey data in 15 developing countries in the 1980 s’ the pregnancy rate among OC users was about one per 1,000 per year.

Long term effectiveness of the pill requires sustained correct and consistent use. A recent review of 53 reports on contraceptive effectiveness concluded that no average about 7% of OC users are likely to become pregnant in the first three years of use, but the percentage varies depending on whether women take the pill correctly. Among the generally consistent and conscientious users, 3.8% would become pregnant within three years (365).
Preventing entopic Pregnancy

Protection against ectopic pregnancy is a benefit of all contraceptive methods, to varying degrees. Because they consistently stop ovulation, all combined OCs very effectively prevent ectopic pregnancies (117, 336). Ectopic pregnancy, which occurs when a fertilized ovum develops outside the uterine cavity, can be life-threatening (181). Ectopic pregnancy is fairly common. One US study found that ectopic pregnancy was the reason for 1 in every 13 emergency room visits during the first trimester of pregnancy (446). In the US ectopic pregnancy is the leading cause of pregnancy related death in the first trimester. In 1992 ectopic pregnancies accounted for 2% of reported pregnancies and 9% of all pregnancy related deaths in the US (478).

Benefits of oral contraceptives for Adolescents

Dysmenorrhea is one of the most frequent and debilitating conditions experienced by adolescents. Most women have moderate to complete relief within a few months after starting OC use. (Larsson G, et al. Contraception 1992; 46: 327-334).

Adolescents who experience relief of dysmenorrhea are more likely to use OCs consistently and correctly. Studies have documented a significant reduction in the risk of benign breast disease among OC users, similarly, numerous studies have documented a significant reduction in the frequency of functional ovarian cysts requiring surgery among users of high dose monophasic OC pills with more than 35 μg of estrogen. These findings may be extended to users of newer OC pills with lower levels of hormones. (Lanes SF, et al. Am J Obstet Gynecol 1992).

Many adolescents have marginal iron Stores and iron deficiency anemia is a common problem. Because menstrual flow and its duration are
decreased by nearly 50% with the use of OCs, iron stores can increase significantly. (Robinson JC, et al. *Am J Obstet Gynecol* 1992).

However, only 40% of adolescents seek medical contraceptive services with in the first year of sexual activity. (Alan Guttmacher Institute, *Sex and America’s teenagers. New York: AGI, 1994*).

Pelvic inflammatory disease (PID), ectopic pregnancy and toxic shock syndrome. Endometrial and ovarian cancer. Oral contraceptive use helps reduce the risk of life- treating conditions, such as ovarian and endometrial cancers, are rare among adolescents, but if OCs are taken for more than one year, the protective effects last for at least 19 years after discontinuation of use. (Rosenberg L, et al. *Am J Epidemiol* 1994).

Chronic anovulation, which may have its onset in the adolescent’s years, can be treated with OCs. Oral contraceptives not only induce regular cyclic menses, but also suppress the hormone imbalance that occurs with chronic an anovulation. This has a positive effect on the lipoprotein profile, thereby theoretically decreasing the long-term risk of cardiovascular disease. Oral contraceptive use also interrupts the steady state effect of estrogen associated with anovulation on the endometrium preventing dysfunctional uterine bleeding and endometrial hyperplasia. (Speroff L, et al. 1996)

Correct and consistent use of all forms of contraception is an integral part of the prevention of adolescent pregnancy. The percentage of women using any method of birth control at first intercourse increased from 50% among those beginning coitus before 1980 to 76% for those beginning coitus in the 1990s’. (JC Amba et al. *Vital Health state1997; 19:6*)

Acne improves significantly with most OC pill formulations. This is contrary to the common belief among adolescents that most OCs women acne. In particular, OCs containing third generation progestins may have
an additional benefit for adolescents with acne. Based on the results of placebo-controlled randomized clinical trials of the triphasic norgestimate OC, the U.S. Food and Drug Administration recently added treatment of acne to the labeling for this formulation. (Redmond GP, et al. Obstet Gynecol 1997).

Oral contraceptive pills are the most popular method of contraception among female adolescents. In a 1995 survey, 44% of adolescents at risk for pregnancy chose oral contraceptives (OCs) compared with 37% who chose condoms, 10% who chose injectables contraceptives, and 3% who chose contraceptive implants. (U. Piccinino et al. 1998).

Combination OCs have a beneficial effect on a number of conditions that can affect an adolescent’s quality of life, including dysmenorrhea, benign breast disease, functional ovarian cysts, iron deficiency anaemia, acne and menstrual irregularity. In the United States, adult women and adolescents remain misinformed about the health effects of OCs: In a 1998 survey, half of the respondents were not aware of any OC benefits beyond preventing pregnancy. (Association of professors of gynecology and obstetrics). Washington, DC : APGO, October 6, 1998).

Adolescents have the highest rate of hospitalization for PID in the United States. Oral contraceptives reduce the risk of developing PID by altering the cervical mucus. Other mechanism for this risk reduction may induce altering the endometrial lining and decreasing the ascent of bacteria into the upper genital tract. (Hatcher RA, et al. Contraceptive technology, 17th Ed. 1998).

Compared with earlier, higher-dose pills, current low-dose formulations have considerably lowered the risk of heart attack, stroke and blood clots in the deep leg veins attributed to OCs use. Research has better defined which women would face appreciable risk of heart attack or stroke if they used OCs—women over age 35 year who smoke or who have high
blood pressure. For all other women, using OCs is clearly safer than child bearing in both developing and developed countries.

**OCs for Emergencies:** Combined and progestin-only OCs containing the hormone levonorgestrel can be used for emergency contraception: If the correct dose is started within 72 hours after unprotected intercourse, it reduces the chances of pregnancy. This has long been known, but only recently has the word spread. Now OC tablets are being packaged as emergency contraceptive pills, and levonorgestrel – only tablets, which are more effective and cause less nausea and vomiting, are being introduced especially for this purpose. While not as effective as regular use of OCs or most other modern methods, emergency contraceptive pills meet a crucial need– another important benefit of one of the world’s most widely used family planning methods. *(Oral contraceptives – An update, Population Reports, Series A, November 9, 2000)*

**Non-Contraceptive Health Benefits of oral contraceptives:**

**Prevention of osteoporosis:**

Osteoporosis is a major health problem that results in significant morbidity and mortality. Over 25 million people are affected with osteoporosis in the United States, with an annual estimated cost of $8 billion to $10 billion. Twelve to 20 percent of women who have a hip fracture die within two to three months of the fracture, and at least 50 percent require assistance to perform daily activities after fracture. After 30 years of age, bone resorption gradually exceeds bone formation, and the processes leading to osteoporosis begins, long before menopause. Therefore, interventions to maximize formation of bone mass during the perimenopausal years are essential.
In addition to adequate calcium supplementation and weight-bearing exercise, the use of low-doses contraceptives appears to be associated with a significant increase in bone density. Data from several studies suggest that perimenopausal administration of low-dose oral contraceptive pills can help prevent the acceleration of bone turnover and substantially reverse the decreasing bone density and resultant osteoporosis that occur during the menopausal years [Riggs BL, De cherney et.al. Am J obstet Gynecol 1996]

Other suggested benefits of oral contraceptives:

The use of oral contraceptives also provides protection against benign breast disease, ectopic pregnancy, salpingitis, dysmenorrhea and iron deficiency anaemia. Growing evidence suggests that oral contraceptive use may protect against other conditions, including colorectal cancer, uterine fibroid tumors, toxic shock syndrome, Alzheimer’s disease and rheumatoid arthritis. [Grimes DA, et al. The contraception Report. 1997.]

New findings from the women’s Health Initiative:

Because of the cardiovascular risks associated with early birth control pills, research has continued to focus on this area. Most of this research has found that women using the pill have a slightly elevated risk of heart disease, blood clots, and stroke. The risks have decreased significantly with the advent of the low-dose pill, but remain particularly high for women who smoke, have high blood pressure or diabetes.

Now, a new study is turning this fairly established wisdom on its head. In October 2004, at the annual meeting of the American society of Reproductive Endocrinology, Rahi Victory, MD, of the wayne state medical school in Detroit, Michigan, presented preliminary findings from data on the group of more than 160,000 women participating in the
Women’s Health Initiative (WHI) study. These women were between the age of 50 to 79 at the time the Study began, and about one third (67,000) reported using oral contraceptives at some point in their lives. Contrary to earlier studies, Dr. Victory found that women who used oral contraceptives actually had about an 8% lower risk of developing cardiovascular disease than non-users. Decreases occurred in the rates of stroke, heart-attacks, high blood pressure, and high cholesterol levels. Moreover, the longer birth control pills were used, the larger were the reductions in risk. There were some findings, however, that mirrored those of other studies; increasing age, smoking, diabetes and being overweight significantly increased the risks of heart and circulatory problems in women who used the pill.

Ovarian and Endometrial Cancer Prevention:

Although Dr. Victory’s study is far from conclusive at this point, additional studies have established clear benefits to using oral contraceptives for several health issues other than heart health. Most promising of these, perhaps, is the pill’s strong protective power against certain types of cancer; Particularly cancers of the ovaries and endometrium (the lining of the uterus).

The largest investigation to date, the cancer and steroid Hormone study (CASH). Showed a decrease averaging 40 percent in the development of ovarian cancer in women who had taken oral contraceptives. (The cancer and steroid Hormone study. 1987)

Another Benefit of low-dose oral contraceptive use during the perimenopausal years is a reduction the risk of endometrial cancer. Several studies indicate that oral contraceptives protect against endometrial cancer in a duration-dependent manner. The CASH study reported that after 12 to 23 months of oral contraceptive use, the age-adjusted risk of
developing endometrial cancer was 40 percent less than the risk in women who have never used oral contraceptives. After 10 or more years of oral contraceptive use, the risk is 60 percent less. (*The cancer and steroid Hormone study...... Engle J Med 1987*).

As a result of reports that have appeared in the lay press over the past few years, ovarian cancer is a significant fear among perimenopausal and postmenopausal women, even though its actual incidence is very low. Unfortunately, no proven screening test for ovarian cancer exists, and neither CA-125 Screening nor periodic pelvic ultra-sound examinations have been especially helpful. Recent studies have indicated that the risk of developing ovarian cancer is reduced in women who have used oral contraceptives compared with women who have never used them. (*Schelesselman JJ. Contraception 1989*).

A protective effect has been observed with as little as three to six months of oral contraceptive use, with further decreases in risk seen with longer periods of use. For example, use of oral contraceptives for seven years or longer confers about a 60 to 80 percent reduction in the risk of developing ovarian cancer. (*Schelesselman JJ. 1989*)

**Drawbacks of and fears about oral contraceptive pills use**

Patients may decide not to use oral contraceptive pills for a number of reasons. One reason is that this form of contraception provides no protection against infection. In addition, Some women are concerned about the side effects of systemic hormonal medications, and others have actual contraindications to the use of oral contraceptive pills.

If a patient’s sexual practice puts her at risk for sexually transmitted infections, counseling about the use of male or female condoms is appropriate. It is also reasonable to add an oral contraceptive pill for effective pregnancy prevention. For the typical user who feels that 50
pregnancies in 1,000 oral contraceptive pill users in an unacceptably high failure rate, adding a second contraceptive method increases efficacy. Barrier contraceptive methods should be recommended for all women to decrease the spread of human herpesvirus, human immunodeficiency virus and human papillomavirus infections. (Hatcher RA, et al. Contraceptive technology. 17th rev. ed. 1998)

**Oral Contraceptives and Cancer Risk**

**Oral Contraceptive and Breast cancer:**

A women's risk of developing breast cancer depends on several factors, some of which are related to her natural hormones. Hormonal factors that increase the risk of breast cancer include conditions that allow high levels of estrogen to persist for long periods of time, such as early age at first menstruation (before age 12), late age at menopause (after age 55), having children after age 30, and not having children at all. A women's risk of breast cancer increases with the amount of time she is exposed to estrogen.

The return of risk to normal levels after 10 years or more of not taking OCs was consistent regardless of family history of breast cancer, reproductive history, geographic area of residence, ethnic background, differences in study designs, dose and type of hormone, and duration of use. The change in risk also generally held true for age at first use; however, for reasons that were not fully understood, there was a continued elevated risk among women who had started to use OCs before age 20.

Scientists suggest that the slightly elevated risk seen in both current OC users and those who had stopped use less than 10 years previously may not be due to the contraceptive itself. The slightly elevated risk may result from the potential of estrogen to promote the growth of breast cancer cells.
that are already present, rather than its potential to initiate changes in normal cell leading to the development of cancer.

Furthermore, the observation that the slightly elevated risk of developing breast cancer that was seen in this study peaked during use, declined gradually after OC use had stopped, then return to normal risk levels 10 years or more after stopping, is not consistent with the usual process of carcinogenesis (the process by which normal cells are transformed into cancer cells). It is more typical for cancer risk to peak decades after exposure, not immediately afterward. Cancer usually is more likely to occur with increased duration and/or degree of exposure to a carcinogen (cancer-causing substance). In this analytical study, neither the dose and type of hormone nor the duration of use affected the risk of developing breast cancer. *(Thomas DB. Contraception 1991)*.

Because many of the risk factors for breast cancer are related to natural hormones, and because OCs work by manipulating these hormones, there has been some concern about the possible effects of medicines such as OCs on breast cancer risk, especially if women take them for many years, beginning at a young age, and to follow them as they become older.

Studies examining the use of OCs as a risk factor for breast cancer have produced inconsistent results. Scientist suggest the inconsistent findings may have occurred because participants in different studies used OCs in different dose and forms. In addition, other factors that influence baseline hormone levels in the women under study may have led to different results among the studies. In general, most studies have not found an overall increased risk for breast cancer associated with OC use. In June 1995, however, investigators at the National Cancer Institute (NCI) reported an increased risk of developing breast cancer among women under age 35 who had used birth control pills for at least 6 months, compared with those who had never used OCs. They also saw a slightly
lower, but still elevated, risk among long-term OC users, especially those who had started taking the pill before age 18. (Brinton LA, et al. *Journal of the National Cancer Institute* 1995).

A 1996 analysis of world wide epidemiologic date, which included information from the 1995 study, found that women who were current or recent users of birth control pills had a slightly elevated risk of developing breast cancer. However, 10 years or more after they stopped using OCs, their risk of developing breast cancer returned to the same level as if they had never used birth control pills. The conduct this analysis, the researchers examined the results of 54 studies conducted in 25 countries that involved 53,297 women with breast cancer and 100,239 women without breast cancer. More than 200 researches participated in this combined exhaustive analysis of their original studies, which represented about 90 percent of the epidemiological studies throughout the world that had investigated the possible relationship between OCs and breast cancer. (Miller Dr. et al, *American Journal of Epidemiology* 1996).

**Ovarian and Endometrial Cancers:**

Many studies have found that using OCs reduces a woman’s risk of ovarian cancer by 40 to 50 percent compared with women who have not used OCs. The centers for Disease control and prevention’s (CDC) cancer and steroid Hormone study (CASH), along with other research conducted over the past 20 years, shows that the longer a woman uses OCs, the lower her risk of ovarian cancer. Moreover, this lowered risk persists long after OC use ceases. The CASH study found that the reduced risk of ovarian cancer is seen in women who have used OCs for as little as 3 to 6 months, and that it continues for 15 years after use ends. Other studies have confirmed that the reduced risk of ovarian cancer continues for at least 10 to 15 years after a woman has stopped taking OCs. Several hypothesis
have been offered to explain how oral contraceptives might protect against ovarian cancer, such as a reduction in the number of ovulations a woman has during her life-time, but the exact mechanism is still not known. (*The centers for Disease control. Journal or the American medical Association 1983*)

Studies have consistently shown that using OCs reduces the risk of ovarian cancer. In a 1992 analysis of 20 studies of OC use and ovarian cancer, researchers from Harvard medical school found that the risk or ovarian cancer decreased with increasing duration of OC use. Results showed a 10 to 12 percent decrease in risk after 1 year of use, and approximately a 50 percent decrease after 5 years of use. (*Hankinson SE, et al. obstetrics and Gynecology 1992*).

Researchers have also found that OC use may reduce the risk of endometrial cancer. Findings from the CASH study and other reports shows that combination OC use can protect against the development of endometrial cancer. The CASH study found that using combination OCs for at least 1 year reduced the risk of developing endometrial cancer to half of that seen for women who never took birth control pills. In addition, the beneficial effect of OC use persisted for at least 15 years after OC users stopped taking birth control pills. Some researchers have found that the protective effect of OCs against endometrial cancer increases with the length of time combination OCs are used, but results have not been consistent.

The reduction in risk of ovarian and endometrial cancers from OC use does not apply to the sequential type of pill, in which each monthly cycle contains 16 estrogen pills followed by 5 estrogen-plus-progesterone pills. (sequential OCs were taken off the market in 1976, so few women have been exposed to them) Researchers believe OCs reduce cancer risk only when the estrogen content of birth control pills is balanced by

**Cancer of the cervix:**

One reason that the association is unclear is that two of the major risk factors for cervical cancer (early age at first intercourse, especially age 16 or younger, and a history of multiple sex partners) are related to sexual behavior. Because these risk factors may be different between women who use OCs and those who have never used them, it is difficult for researchers to determine the exact role that OCs may play in the development of cervical cancer. (Brinton LA, et al. International Journal of cancer 1986.)

There is some evidence that long-term use of OCs may increase the risk of cancer of the cervix (the narrow, lower portion of the uterus). The results of Studies conducted by NCI Scientists and other researchers support a 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 risk of cervical cancer remains unclear. (Brinton LA. Contraception 1991;43 (6):581595.)

There is evidence that pill users who never use a barrier method of contraception or who have a history of genital infections are at a higher risk for developing cervical cancer. This association supports the theory that OCs may act together with sexually transmitted agents (such as HPVs) in the development of cervical cancer. Researchers continue to investigate the exact nature of the relationship between OC use and cancer of the cervix.

OC product labels have been revised to inform women of the possible risk of cervical cancer. The product labels also warn that birth control pills do not protect against human immunodeficiency virus (HIV)
and other sexually transmitted diseases such as HPV, chlamydia, and genital herpes. (Ylitalo N, et al. International Journal of cancer 1992.)

The two major risk factors that contribute to the development of cervical cancer are also risk factors that contribute to the development of human papillomavirus (HPV) infection in the cervix of the more than 100 types of HPV, over 30 types can be passed from one person to another through sexually contact. HPV is one of the most common sexually transmitted diseases. Certain HPVs. Particularly HPV type 16, are known to cause cervical cancer. Compared to non-OC users, women who use OCs may be less likely to use barrier methods of contraception (such as condoms). Since condoms can prevent the transmission of HPVs, OC users who do not use them may be at increased risk of becoming infected with HPVs. Therefore, the increased risk of cervical cancer that some studies found to be caused by prolonged OC use may actually be the result of HPV infection. (Daling JR, et al. Cancer Epidemiology Biomarkers, and Prevention 1996.)

Liver Tumors:

There is some evidence that OCs may increase the risk of certain malignant (cancerous) liver tumors. However, the risk is difficult to evaluate because of different patterns of OC use and because these tumors are rare in American women (the incidence is approximately 2 cases per 100,000 women). A benign (non cancerous) tumor of the liver called hepatic adenoma has also been found to occur, although rarely, among OC users. These tumors do not spread, but they may rupture and cause internal bleeding. (Palmer J, et al. L.C. American Journal of Epidemiology 1989-1991)
Oral contraceptives and stroke:

"Stroke" is a medical term commonly used to mean damage to part of the brain caused by a lack of blood flow. Blood flow may be reduced by a blood clot, an embolus (a clot forming in one place and moving to another place), or a rupture artery that delivers blood to that part of the brain. "Risk factors" increase the chance that someone will have a stroke. Some of the most common risk factors for stroke include high blood pressure, diabetes, high blood cholesterol, and smoking.

In patients with migraine without aura, taking OCs seems to slightly increase the risk of stroke, particularly in women during their child-bearing years. OCs containing low doses of estrogen (35 micrograms or less) do not appear to substantially increase the rate of stroke in women without traditional stroke risk factors. Low-dose OCs also may carry less risk of life-threatening events than can occur with pregnancy. There is, however, a greater risk of stroke with OC use in older women (over 35 years of age) and in those who smoke, have hypertension or diabetes, or have a history of stroke or transient ischemic stroke (also known as "TIA").

Recent data suggests that combined OC pills, including those with low estrogen levels, increase the risk of stroke in women with migraine even if no other risk factors for stroke exist. The absolute risk of stroke in this population, however, is small. Therefore it is difficult to make any definitive recommendations.

Women who have migraine with aura (especially prolonged or complicated auras involving numbness, weakness or loss of vision) may have an increased risk of a stroke. How high is that risk? Unfortunately, no one knows for sure; some estimates put it at around 14 times the risk of someone in the general population. In the United Kingdom, OCs are not traditionally prescribed for women who have migraine with aura. In contrast, some clinicians think that aspirin and migraine-preventing
medications may give some protection against stroke for migraine sufferers. Women with migraine who take OCs and develop aura for the first time, who have more severe aura symptoms, or whose headaches worsen significantly should discontinue using OCs and contact their doctor immediately.

If the decision is made to use OCs, using a lower dose of estrogen and taking it continuously (skipping the placebo pill or pill-free week) may be the most effective way to avoid worsening headaches. Many experts also recommend choosing an OC that has stable levels of hormones rather than changing doses throughout the month. This is based on the theory that increases and decreases in circulating levels of estrogen may not be well tolerated by women with headaches influenced by hormones.

The question remains whether putting these two things together (migraine and using OCs) increases the risk of a stroke to unacceptable levels. Most experts agree that women who have migraine without aura, and have no risk factors for stroke, can probably safely take OCs. The risk of unintended pregnancy for those women may outweigh the small increase in risk of stroke. In migraine with aura, there is differing opinion among experts. If the aura symptoms are not complicated and the woman has no other risk factors for stroke, some experts would be comfortable using low-dose OCs. In light of this uncertainty, using OCs in patients with migraine is a decision that needs to be made on an individual basis and discussed with the woman’s treating physician. *(Mt. Royal, NJ 08061, American Council for Headache Education, January 18, 2006)*

**Oral contraceptive and Haemorrhagic Stroke**

Haemorrhagic stroke in users of steroid contraceptives have been examined in various ways. Some studies have considered only episodes of subarachnoid haemorrhage, whereas others have included other types of
cerebral haemorrhage. In 1973, the collaborative group for the study of stroke in young women, reported that the risk of haemorrhagic stroke in current users of oral contraceptives was twice that among non-users. Although not statistically significant, this result provided the first suggestion that users of oral contraceptives may be at increased risk of haemorrhage as well as ischemic stroke. (Collaborative group for the study of stroke in young women. 1973).

Most recent studies have found smoking and hypertension to be important independent risk factors for haemorrhagic stroke. Only the WHO study, however, had sufficient statistical power to examine the risk of haemorrhagic stroke in women with different characteristics. In both developing and European countries, current users of combined oral contraceptives aged 35 years or more had a significantly increased relative risk of haemorrhagic stroke compared with non-users, but younger users did not. The relative risk of haemorrhagic stroke in current users of combined oral contraceptives who smoked was 3-4 times that of non-users who did not smoke. Compared with non-users without a history of hypertension, current users with such a history had a substantially higher relative risk of haemorrhagic stroke. The relative risk was not affected by whether the women reported having had her blood pressure checked before the current episode of use. (WHO collaborative study of cardiovascular disease and steroid hormone contraception. Lancet, 1996.)

The Scientific group found no evidence to date that either the estrogen or the progestogen constituents of combined oral contraceptives affect the risk of haemorrhagic stroke. Sufficient data were also not available on the risk of haemorrhagic stroke associated with use of the various types of progestogen-only contraceptives.
The scientific group concluded that:

- The incidence of fatal and non-fatal haemorrhagic stroke is very low in women of reproductive age in both developed and developing countries.

In women aged less than 35 years, who do not smoke, and who do not have hypertension, the relative risk of haemorrhagic stroke associated with use of combined oral contraceptives is not increased. There is no increase in the risk of haemorrhagic stroke with increasing duration of use of oral contraceptive. Women who have previously used oral contraceptives are at no greater risk of haemorrhagic stroke than women who have never used them. These conclusions appear to apply equally in developed and developing countries.

- Women with hypertension have an increased absolute risk of haemorrhagic stroke. The relative risk of haemorrhagic stroke in current users of combined oral contraceptives with hypertension may be 10 times that in current users without hypertension. This conclusion appears to apply equally in developed and developing countries.

- The risk of haemorrhagic stroke in women who smoke is up to twice that in non-smokers; in women who are current users of combined oral contraceptives and who smoke, the relative risk is about 3. This conclusion appears to apply equally in developed and developing countries.

- The incidence of haemorrhagic stroke increases with age, and current use of combined oral contraceptives appears to magnify this effect of aging.
There is no evidence that either the estrogen or the progestogen constituent of combined oral contraceptives is related to the risk of haemorrhagic stroke.

Possible Biological mechanism for cardiovascular effects:
The Complexity of the mechanism underlying cardiovascular disease has been increasingly recognized over recent years, combined oral contraceptives effect lipoprotein and carbohydrate metabolism, haemostasis, and mechanisms regulating blood pressure. An influence on the functioning of the endothelium of blood vessels and arterial tone also seems likely. The scientific group suggested that the potential significance of these changes should be investigated and interpreted using new models of vascular pathophysiology.

The scientific group concluded that:
- Epidemiological observations are more likely to be accepted if they are biologically possible, although the absence of such an explanation does not exclude a causal relationship.
- The biological mechanisms underlying cardiovascular disease involve a complex interplay between lipoprotein metabolism, hormonal regulators such as insulin coagulation and fibrinolysis, the reninangiotensin aldosterone system, and the functioning of the endothelium of blood vessels.
- Combined oral contraceptives do no increase the risk of developing diabetes mellitus. They have little effect on fasting plasma concentrations of glucose and insulin, but cause modest elevations in the plasma levels of glucose and insulin after an oral glucose challenge and may increase insulin resistance. The clinical significance of such changes and may increase insulin resistance.
The clinical significance of such changes in otherwise healthy young women is unknown, especially in relation to arterial disease.

- The changes in metabolism of lipoprotein in plasma induced by use of combined oral contraceptives have been extensively studied. Low-dose combined oral contraceptives increase fasting plasma levels of triglycerides but have only minor effects on low-density lipoproteins, lipoprotein (a) or total cholesterol. The effect on HDL depends on the balance of estrogen and progesterone. The clinical significance of such changes is uncertain in the context of current low-dose formulations.

Combined oral contraceptives alter the plasma concentrations of many components (including their activation markers) of both the coagulation and fibrinolytic systems. These changes are less marked with combined oral contraceptives containing low doses of ethinylestradiol and even less so with progestogen only contraceptives.

Hereditary conditions such as antithrombin III defect and factor V leiden mutation predispose women to venous thromboembolism. These disorders may underlie a large proportion of idiopathic venous thromboembolic events, perhaps one-third of those seen in Caucasian women. This effect is increased in women using combined oral contraceptives.

- The prevalence of hereditary conditions such as antithrombin III defect and factor V leiden mutation is about 5% in Caucasian women but is lower in other populations. The positive predictive value of screening for these disorders is very low.

- Even low-dose combined oral contraceptives cause modest elevations in blood pressure which may increase the risk of arterial disease. In healthy young women with a low background risk of arterial disease, small increases in blood pressure attributable to use
of combined oral contraception are likely to have minimal effects on the absolute risk of arterial disease.

- Comparative studies of users of low-dose combined oral contraceptives suggest that the dose and type of the progestogen component influence the effect of these preparations on lipid and lipoprotein metabolism and haemostasis. The clinical significance of these differences is uncertain.

**Oral contraceptives and venous thromboembolism:**

Earlier studies of use of oral contraception and venous thromboembolism found little change in risk with increasing duration of use. The WHO study showed little evidence overall of an appreciable change in risk with duration of use, although the size of the relative risk diminished slightly during the first few years. A comparison between women who had used combined oral contraceptives for the first time and those who had never used them in the transnational study indicated a 10-fold increased risk during the first year of use which fell to a twofold increase in subsequent years. Post users of combined oral contraceptives are not at greater risk of venous thromboembolic disease than women who have not never use them. The risk among current users falls to that among non-users within 3 months of stopping oral contraceptives.

The relative risk of venous thromboembolism associated with current use of oral contraceptives does not appear to vary with age. The incidence of venous thromboembolic disease, however, rises with age. This means that the absolute risk of venous thromboembolic disease attributable to oral contraception is higher in older than in young women. In the WHO study, oral contraceptives users who were obese had a higher relative risk than did users who were not obese in both developing and developed countries.
Recent studies have shown that women with hereditary clotting defects are at a much higher risk of venous thromboembolism if they use oral contraceptives. Current users of oral contraceptive with factor V Leiden mutation had a relative risk of vein thrombosis of 35 compared with non-users without this mutation. Even with such a high relative risk, however, the absolute risk was still low: around three additional cases of venous thromboembolism per year 1000 users with factor V Leiden mutation compared with users without this defect. (*Vandenbroucke JP et al. Lancet 1994*).

The first epidemiological evidence of implicating use of combined oral contraceptives with an increased risk of venous thromboembolism (blood clots in veins) appeared in 1967. All of the studies conducted since then have found that current users of combined oral contraceptives have a higher risk of venous thromboembolic disease than women not using OCs. In most studies the relative risk were statistically significant. (*WHO collaborative study of cardiovascular disease and steroid hormone contraception. Lancet, 1995.*).

Early studies suggested that reduction in the estrogen content of combined oral contraceptives might lower the risk of deep vein thrombosis and pulmonary embolism; however, the evidence was not entirely consistent. There is not convincing evidence that the risks have declined substantially over time, or with reductions in estrogen content. The influence of the progestogen component of combined oral contraceptives on the risk of venous thromboembolism has, until recently, received comparatively little attention.

Since the end of 1995, four studies have reported that users of low dose (<50µg of estrogen) combined oral contraceptives containing desogestrel or gestodene have a higher risk of venous thromboembolic disease than user of low-dose contraceptives containing levonorgestrel.
Comparison between results had been complicated by the use of different reference groups. The only published study which has reported on the risks of venous thromboembolic disease associated with the use of progestogen only pills compared these preparations with combined oral contraceptives containing levonorgestrel. The estimated relative risk was 1.3 (Spitzer WO, et. al. 1996).

The Scientific group concluded that:

- Current users of combined oral contraceptives have a low absolute risk of venous thromboembolism, which is nonetheless 3-6 times that in non-users. The risk is probably highest in the first year of use and declines thereafter, but persists until discontinuation.

- After use of combined oral contraceptives is discontinued, the risk of venous thromboembolism drops rapidly to that non-users.

- Among users of combined oral contraceptives preparations containing less than 50µg of ethinylestradiol, the risk of venous thromboembolism is not related to the dose of estrogen.

- Combined oral contraceptives containing desogestrel or gestodene probably carry a small risk of venous thromboembolism beyond that attributable to combined oral contraceptives containing levonorgestrel. These are insufficient data to draw conclusions with regard to combined oral contraceptives containing norgestimate.

- The absolute risk of venous thromboembolism attributable to use of OCs rise with increasing age, obesity, recent surgery, and some forms of thrombophilia. The effects of other risk factors for venous thromboembolism have not been quantified in users of combined oral contraceptives.

- Cigarette smoking and raised blood pressure, which are important risk factors for arterial disease, do not appear to elevate the risk of venous thromboembolic disease.
There are insufficient data to conclude whether there is a relation between venous thromboembolism and use of progestogen – only contraceptives.

The relative risks of venous thromboembolic disease observed in users of combined oral contraceptives in developed countries appear to be applicable to developing countries.

(*WHO Collaborative study of Cardiovascular disease and steroid Hormone contraception. Lancet, 1995*).

The risk of venous thromboembolism is highest during the first year of oral contraceptive pill use and is not related to the estrogen component of currently available pill formulations.

**Metabolic effects of oral contraceptives:**

Different metabolic effects of contraceptive steroids are produced by the estrogenic component, ethinyl estradiol, as well as the progestin. In general the severity of these adverse metabolic effects is directly correlated with the dosage and potency (biologic activity) of steroid in the formulation. During the past 40 years the amount of both the estrogenic and progestogenic component of formulations has decreased markedly and has been accompanied by a lower incidence and severity of the adverse metabolic effects.

**Carbohydrate Metabolism:**

When formulations with a high dose of progestin are administered, 4-16% of women (depending on their age) have an abnormal response to the glucose tolerance test. The incidence of abnormal test results is mainly related to the dose and potency of the progestin, since estrogen has little effect upon carbohydrate metabolism.

Some studies have shown that formulations with a low dose of progestin do not significantly alter levels of glucose, insulin or glucagon
after a glucose load in healthy women or in those with a history of
gestational diabetes. However, other studies indicate that the multiphasic
formulations with norgestrel, but not those with norethindrone, produce
some deterioration of glucose tolerance in normal women, as well as in
those with a history of gestational diabetes. When one is prescribing these
agents for women with a history of glucose intolerance, it is preferable to
use formulations with a low dose of a progestin.

Kjos et al. have shown that women with a history of gestational
diabetes ingesting these agents have no greater risk of developing diabetes
than a control group using other methods of contraception.

Data from 20 years experience with use of mainly high-dose
formulations in the Royal college of general practitioners study revealed no
increased risk of developing diabetes mellitus among current OC users or
former OC users, even among those women who had used OCs for 10
years or longer.

**Protein Metabolism**: The synthetic estrogens used in OCs increase the
hepatic production of several globulins, some of which are involved in the
coagulation process. Another globulin, angiotensinogen, may be converted
to angiotensin and increase blood pressure in some users. The circulating
levels of each of these globulins is directly correlated with the amount of
estrogen in the OC formulation.

**Epidemiologic studies have shown** that the incidence of both
venous and arterial thrombosis is also directly related to the dose of
estrogen.

**Godsland If, Crook D, et al.** have shown that Angiotensionogen
levels are lower in women who formulations with 30-35\(\mu\)g of ethinyl
estradiol than in those who ingest formulations with 50\(\mu\)g.

**However, wilson et, al.** still observed a significant increase in blood
pressure in some women who received the lower dosage of estrogen.
Thus, blood pressure should be monitored in all users of OCs. Indirect evidence suggests that the progestin component may also affect blood pressure. However, women who receive progestins without estrogen do not have an increase in blood pressure over time, indicating that the estrogen component is the major factor in causing elevated blood pressure in certain users of OCs.

**Lipid Metabolism:**

Studies have measured lipid levels before and after the ingestion of several low-dose estrogen-progesterin formulations, including the triphasic formulation containing levonorgestrel. These found no adverse alterations in the levels of HDL cholesterol.

In two prospective randomized studies of the triphasic formulations currently being marketed in the USA., it has been reported that each had similar effects which were clinically insignificant upon carbohydrate and lipid metabolism, including changes in HDL cholesterol and LDL cholesterol.

Studies with formulations containing the three most recently synthesized progestins indicate that these also produce *no alteration in carbohydrate metabolism and have beneficial effects upon the lipid profile, raising HDL cholesterol and lowering LDL cholesterol*. Thus the most recently developed low-dose OCs containing desogestrel or norgestimate have a beneficial effect upon lipid metabolism. *Godsland IF, Crook D, et al, contraception 1995.*

Adverse alterations in high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol are produced by all the progestins in OCs and the degree of change in the levels of these lipids is related to the amount and potency of the progestin. Because the estrogen component has an effect opposite to that of the progestin, a decrease in HDL cholesterol levels after the ingestion of various formulations
containing 50 μg of estrogen has been noted only for one formulation containing norgestrel. **Godslan If, fertil steril 2001.**

**Other metabolic effects:**

The symptoms most frequently produced by the estrogentic component include nausea (a central nervous system effect), breast tenderness, and fluid retention, which usually does not exceed 3-4 lb (1.5-2 kg) of body weight, due to decreased sodium excretion. Minor, clinically insignificant changes in circulating vitamin levels also occurred after ingestion of the higher dosage OCs. These changes include a decrease in levels of the B complex vitamins and ascorbic acid and increases in levels of vitamin-A. Even with the use of the high-steroid-dose agents, dietary vitamin supplementation was not necessary as the changes in circulating vitamin levels were small and clinically insignificant. Estrogen can also cause cholasma (pigmentation of the molar eminences), which is accentuated by sunlight and usually takes a long time to disappear after OCs are discontinued. The incidence of all these estrogentic side-effects is much lower now than occurred previously because the formulations in use today contain only one fifth as much estrogen as the formulations used in the 1960s. **Godslan If, Crook D, et al.**

**Nutrition and oral contraceptives:**

Much research has focused on the possible changes in general health and nutritional needs of women taking birth control pills.

Our bodies naturally produce hormones to regulate many metabolic functions. Hormones are powerful chemicals that can effect many parts of the body. Much research has been conducted to investigate other changes that occur in women who take birth control pills and who, therefore, have increased amounts of female hormones. These can include changes in general health as well as in nutritional needs.
In general, the Food and Drug Administration (FDA) advises any woman who takes birth control pills to request from her doctor, druggist or health department, a government pamphlet that explains in greater details the uses, benefits and risks of birth control pills.

In terms of nutrition, the women on birth control pills need different amounts of some vitamins and minerals. The vitamins include Vitamin B-6, folic acid, Riboflavin, Vitamin C and Vitamin-A. Minerals include iron, Zinc and copper.

**Vitamins:**

**Vitamin B-6:** Many studies indicate that B-6 metabolism is different in women who take oral contraceptives. These findings are based on blood analyses as well as on measurements of how much B-6 is lost from the body through urine. The current scientific consensus is that these differences do not warrant taking more vitamin B-6 than that already recommended for women in various age groups.

Women who take oral contraceptives have a different form of Vitamin B-6 in blood. This change also occurs during pregnancy.

**Folic Acid:**

In several cases, women taking oral contraceptives developed folic acid deficiency. However, it appears that many of these women had low intake of folic acid or problems with intestinal absorption prior to taking birth control pills. Again, women on birth control pills should regularly eat good sources of folic acid. Good folate nutrition is especially important for women who become pregnant shortly after they stop taking oral contraceptives.

**Riboflavin (vitamin B-2):**

If a women has a riboflavin deficiency before she starts oral contraceptives, birth control pills will aggravate that condition. Riboflavin
deficiency. Caused by low intake is more common among lower-income women of child-bearing age who may not have access to good food sources, such as milk, meat and dark green leafy vegetables. Women who take oral contraceptives should plan their riboflavin intake. NRC (National Research Council, Food and Nutrition Board, Committee on Dietary Allowances) RDA.

**Vitamin C:** Vitamin C can be measured in the blood’s liquid or plasma portion, as well as in cellular components including platelets and white-blood cells or leukocytes. Decreases in Vitamin C in Plasma and cellular components have been reported in women who take birth control pills. These decreases are not well understood, but they may relate to changes in copper metabolism. However, no increase has been made in the RDA for Vitamin-C for women who take oral contraceptives beyond what is currently recommended for their age group.

**Vitamin A:** A frequent finding is that blood vitamin A levels are higher in women who use birth control pills. On the surface, this might seem beneficial.

**Minerals**

**Iron:** Iron is one of the few nutrient where researchers have suggested a lower amount for women who take birth control pills. Some women using oral contraceptives lose less menstrual blood. Iron is needed to make hemoglobin, the red-colored substances in blood that carries oxygen. It has been argued that if less blood is lost each month, less blood needs to be manufactured. Therefore, the recommended iron intake might be lowered. Despite the seeming logic of this argument, other measurements of iron status do not support the idea of decreased dietary iron need in women who take birth control pills. (NRC, 1998. Second DRI Report. National Academy of Sciences. Washington, D.C.)
Zinc:

Several studies have reported reduced zinc levels in blood plasma of women on birth control pills. However, the zinc level in red blood cells are reportedly increased in oral contraceptive users. This suggests that the zinc may be redistributed in the blood of women on the pill. The meaning of these changes is not understood. At present, the RDA for zinc for users of oral contraceptives is the same as that for non-users.

Copper: Plasma copper levels often are increased considerably in women using birth control pills. A copper-carrying protein called ceruloplasmin can destroy vitamin-C by a process called oxidation. It has been suggested that the increased blood copper levels caused by birth control pills may relate to the decreased blood vitamin C levels.

Nutritional Recommendations for Pill users:

The effects of the hormones in oral contraceptives obviously reach for beyond preventing ovulation. Much research has been and will be conducted on the changes in general health and nutritional needs of women who take birth control pills.

Today, there is no conclusive evidence that ‘the pill’ in general alters nutritional requirements. However, this generalization assumes that women who take birth control pills have adequate diets. Women whose diets are not adequate will only aggravate or worsen nutritional problems with birth control pills. This is especially true for women with inadequate diets who become pregnant after they stop taking birth control pills.

The best general advice for a women on birth control pills is to plan a diet that regularly includes moderate amounts of a variety of foods, including good sources of the vitamins and minerals. (NRC. 1989. RDA. National Academy of Sciences. Washington; D.C.)