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Oral Contraceptives

*History, Pharmacology, Metabolic Effects,
Side Effects, and Health Benefits*

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CONTENTS

INTRODUCTION
LEGAL HISTORY
MECHANISM OF ACTION
CLINICAL EFFECTIVENESS
ADVANTAGES OF LOW-DOSE OCS
DISADVANTAGES OF LOW-DOSE OCS
PHARMACOLOGY
METABOLIC EFFECTS AND SIDE EFFECTS:
ESTROGEN AND PROGESTIN
REPRODUCTIVE EFFECTS OF LOW-DOSE OCS
NEOPLASTIC EFFECTS OF LOW-DOSE OCS
DRUG INTERACTIONS
CONTRACEPTIVE HEALTH BENEFITS
NON-CONTRACEPTIVE HEALTH BENEFITS
REFERENCES

INTRODUCTION

Because of social, political, financial, or legal reasons, many contraceptive methods have been removed from the contraceptive armamentarium, sometimes almost as quickly as they were introduced. The original subdermal implant, a monthly intramuscular injection containing medroxyprogesterone acetate and estradiol cypionate, and a multitude of intrauterine devices have all been withdrawn from the US market after facing insurmountable problems. Over the last 45 years, however, oral contraceptives (OCs) have undergone extensive study,

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Fig. 1. Current options for oral contraception.

continual development and significant improvements. Unlike the original OCs, new low-dose OCs, as shown in Fig. 1, have few health risks when used in properly selected users and many health benefits. Currently, more than 100 million women worldwide and 18 million women in the United States rely on OCs (1).

LEGAL HISTORY

The birth control pill was first introduced in 1960, but for many years its use was illegal in many states. In 1965, the Supreme Court took up the case of *Estelle Griswold*, executive director of the Planned Parenthood League in New Haven, CT. She and others at the Planned Parenthood Center were arrested for giving information and instruction to married couples about how to prevent pregnancies. Justice William Douglas, writing for the majority in the 7–2 opinion, cited constitutional guarantees of privacy that prevented the government from interfering in people’s bedrooms. Since this landmark decision, OCs have become one of the most widely used contraceptive methods.

Connecticut Law Found Unconstitutional “Any person who uses any drug, medicinal article or instrument for the purpose of preventing conception shall be fined not less than fifty dollars or imprisoned not less than sixty days nor more than one year or be both fined and imprisoned.”

Development History

- OCs are the most widely studied pharmaceutical (2).
- Many misperceptions regarding OCs still exist, and many women are unaware of the significant non-contraceptive health benefits associated with OC use.

In 1951, Carl Djerrasi synthesized the first orally active progestin norethindrone from its plant source. In 1953, Cotton synthesized norethynodrel. During the process of synthesis of norethynodrel, a small amount of the estrogen, mestranol (ethinyl estradiol-3-methyl ether), was serendipitously produced as a byproduct. This discovery led to the introduction of the first OC in the United States in 1960 that contained a large amount of these compounds, namely 150 μg of mestranol and 9.85 mg of norethynodrel. During the next several decades, after scientists learned how to independently synthesize mestranol and ethinyl estradiol (EE) from the plant source, EE gradually replaced mestranol in OC formulations.

Because orally administered estrogen is thrombophilic and increases the risk of both arterial and venous thrombosis in a dose-dependent manner, an effort was made to reduce the dose of EE in OC formulations. In the United States, the estrogen dose was initially lowered from 150 μg of mestranol to 50 μg and then EE was lowered to 20 μg . Mestranol is more potent than EE per unit weight, and 50 μg of mestranol is roughly equivalent to 35 μg of EE (3). The true low-dose formulations are those with less than 35 μg . A formulation with 15 μg EE is now marketed in Europe.

The dose of progestin was also reduced and newer, more potent progestins than norethynodrel were developed. Most modern OCs contain progestins derived from norethindrone or norgestrel (Table 1). These progestins chemically resemble testosterone and have a low degree of androgenic activity. The more recently introduced progestins (norgestimate, desogestrel, and gestodene) are also derivatives of testosterone but are more selective and have less androgenic activity. The anti-progestogen mifepristone was derived by manipulation of the norethindrone molecule and tibolone is a derivative of norethynodrel (Fig. 2).

In 2001, a new oral contraceptive, Yasmin[®], was introduced containing drospirenone (DRSP), a progestin structurally related to spironolactone (Table 1). This progestin exhibits progestogenic, antimineralocorticoid, and antiandrogenic activities. A transdermal method (Ortho Evra[®]) received regulatory approval for use in the United States in 2001. The transdermal contraceptive system was designed to release a constant rate of 150 μg of norelgestromin (the active metabolite of norgestimate) and 20 μg of EE into the systemic circulation each day. Marketing of the contraceptive vaginal ring (NuvaRing[®]) that daily releases 120 μg of etonogestrel, the biologically active metabolite of desogestrel, and 15 μg of EE began in 2002.

Table 1
Family of Progestins

<i>Progesterone</i>		
<i>Parent compounds</i>		
	<i>Testosterone</i>	<i>Spirolactone</i>
<i>Derivatives</i>		
17α-acetoxyprogesterone	19-nortestosterone	17α-spironolactone
Pregnane derivatives	Estrane derivatives	Gonane derivatives
Megestrol acetate	Norethindrone (OCs)	Norgestrel (OCs)
Medroxyprogesterone acetate (DMPA)	Norethindrone acetate (OCs)	Levonorgestrel (OCs)
Chlormadinone acetate	Ethinodiol diacetate (OCs)	Desogestrel (OCs)
Cyproterone acetate	Mefipristenone (RU-486)	Etonogestrel (implant, ring)
	Norethynodrel	Gestodene (OCs)
	Tibolone	Norgestimate (OCs)
		Norelgestromin (patch)

The parent compounds progesterone, testosterone, and spironolactone and their derivatives. Some of these derivatives are further modified to produce other derivatives. Many are currently marketed in the United States in hormonal contraceptives including OCs, the contraceptive patch, ring, implant, or DMPA injection. Gestodene, chlormadinone, and cyproterone acetate are progestin derivatives that are marketed as European OCs but not in the United States.

Adapted from ref. 3a.

OC, oral contraceptive.

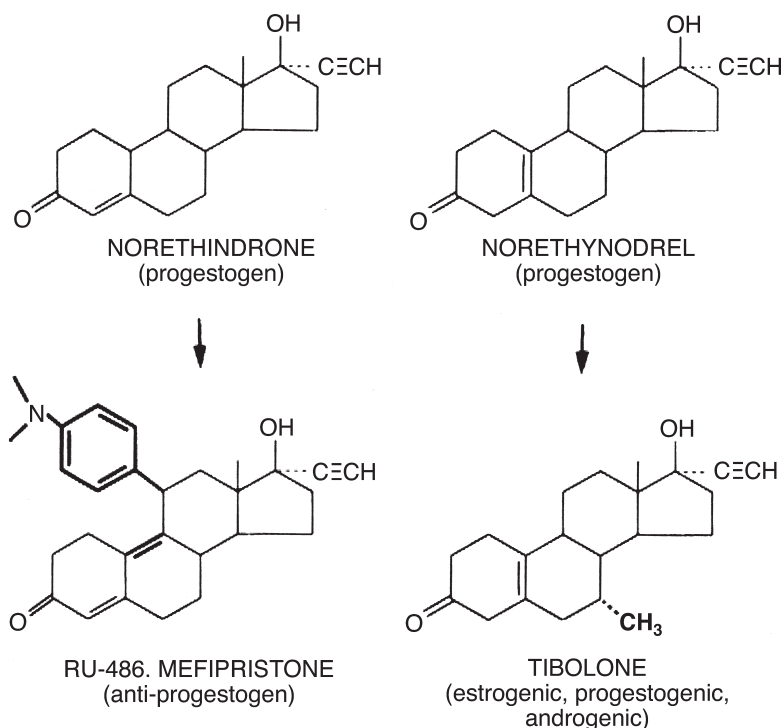


Fig. 2. Manipulation of norethindrone—a strong progestogen—results in an antihormone (RU-486). Tibolone is a derivative of the progestogen norethynodrel and displays a mixture of estrogenic, progestogenic, and androgenic properties. (From ref. 135 with permission.)

In 2003, the Food and Drug Administration (FDA) approved an extended regimen OC product (Seasonale®) containing 30 µg of EE and 150 mg of levonorgestrel (Fig. 3). Active pills are taken for 84 days followed by a 7-day pill-free interval to reduce the number of scheduled withdrawal bleeding episodes from 13 to 4 per year. Several new lower dose (20 µg EE) extended-regimen OCs, and a continuous-regimen OC (Lybrel™), are in development and should be available in the near future.

Several recently developed OCs also altered the traditional hormone-free interval. Whereas the extended regimen OC was developed to reduce the number of withdrawal menses, this new OC shortened the 7-day interval to a 4-day interval to improve bleeding profiles and decrease the incidence of ovulation and pregnancy that may occur when there is a delay in restarting the active pills in the beginning of a new cycle (4). The US Food and Drug Administration has approved a new OC called Yaz® containing 20 µg ethinyl estradiol and 3 mg DRSP with a dosing regimen of 24 active pills followed by 4 days of placebo.



Fig. 3. Extended-cycle pill that comes with three packets.

MECHANISM OF ACTION

There are three major types of OC formulations: fixed-dose combination, combination phasic, and daily progestin-only (*see* Chapter 4). The combination estrogen–progestin formulations consistently inhibit the midcycle luteinizing hormone surge and effectively prevent ovulation. Several studies demonstrated a direct inhibitory effect on the pituitary and the hypothalamus (5). The progestin-only formulations have a lower dose of progestin than the combined agents and do not consistently inhibit ovulation.

All formulations act on other areas of the reproductive tract by altering the following:

- Cervical mucus: making it viscid, thick, and scanty, thus preventing sperm penetration and inhibiting capacitation of the sperm.
- Decreasing motility of the uterus and oviduct thus inhibiting ova and sperm transport.
- Diminishing endometrial glandular production of glycogen making less energy available for the blastocyst to survive in the uterine cavity.
- Decreasing ovarian responsiveness to gonadotropin stimulation.

Because the doses of steroids in currently marketed OCs are low, neither gonadotropin production nor ovarian steroidogenesis is completely suppressed. Complete absence of follicular activity, as was often noted during high-dose OC use, no longer occurs (6).

The magnitude of hypothalamic–pituitary suppression is unrelated to the age of the woman or the duration of steroid use, but is related to the potency of the progestin and estrogen in the formulation. The magnitude of the hypothalamic–pituitary suppression is correlated with the incidence and severity of prolonged amenorrhea after stopping OCs. After discontinuing current low-dose formulations, return to ovulation is usually rapid. However, because the suppression is so quickly reversible, there is less room for error when using current low-dose OCs. Extending the pill-free interval for more than 7 days may result in breakthrough ovulation and pregnancy. Women should be advised that the most important pills to remember to take are the first ones of each cycle. The new low-dose OC Yaz shortens the pill-free interval to 4 days to potentially increase effectiveness with typical use.

CLINICAL EFFECTIVENESS

No significant differences in clinical effectiveness have been demonstrated for the various combination OCs currently available. With perfect use, the pregnancy rate is 0.2–0.3% at the end of 1 year with all products. However, the typical use failure rate is higher and varies between 3 and 8% depending on the population. The risk of contraception failure is highest if pills are missed at the beginning of the cycle. Because the contraceptive patch and ring have basically the same mechanism of action, their perfect and typical use failure rate is considered to be the same as combination OCs (7). OCs, the contraceptive patch, and ring are very effective but are considered to be in the second tier of contraceptive effectiveness. The first tier methods, intrauterine devices, implants, and injections, have lower typical failure rates as they are not as subject to user error.

A recent study suggested that high body weight may alter the metabolism of the steroids in low-dose OCs enough to reduce their effectiveness. In a retrospective study, women weighing more than 160 lb (70.5 kg) taking OC formulations with less than 50 µg had a failure rate 2.6 times greater than women with lower body weight, and a 4.5 times greater failure rate when using formulations with less than 35 µg (8). A lower contraceptive effectiveness was also reported in patch users weighing more than 198 lb (9). The risks associated with using a pill with higher amounts of EE should be balanced against this possible increased failure rate when deciding on an appropriate formulation.

Progestin-only pills (POPs), often referred to as “minipills,” have about 25–70% of the progestin dose contained in combination OCs. POPs, even if taken at the same time each day, are slightly less effective than combination pills. With perfect use, POPs’ failure rate is 0.5%. As with combination OCs, data indicates

the failure rates with POPs are higher for users who weigh more than 127.4 lb (57.8 kg; *see* Chapter 4).

ADVANTAGES OF LOW-DOSE OCS

OCs are:

- Highly effective if taken correctly.
- Relatively easy to use and require no special precautions at the time of intercourse.
- Rapidly reversible: most women become pregnant within 2–3 months after discontinuing use.
- Safe: healthy, nonsmoking, normotensive women can use OCs safely throughout their reproductive years.
- Low cost for women covered by various family planning programs (can be as low as \$1.50 per month).
- OCs are associated with a long list of contraceptive and non-contraceptive health benefits that are detailed extensively in sections below. OCs are associated with:
 - Decreased menstrual blood loss, decreased menstrual cramping, control of bleeding patterns.
 - Decreased dysmenorrhea.
 - Decreased androgen-related problems and premenstrual syndrome.
 - Decreased risk of pelvic inflammatory disease (PID), ovarian cysts, and benign breast disease.
 - Decreased risk of ovarian and endometrial cancer.

DISADVANTAGES OF LOW-DOSE OCS

- The major disadvantage of OCs is that they must be taken daily.
 - Studies show that in some populations 11% discontinue pills in the first month of use, 28% discontinue by 6 months and 33–50% discontinue by 1 year (10).
- OCs do not provide protection from STDs or HIV transmission (lower tract infections).
- The cost of OCs to women not on special family planning programs generally ranges from \$15 to \$50 per cycle. (The generic brands are generally less expensive.) The contraceptive ring and patch cost around \$40 per cycle.
- The side effects of OCs include the following:
 - Breast tenderness, nausea, headache.
 - Mood changes, bloating.
- The risks of OC use include the following:
 - Venous thromboembolism (venous thrombosis and pulmonary embolism). Although OCs increase the risk of venous thromboembolism two- to four-fold, the risk is half compared with the risk associated with pregnancy (Chapter 3, Table 1).

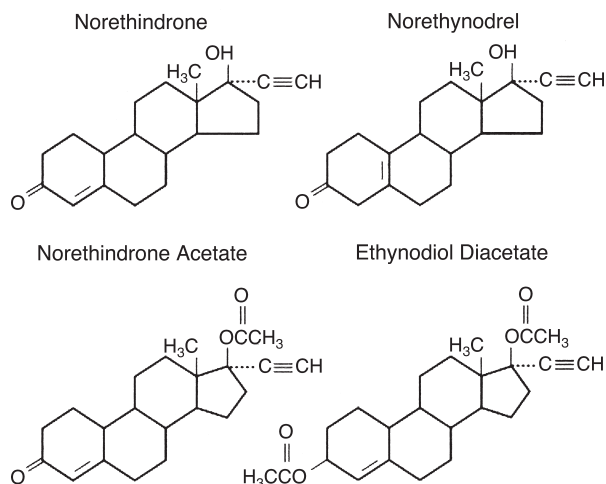


Fig. 4. Chemical structure of the estrane progestins, derivatives of norethindrone, used in oral contraceptives. (© 2004 Elsevier, reprinted from ref. 136 with permission.)

- Ischemic or hemorrhagic stroke. Several studies indicate that young users of low-dose OCs who do not smoke and have no risk factors for cardiovascular disease have no increased risk.
- Myocardial infarction. Several studies show no increased risk in healthy low-dose estrogen OC users who do not smoke and do not have significant cardiovascular disease risk factors (11,12).
- Breast cancer. There is conflicting information, but during use, some studies show a very small increase in the diagnosis of breast cancer in users and others show no change in risk. There is evidence that OCs do not cause breast cancer but may promote an existing lesion. The length of use does not affect risk and the risk returns to baseline after discontinuation (13).

PHARMACOLOGY

All currently marketed combination OCs are composed of a synthetic estrogen plus a progestin. The progestin component provides most of the contraceptive protection while the estrogen provides cycle control and boosts the contraceptive effectiveness of the progestin.

All but one of the synthetic progestins currently marketed in the United States in hormonal contraceptives are derivatives of either 19-nortestosterone or 17 α -acetoxyprogesterone (*see* Chapter 7) as shown in Table 1. The derivatives of 19-nortestosterone are either estranes or gonanes. The original OC containing norethynodrel, an estrane derivative of 19-nortestosterone, is no longer marketed, but the estrane norethindrone and its derivatives along with levonorgestrel and other gonane derivatives are used in currently marketed formulations (Fig. 4).

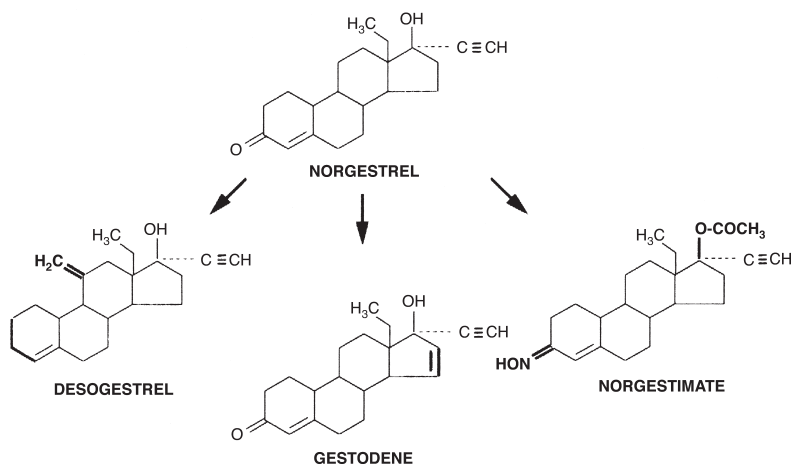


Fig. 5. Gonane progestogens derived from manipulation of the norgestrel molecule. (From ref. 135 with permission.)

The gonane derivatives have greater progestational activity per unit weight than estranes. Modifications in the chemical structure of gonane derivatives resulted in compounds that have altered biological activity. The magnitude of difference in androgenic and progestational effects produced by each progestin is called selectivity. The so-called “third-generation” progestins, norgestimate, desogestrel, and gestodene, derived from the gonane norgestrel, have high selectivity and demonstrate high progestational activity and low androgenic activity when compared with the other gonanes (Fig. 5). The OC formulations containing desogestrel, norgestimate, and gestodene are called third-generation OCs. The patch contains norelgestromin, a metabolite of norgestimate, and the ring and implant contain etonogestrel, a metabolite of desogestrel.

There has recently been introduced a new progestin, DRSP (Fig. 6), that is an entirely different progestin. It is structurally related to spironolactone and in addition to its progestogenic activity, exhibits antimineralocorticoid and antiandrogenic activities.

The newer selective progestins, including DRSP, do not counter the effects of the estrogen component as strongly as the older progestins, and are associated with higher sex hormone-binding globulin (SHBG) and other liver globulins compared with combination products with the same estrogen dose and a less selective progestin. Adjustment of the new progestin products with a lower dose of estrogen is being studied and may result in a better safety profile.

Only two estrogens are used in OCs in the United States. The so-called first-generation OCs contain 50 μg of either EE or mestranol (Fig. 7). The second-generation OCs contain 20–35 μg of EE. OCs containing one of the three newer gonane progestins and are called third-generation OCs.

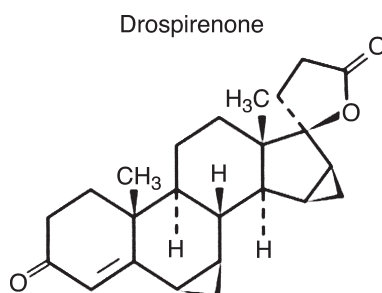


Fig. 6. Chemical structure of drospirenone. (© 2004 Elsevier, reprinted from ref. 136 with permission.)

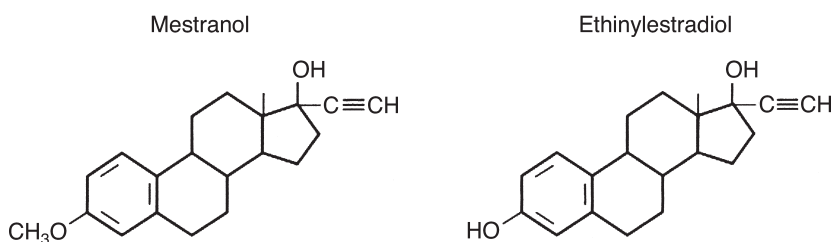


Fig. 7. Structure of the two estrogens used in combination oral contraceptives. (© 2004 Elsevier, reprinted from ref. 136 with permission.)

All the synthetic estrogens and progestins in OCs have an ethinyl group at position C17 (Fig. 8). The presence of this ethinyl group enhances the oral activity of these agents because they are not as rapidly metabolized as they pass through the intestinal mucosa and the liver through the portal system. EE has about 100 times the potency of an equivalent weight of conjugated equine estrogen or estrone sulfate for stimulating synthesis of hepatic proteins.

The two estrogens used in OCs, EE and its 3-methyl ether, mestranol, have different biological potency. Mestranol must be demethylated to EE to bind to the estrogen cytosol receptor and become biologically active. The degree of conversion of mestranol to EE varies among individuals, although overall, EE is about 1.7 times as potent as the same weight of mestranol (14).

METABOLIC EFFECTS AND SIDE EFFECTS: ESTROGEN AND PROGESTIN

In addition to their contraceptive actions, OCs have many other metabolic effects (Table 2). These metabolic effects may be associated with mild or moderate side effects that often disappear over time or after switching to another formulation. The magnitude of the effects is directly related to the potency and

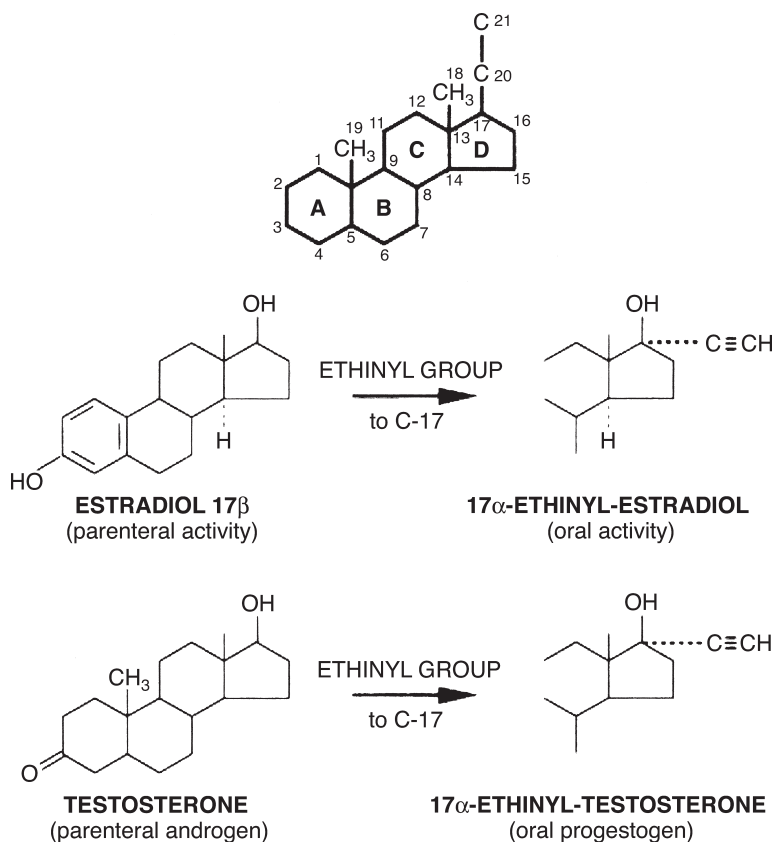


Fig. 8. The importance of the ethinyl group ($\text{C}\equiv\text{CH}$) on C-17 for oral activity of steroids. Introduction of the ethinyl group into the estradiol molecule resulted in the first orally active synthetic estrogen—ethinyl-estradiol. Similar manipulation of the testosterone molecule resulted in the first orally active progestogenic agent—ethinyl testosterone. The numbering system of the steroid molecule is given for reference. (From ref. 135 with permission.)

dosage of the steroids in the formulations, thus the trend toward lower-dose OCs. Fortunately, serious adverse complications are rare in healthy young women and in properly selected perimenopausal (Chapter 14) or medically complicated women (Chapter 15).

Estrogen-Related Problems

The most common estrogen-related symptoms include nausea (a central nervous system effect), breast tenderness, increased breast size, headaches, and cyclic fluid retention. The fluid retention is a result of an increased estrogen-stimulated aldosterone secretion causing decreased sodium excretion. The cyclic

Table 2
Clinical and Metabolic Effects of Contraceptive Steroids (Progestins)

	<i>Metabolic effects</i>	<i>Possible associated clinical effects</i>
<u>Estrogens: ethinyl estradiol</u>		
Hepatic proteins		
Albumin	Decrease	
Angiotensinogen	Increase	Increased blood pressure
Clotting factors	Increase	Hypercoagulability, increased DVT risk
Carrier proteins	Increase	
SHBG	Increase	Lowers circulating free testosterone and other circulating sex steroids, lowered libido
TBG	Increase	Lowers free thyroid hormones; may prompt adjustment of oral dose
CBG	Increase	
Transferrin	Increase	
Ceruloplasmin		
Glucose tolerance	Small decrease, especially with high-dose OCs	Increased insulin resistance
Plasma insulin	Slight increase	Possible increased CVD risk
<u>Lipids</u>		
Cholesterol	Increase	Possible increased CVD risk
Triglycerides	Increase	Possible increased CVD risk
HDL cholesterol	Increase	Possible decreased CVD risk
LDL cholesterol	Decrease	Possible decreased CVD risk
Sodium excretion	Decrease	Cyclic fluid retention, edema
Vitamins		
B complex	Decrease	Rare vitamin deficiency with older, high-dose OCs
Ascorbic acid	Decrease	
Vitamin A	Increase	
Breast	Stimulate	Breast tenderness, increase in breast size
Endometrial estrogen receptors	Increase	Endometrial stimulation, increased bleeding, endometrial hyperstimulation
Skin		
5 α -reductase and other androgen receptors	Decrease	Decreased sebum (oily skin), acne, hirsutism, and other androgenic problems
Pigmentation	Increase	Increased facial pigmentation
Other	Increase	Telangiectasia
<u>Progestins: 19-nortestosterone derivatives</u>		
Hepatic proteins		
SHBG	Decrease	Increased free circulating testosterone and other sex steroids, increased androgen activity

(continued)

Table 2 (*Continued*)
Clinical and Metabolic Effects of Contraceptive Steroids (Progestins)

	<i>Metabolic effects</i>	<i>Possible associated clinical effects</i>
APC, clotting factors	Possibly oppose thrombotic effect of estrogen	
Glucose tolerance	Decrease	Possible increased CVD risk
Insulin resistance	Increase	
Cholesterol	Decrease	Possible decreased CVD risk
Triglycerides	Decrease	Possible decreased CVD risk
HDL cholesterol	Decrease	Possible increased CVD risk
LDL cholesterol	Increase	Possible increased CVD risk
Appetite		
Nitrogen Retention	Increase	Increased body weight, bloating
Skin		
Androgen Activity	Increase	Increased sebum (oily skin), acne, hirsutism
CNS effects	Increased activity	Nervousness, fatigue, depression, tiredness, PMS symptoms
Endometrial steroid receptors	Decrease	Less menstrual bleeding, no withdrawal bleeding

Metabolic and clinical effects are related to dose, potency, and particularly estrogen and progestin, and are often minimal in current low-dose oral contraceptives.

CBG, corticosteroid-binding globulin; TBG, thyroid-binding globulin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CVD, cardiovascular disease; OC, oral contraceptive; APC, activated protein C; CNS, central nervous system; SHBG, sex hormone-binding globulin; PMS, premenstrual syndrome.

Adapted from ref. 136.

fluid retention generally does not exceed 3–4 lb. There are minor, clinically insignificant changes in circulating vitamins. Estrogen can also cause melasma, an increased pigmentation on the malar eminences. Melasma often takes a long time to disappear and is accentuated by sunlight. The incidences of all of these estrogen-related adverse effects are much lower than those seen with use of older high-dose OCs.

Estrogen can increase the concentration of cholesterol in gallbladder bile and older formulations were associated with an increased incidence of cholelithiasis and cholecystitis. Newer, low-dose OCs appear to avoid these side effects. The results of a large British Family Planning Association study (15) and a case-control study (16) indicate that use of OCs does not increase the incidence of gallbladder disease in women, even if used for more than 8 years (17).

MOOD AND DEPRESSION

- Low-dose OCs have not been linked with depression (18), although positive and negative mood changes can occur in certain individuals with particular formulations.

In 1984, the Royal College of General Practitioners cohort study reported that the incidence of depression in OC users was positively correlated with the dose of estrogen in the formulation (19). It has been postulated that the high dosages of the synthetic estrogen in OCs divert tryptophan metabolism from its minor pathway in the brain to its major pathway in the liver. The end product, serotonin, is thus decreased in the central nervous system, resulting in depression. In this study, women using OCs containing less than 50 µg of estrogen did not have an increased incidence of depression. By contrast, postmenopausal women receiving physiological doses of estrogen report an improved mood, whereas the addition of a progestin increases depression, tension, irritability, and fatigue (20).

CARBOHYDRATE METABOLISM

- Low-dose OCs do not adversely alter glucose metabolism (21–23).

The adverse effect of high-dose OCs on glucose metabolism is primarily related to the potency and dose of progestin. Although estrogens may act synergistically with the progestin to further impair glucose tolerance, in general, the higher the dose and potency of the progestin, the greater the magnitude of impaired glucose tolerance. However, formulations with low doses of progestins, including levonorgestrel, do not significantly alter levels of glucose, insulin, or glucagons after a glucose load in healthy women (24) or in those with a history of gestational diabetes (25). Data from 20 years of experience of women using OCs was reported in a large cohort study. There was no increased risk of diabetes mellitus among current OC users or former OC users, even among women using OCs for 10 years or more (26). Recent short-term studies of low-dose OCs also show no increase in diabetes mellitus (27).

HEPATIC PROTEINS

Synthetic estrogens in OCs stimulate increases in hepatic production of several globulins in a dose-dependent manner. The progestin component suppresses the synthesis of SHBG but has little influence on other hepatic production. Estrogen increases the production of the following hepatic proteins:

- Clotting factors: factors V, VIII, and X, and fibrinogen (enhance thrombosis) (28).
 - Epidemiological studies show the increased risk of both arterial and venous thrombosis is directly related to the dose of estrogen (29).
- Blood pressure factors: angiotensinogen.
 - About 0.4% of low-dose OC users became hypertensive in the Nurses Health Study (30).

- SHBG: measurement of SHBG is one way to determine the relative estrogenic/androgenic balance of different OC formulations. Formulations with the greatest increases are particularly useful in treating women with symptoms of hyperandrogenism.
 - Greatest increase in SHBG levels occur following ingestion of OC formulations containing desogestrel, cyproterone acetate, and gestodene and, to a lesser degree, those with low-dose norethindrone and levonorgestrel (31).
 - SHBG levels have also been linked to increases in activated protein C (APC) resistance and thrombosis. Some data suggest that increases in SHBG with OCs could be interpreted as a measure of total estrogenicity and used as a predictor of the risk of venous thromboembolism (VTE) (32–34). (Further research is needed to define the best balance of new progestins with low doses of estrogen.)

LIPIDS

The estrogen component of OCs increases high-density lipoprotein (HDL) cholesterol, total cholesterol, and triglycerides, and decreases low-density lipoprotein (LDL) cholesterol. The progestin component has the reverse effect. Older progestin-dominant formulations had adverse effects on the lipid profiles producing decreases in HDL cholesterol and increases in LDL cholesterol levels. Because estrogen has a more potent effect on triglycerides than progestin, the older formulations also showed significant increases in triglycerides.

The newer, low-dose OCs still show increases in triglyceride, but generally produce little or no adverse changes in HDL or LDL cholesterol (35,36). No long-term effects of these changes in lipid parameters are reported in past users.

COAGULATION PARAMETERS

OCs have multiple effects on coagulation parameters.

- OCs enhance thrombosis (through increases in fibrinogen), inhibit coagulation (protein C, protein S, and antithrombin), enhance fibrinolysis (plasminogen), and inhibit fibrinolysis (plasminogen activator-inhibitor 1).
- OCs diminish the efficacy with which APC naturally downregulates thrombin formation, designated as acquired APC resistance. Several reports indicate that the use of third-generation OCs is associated with increased acquired APC resistance compared with use of second-generation OCs (37,38).
- Changes in coagulation parameters in OC users are small and have a limited clinical impact in healthy users.
- Women with inherited coagulation disorders, such as deficiency of protein C, protein S, antithrombin, or APC resistance, have several-fold increased risk of thrombosis if they use combination OCs (39).
 - The annual incidence of deep venous thrombosis in women of reproductive age with an APC resistance is about 6 per 10,000 but is increased to 30 per 10,000 during use of OCs.

- At the present, screening for these coagulation deficiencies is not recommended before initiating OCs unless a woman has a personal or strong family history of thrombotic events, although screening is certainly indicated in women with a VTE, especially if it occurs during the early use of OCs (40).

CARDIOVASCULAR EVENTS

Venous Thromboembolism

- The risk of VTE is directly related to the dose of estrogen in the OC but is lower than the rate associated with pregnancy (42).
 - Inherited disorders, such as factor V Leiden mutation, protein S and C synthesis, or prothrombin mutation disorders (found in 0.5 to 5% of reproductive aged women), can dramatically increase an OC user's risk of VTE.
 - Women with a strong family or personal history of clotting problems should not use estrogen-containing OCs and should undergo screening.
- Thrombosis can occur in a variety of sites including leg or thigh veins, lung, eye, intestines, brain, or heart.

The risk of VTE is directly related to the dose of estrogen in the OC. The background rate VTE in reproductive age women is about 0.8 per 10,000 woman-years. The rate in OC users taking pills with 20 to 50 µg EE is reported to be 3 per 10,000 woman-years. Although this is about four times the background rate of reproductive-age women, it is half the rate of 6 per 10,000 woman-years associated with pregnancy (43).

Controversy exists as to whether or not the OCs containing gestodene and desogestrel are associated with an increased risk of VTE or whether the increased risk (1.5 to 2.5 times the risk with levonorgestrel low-dose OCs) reported in several studies (44–46) may result from certain types of bias. Selection, diagnostic, and reference biases could account for the differences, but a causal relationship may exist (47,48). Lower rates of myocardial infarction with third-generation products is also reported (49).

It has been suggested that the phenomenon designated as acquired APC resistance (increased resistance to the anticoagulant action of APC) is more pronounced in women using third-generation versus second-generation OCs (50). The fact that the third-generation progestins do not oppose the various effects of estrogen as strongly as older progestins may play a role. The newer selective progestins may not counter the thrombotic effect of the estrogen component in combined OCs as well as the older progestins (51). The trend toward even lower doses of EE may be particularly beneficial for new OCs with the new progestins.

Myocardial Infarction

The cause of the increased incidence of cardiovascular disease including myocardial infarction, in users of OCs appears to be thrombosis not atherosclerosis (41).

A recent World Health Organization technical report states that women who do not smoke, have their blood pressure checked, and do not have hypertension or diabetes mellitus have no increased risk of myocardial infarction (MI) if they use combined OCs, regardless of their age (52). However, women with these risk factors or those with known vascular disease/vessel narrowing should not use OCs because they are at significantly increased risk.

- The increase in MI attributable to OCs is due to estrogen-induced arterial thrombosis not atherosclerosis.
- The increased risk of MI with OC use only occurs in women with known risk factors (53).
 - The risk of death attributable to OC use in low-risk women is lower than their risk of death from pregnancy, regardless of their age.
 - Large increases in the relative risk of MI or stroke (7- to 100-fold increase) are reported for OC users who smoke or have hypertension (54).
 - Because of their narrowed vessels, women with underlying vascular disease are at highest risk for the estrogen-induced changes in thrombosis.
 - For many years, uncontrolled hypertension or women over age 35 who smoke cigarettes have been contraindications to the use of OCs.

Nearly all the published epidemiological studies confirm that there is no increased risk of MI among former users of OCs (55). Studies with cynomolgus macaque monkeys found that, although ingestion of OCs containing high doses of norgestrel and EE resulted in lowered HDL cholesterol, these animals had a significantly smaller amount of coronary artery atherosclerosis than did a control group of female monkeys not ingesting OCs but fed the same atherogenic diet after 2 years of use (56). This study suggests that the estrogen component of OCs does not promote atherosclerosis but rather has a direct protective effect on the coronary arteries.

Since the 1970s, epidemiological studies have reported significantly increased risk of MI, mainly among older OC users who had risk factors that caused arterial narrowing, such as hypertension, diabetes mellitus, or smoking (57,58). A case-control study analyzed the risk of MI after OC use in women admitted to hospitals in northeastern United States between 1985 and 1999. The relative risk of MI among current OC users was not significantly increased; however, among women who smoked at least 25 cigarettes a day, current OC use increased the risk of MI 32-fold compared with nonsmokers not using OCs. However, smoking alone was an independent risk factor and increased the risk of MI about 12-fold even without use of OCs (59). A more recent meta-analysis reported that current use of OCs increased this risk of MI by 2.48 (60). In a rigorous meta-analysis, low-dose OCs with second- and third-generation progestogens increased the risk of cardiac and vascular arterial events; the increased risk seemed less robust for the use of third-generation OCs. The authors link much of the increased risk to baseline risk factors including hypertension, migraines, smoking, or metabolic syndrome (61).

Stroke

- Recent studies of low-dose OCs show no increased risk of stroke for nonsmoking women without risk factors for cardiovascular disease (62–64).
- OC users who smoke or have hypertension or migraines with aura have a three-fold increased risk of stroke compared with nonusers (65).

As occurred with MI, the epidemiological studies of OCs that show increased risk of stroke in OC users, indicated that the increased risk was mainly limited to older women who also smoked or were hypertensive. There appears to be no difference between second- and third-generation OCs (66).

Hypertension

The OC-induced increases in angiotensin II and aldosterone may be associated with increases in systolic or diastolic blood pressure in some women. A significant increase is seen in only 1 to 3% of users. Blood pressure normalizes within 2 to 3 months after OC discontinuation.

Progestin-Related Problems

Because progestins are derivatives of testosterone, the progestin components of OCs may have androgenic side effects. With the use of low-dose progestins or new, low-androgenic progestins, these side effects are reduced. Additionally, all current combination OCs suppress endogenous testosterone production and increase SHBG that binds up free testosterone. Therefore, most combination OCs actually decrease androgenic activity and androgenic problems, including acne, hirsutism, and oily skin. Some products have a particularly good anti-androgenic action and have specific FDA approval for treatment of acne.

Other androgenic and progestogenic side effects include cyclic mood changes, increased appetite, tiredness, anxiety, and depression. Progestin's impact on lipids, glucose metabolism, hepatic proteins, skin, and CNS effects are listed in Table 2.

ANDROGENIC EFFECTS

- Most currently marketed OCs have a beneficial impact on acne or facial hair through multiple estrogenic actions (increases in SHBG, direct skin effects, and suppression of endogenous androgens).

Although all low-dose OCs are associated with a reduction in androgen-related problems, the gonane and estrane progestins are structurally related to testosterone and may produce certain androgenic side effects. These include nervousness, acne, weight gain, and increased sebum production. The current low-dose OCs have less androgenic side effects than the high-dose OCs of the past because of lower doses of progestins. For women with primary complaints of moderate to severe acne or other manifestations of hyperandrogenism, OCs with norgestimate, desogestrel, and DRSP are considered the formulations of choice.

REPRODUCTIVE EFFECTS OF LOW-DOSE OCS

There is a slight delay in the return of ovulation in women discontinuing use of OCs. For about 2 years after stopping, the rate of return of fertility is lower in previous OC users compared with previous barrier method users, but eventually the percentage of women in both groups becomes the same (67).

Neither the rates of birth defects (68), spontaneous abortion, or chromosomal abnormalities in abortuses (69) are increased in women conceiving during the first or second month after discontinuing OCs. If OCs are accidentally ingested during the first few months of pregnancy, a large cohort study reported no increased risk of congenital malformations among the offspring (70).

NEOPLASTIC EFFECTS OF LOW-DOSE OCS

Breast Cancer

- OCs have undergone extensive study for more than 40 years in an attempt to determine the relationship between OCs and the development of breast cancer.
- The vast amount of studies show small or no changes in the relative risk of breast cancer during OC use. Following discontinuation of OCs, the risk returns to baseline.
 - It is reassuring that the risk of having had breast cancer diagnosed by age 65 is the same in past users as in never users.
- It appears that the dose or type of either steroid, as well as duration of OC use, is not related to breast cancer risk.

The results of a study by the National Institute of Child Health and Human Development are very reassuring (71). This study reported that current or prior use of OCs did not affect a women's risk of diagnosis of breast cancer between the ages of 35 and 64; the relative risk (RR) estimates were 1.0 and 0.9 for current or prior OC users compared with nonusers, respectively. The risk was not increased among women who had taken OCs for long periods of time or had used formulations with high amounts of estrogen. Additionally, women with a family history of breast cancer did not have a further increased risk of breast cancer with OCs use.

It is important to also consider the findings of an international collaborative study that analyzed the data from 54 studies performed in 25 countries, involving more than 53,000 women with breast cancer and more than 100,000 control subjects. Current OCs users had a slightly increased risk of having breast cancer (RR: 1.24, confidence interval [CI]: 1.15–1.30) (72). After discontinuing OCs, the risk declined steadily and by 10 years, the risk was no longer significant (RR: 1.01, CI: 0.96–1.05). The cancers diagnosed in women taking OCs in this study were less advanced clinically than those in nonusers. The authors concluded that these results could be explained by the fact that breast cancer is diagnosed earlier in OC users than in nonusers or could result from biological effects of the OCs.

- There are two factors that may explain this increased risk of breast cancer: detection bias or a promoter effect. A detection bias would occur if OCs users are more likely to have breast exams or receive mammograms and thus more likely to have their breast cancer diagnosed. Alternatively, the epidemiological findings are compatible with the hypothesis that OCs may act to promote the growth of increase the chance of diagnosis of existing cancers. Like early first-term pregnancy, OCs slightly increase the risk of breast cancer diagnosis at a young age with no appreciable effect on lifetime risk of breast cancer and no change in risk during the perimenopausal years when the disease becomes more common.

Cervical Cancer and Cervical Dysplasia

- Although it is uncertain whether OCs increase the risk of cervical cancer, act as a co-carcinogen, or have no effect, users of OCs as a group have an increased risk of cervical neoplasia and require at least annual screening of cervical cytology, especially if they have used OCs for more than 5 years.

The epidemiological data is conflicting regarding OC use and risk of invasive cervical cancer. Confounding factors may account for the different results in various studies, such as the woman's age at first sexual intercourse, exposure to human papillomavirus (HPV), number of sexual partners, cytological screening (possibly more frequent among OC users), use of barrier contraceptives or spermicides, and cigarette smoking (an independent risk factor). However, most of the studies made statistical correction for these confounding factors.

Pooled data from eight case-control studies reported that the RR of invasive cervical cancer was 0.73 for less than 5 years of OC use, 2.82 for 5–9 years of use, and 4.03 for 10 or more years of use (73). In this analysis, OCs increased the risk of cervical cancer only in women infected with HPV, but not in women without HPV. In an even larger meta-analysis of 28 studies including 12,531 women with cervical cancer, 5 years of OC use was associated with an RR of 1.1. OC use for 5 to 10 years was associated with an RR of 1.6 and an RR of 2.2 after 10 years of use (74).

Endometrial Cancer

- Women who use OCs for at least 1 year have an age-adjusted RR of 0.5 for the diagnosis of endometrial cancer between 40 and 55 years compared with nonusers.

Three cohort studies and 12 case-control studies examined the relationship between endometrial cancer and OCs. All but two of these studies indicated that OCs have a protective effect (75). This protective effect is related to duration of use increasing from 20% reduction with 1 year of use to 40% reduction with 2 years use to about 60% reduction with 4 years of use. It appears that both high- and low-dose formulations are protective (76).

Ovarian Cancer

- The RR of ovarian cancer among ever-users of OCs is around 0.64, a 36% reduction.

Of 20 reports on the use of OCs with subsequent development of ovarian cancer, 18 found a reduction in risk (77). OCs were found to reduce the risk of the four main histological types of epithelial ovarian cancer (serous, endometrioid, clear cell, and mucinous) and the risk of those with low malignant potential. The decreased risk is directly related to the duration of OC use, increasing from about 40% reduction with 4 years of use to a 53% reduction with 8 years and a 60% reduction with 12 years of use.

Liver Adenoma and Cancer

Although rare, the prolonged use of high-dose OCs, particularly those containing mestranol, has been linked to an increased risk of hepatocellular adenoma. Although two British studies reported an increased risk of liver cancer among OC users, data from a large World Health Organization multicenter study found no increased risk of liver cancer associated with OC users in countries with a high prevalence rate of this neoplasm (78).

Colorectal Cancer

Although a meta-analysis published in the year 2000 showed a significant reduction of risk for OC users (0.81 for the case-control studies and 0.84 for the cohort studies), a causal relationship between OCs and colorectal cancer remains to be established (79). Support for the belief that estrogen causes a reduction in colon cancer is provided by multiple studies showing that postmenopausal estrogen use has also been associated with a lower risk of colon cancer.

Pituitary Adenomas

Discontinuing OCs may unmask the amenorrhea associated with a pituitary adenoma, suggesting a causal relationship. However, data from three separate studies document that the incidence of pituitary adenoma among users of OCs is not higher than that among matched nonusers (80).

Malignant Melanoma

The results of many large studies of long duration indicate that OC use does not increase the risk of malignant melanoma (81).

DRUG INTERACTIONS

As a result of substrate competition, synthetic sex steroids can retard the biotransformation of certain drugs, such as phenazone and meperidine. Such interference is generally not clinically significant. However, some drugs can interfere clinically with the action of OCs by inducing liver enzymes that convert

the steroids to more polar, less biologically active metabolites. For this reason, drugs such as barbiturates, carbamazepine, griseofulvin, sulfonamides, antiretinal, cyclophosphamide, and rifampin (82) should not be given concomitantly with OCs (Chapter 3, Table 2).

The clinical data linking certain antibiotics (penicillin, ampicillin, and sulfonamides), antiepileptics (phenytoin), and barbiturates are less clear. A few anecdotal studies have appeared in the literature, but reliable evidence for a clinical inhibitory effect of these drugs on OC effectiveness, such as occurring with rifampin, is not available. The best data is on antiepileptic medications that are known to induce hepatic P450 enzymes and thus increase estrogen metabolism. Based on this data, it is recommended that women with epilepsy requiring medication should consider a 35 µg or higher formulation (83), although a risk-benefit evaluation should be done.

CONTRACEPTIVE HEALTH BENEFITS

In 2003, the Centers for Disease Control and Prevention reported that there was an average of 11.8 pregnancy-related deaths per 100,000 live births during the 1990s in the United States (84). By protecting the user from pregnancy, this risk is substantially reduced. The user is also protected from ectopic pregnancies ($\geq 90\%$ reduced risk) (85), the leading cause of pregnancy-related deaths in the first trimester of pregnancy. It is estimated that OC use prevents 1–7 million abortions worldwide annually. For most healthy, nonsmoking women, the risk of using any contraceptive method is safer than using no method (Chapter 3, Table 1).

NON-CONTRACEPTIVE HEALTH BENEFITS

In addition to their effective contraceptive protection, OCs provide a wide range of other health benefits (86). These benefits are not FDA-approved indications, but the clinician and users may want to consider them in their overall assessment.

- Reduction in the amount of monthly blood loss resulting from a progestin “antiestrogenic” action on the endometrium (87). In an ovulatory cycle, the mean blood loss is about 35 mL, compared with 20 mL in OC users.
 - OCs are often an effective treatment for menorrhagia (88,89).
 - Less iron-deficiency anemia (90,91).
- Fewer menstrual irregularities: OCs are designed to produce regular withdrawal bleeding (92).
 - Less frequent curettage or hysterectomy.
 - Eighty percent improvement in dysfunctional uterine bleeding (93).
- Lowered risk of endometrial cancer.
 - OC use for 1 year reduces the risk by 40% (94) and by 80% after 10 years of use (95).

- Protection lasts for up to 20 years (96).
- Lowered risk of ovarian cancer.
 - Risk is reduced by 40% (97) after ever-use and 80% reduced after 10 years of use (98).
 - Protection lasts for up to 20 years (99).
 - Protection may include women with *BRCA* mutations (100–102) or strong family history of ovarian cancer (103,104), although some studies show that protection is limited to those that are not genetically at risk (105).
 - High-dose progestin OCs may give more protection than low-progestin OCs (106).
- Lowered risk of benign breast disease (107).
 - Reduced risk of cysts, fibrocystic changes, fibroadenomas (108).
 - Progestins inhibit the synthesis of estrogen receptors in breast tissue.
- Less dysmenorrhea (63%) (109).
 - OC use can reduce absences from work or school.
- Lowered incidence of symptomatic endometriosis (110).
- Less premenstrual syndrome symptoms (29%) (111,112).
 - Less bloating, pain, cramping, mastalgia.
 - OCs containing DRSP reported to improve symptoms of water retention, negative affect (113,114).
- Lowered rate of functional cysts (115), although follicular cyst formation may not be eliminated with low-dose OCs (116).
- Lowered incidence of androgen excess conditions.
 - Reduction in acne lesions (117,118) and hirsutism (119,120).
 - All formulations associated with improvements in mild to moderate acne; only Ortho Tri-Cyclen® (121) and Estrostep® have FDA approval for treatment.
- Lowered risk of PID (122) primarily because of reductions in gonorrhea PID.
 - Upper tract infections may be prevented.
 - Thickened cervical mucus preventing the movement of sperms carrying pathogens into the uterus.
 - Less menstrual bleeding with OC use: blood in the cervix may facilitate pathogen transport.
 - There is no decreased risk of chlamydial PID (123) or lower tract infections, such as chlamydia or other STDs.
- Less mittelschmerz (midcycle ovulation pain).
- Reduction in symptomatic endometriosis during use (124,125).
- Reduction in hot flashes and other perimenopausal symptoms (126,127; see Chapter 14).

Possible Non-Contraceptive Benefits

The following potential benefits from OCs are controversial because there are conflicting studies.

- Reduced risk of hip fracture (128), increased bone mineral density (129), mixed findings in a comprehensive review (130).
- Lowered risk or slower growth of uterine fibroids (131).
- Reduced risk of colon cancer (132).
- Reduced risk or slower progression of rheumatoid arthritis (133) or no effect (134).
- Reduced symptoms appearing during menses.
 - Seizures, asthma, porphyria.

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