Non-contraceptive benefits of oral contraceptives

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Abstract: The health benefits of the oral contraceptive (OC) pill are numerous and outweigh the risks of OC use. There are unintended but useful preventive side effects and potential therapeutic uses of OCs apart from contraception itself. Unequivocal evidence for the protective influence of combined OCs against ovarian and endometrial cancers, and colon cancer to a lesser extent, has been found. The pill also reduces the incidence of benign breast disease, functional ovarian cysts, pelvic inflammatory disease requiring hospitalization, ectopic pregnancy, and iron-deficiency anemia. The pill can be used for the treatment of several gynecologic disorders such as dysmenorrhea, irregular or excessive bleeding, acne, hirsutism, and endometriosis-associated pain, whether prescribed solely to treat these symptoms or prescribed to treat them in addition to providing contraception. These health benefits are often underestimated, as they get too little attention from the mass media.

Keywords: the pill, estrogens, progestogens, safety, contraception

Introduction

Although the primary purpose of oral contraceptives (OCs) is to prevent unwanted conception, it is no wonder that the profound effect on the hormonal regulation of the menstrual cycle could entail some major effects on the female genital tract and the endocrine system. Estrogens, besides their anti-ovulatory effect, have a growth-promoting effect on the lining of the genital tract and the glandular breast tissue. Progestogens add to the contraceptive effect of estrogens by suppressing the ovulatory luteinizing hormone surge. They also thicken the cervical mucus, thereby hindering sperm migration into the upper genital tract, and they have an antiproliferative effect on the endometrium, making it less receptive for implantation.1 Both sex steroids have dose-related side effects. Progestogens do not bind exclusively to the progesterone receptor; they can also activate other steroid receptors to a certain degree. Estrogens promote the synthesis of several hepatic proteins and they have a well-established prothrombic effect.2 Although there is no doubt that estrogens increase the risk of thromboembolism two- to four-fold, fatal thromboembolism among young women is extremely rare (1% of cases), and this increased risk should be balanced against the five- to ten-fold increase in risk associated with normal pregnancy. On the other hand, besides the effective protection against unwanted conception, there are a number of beneficial effects. However, unintended but useful preventive side effects should not be equated with a potential therapeutic use of OCs. For instance, it is generally acknowledged that functional ovarian cysts are very rare in women taking combined oral contraceptives (COCs), but giving the
pill to a woman who has developed a functional ovarian cyst will not hasten the disappearance of the cyst.\(^3\)

The mechanisms of the non-contraceptive benefits of COCs can be directly related to the anti-ovulatory effect (eg, prevention of ovarian cancer), the antiproliferative effect of progestogens on the endometrium (eg, prevention of heavy menstrual bleeding, dysmenorrhea, and endometrial carcinoma), or the effects on the endocrine system (eg, the prevention of acne). Adding the non-contraceptive benefits to those of preventing unwanted pregnancy and the potential complications, COCs are associated with a significant reduction in the mortality rate.\(^4\)

In this review both the non-contraceptive therapeutic benefits and the prophylactic benefits of COCs will be discussed.

**Preventive effects of COCs**

**Ovarian cancer**

In 1995, three articles on the increased risk of thromboembolism for users of third-generation pills were published in the *Lancet*, inducing a temporary pill scare. Twelve years later, a January 2008 cover of the same journal stated: “Oral contraceptives have already prevented some 200,000 ovarian cancers and 100,000 deaths from ovarian cancer, and over the next few decades the number of cancers prevented will rise to at least 30,000 per year.”\(^5\) This one statement neutralizes many of the warnings on the serious side effects of OCs and underscores the beneficial non-contraceptive effects of the pill. This publication was not the first to draw attention to the fact that users of COCs are less likely to develop ovarian cancer than nonusers. Since 1980, numerous case-control studies on the relationship between the use of COCs and the risk of ovarian cancer have been performed, and all concur that the risk in pill users is reduced by 30%–50%.\(^6-10\) This protective influence lasts for more than 10 years after cessation of pill use.\(^11\) Although the precise mechanism of the relationship between the number of ovulations and the development of ovarian cancer is not known, the protective effect of COCs is mainly through reducing the number of ovulations.

**Endometrial cancer**

Mueck et al\(^24\) recently published a review of all studies of the relationship between endometrial cancer and hormonal contraception. More than 15 case-control studies and at least four large cohort studies demonstrated a decrease in the risk of endometrial cancer of about 50% if COCs had ever been used. In most of these studies, this protective influence persisted for more than 10, 15, or even 20 years after cessation of COC use. However, in the Royal College of General Practitioners’ Oral Contraception Study, the protective impact of COCs was restricted to 5 years or less after cessation of pill use.\(^25\) An increasing protective influence with longer duration of COC use was found in most studies. The beneficial impact was independent of the composition of the COC (ie, dosage and type of progestogen, combined with ethinyl estradiol 30–50 mg/day). COCs with higher progestogenic potency seem to be more effective.

The mechanism of protection against endometrial cancer is different from that against ovarian cancer. Most endometrial cancers (70%–80%) are induced by chronic estrogenic stimulation. The progestogenic compound of COCs protects from estrogen-induced hyperplasia and changes in proliferative status.

**Colorectal cancer**

Several case-control and cohort studies have focused on the relationship between colon cancer and the use of COCs and...
a number of meta-analyses have been performed; however, the conclusion is not unanimous.

In the Nurses’ Health Study, women who used OCs for 96 months or longer had a 40% lower risk of developing colorectal cancer (risk ratio [RR]: 0.60, 95% confidence interval [CI]: 0.40–0.89; P for trend 0.02) than women who never used OCs.26 In a meta-analysis, the combined RR for colorectal cancer from eight case-control studies and four cohort studies for those who had ever used COCs was 0.82.27 The favorable effect of COC use on the risk of colon cancer was confirmed in a recent meta-analysis by Bosetti et al.28 The summary relative risk of colorectal cancer for those who had ever used COCs vs those who had never used COCs was 0.82 (95% CI: 0.69–0.97) from eleven case-control studies, 0.81 (95% CI: 0.75–0.89) from seven cohort studies, and 0.81 (95% CI: 0.72–0.92) from all studies combined. The results were similar for colon and rectal cancer individually. For both colon and rectal cancer, there was no evident difference according to duration of the COC use. In contrast to these studies, Long et al29 found no risk reduction for distal large bowel cancer through use of OCs. These authors hypothesized that the lack of a protective effect seen in their study may be explained by modern-day formulations of OCs: previous studies showing a protective effect might have disproportionately contained women who used higher-dose estrogen formulations than those predominantly used today. Therefore, it is still unclear whether COCs effectively reduce, albeit moderately, the risk of bowel cancer.

**Functional ovarian cysts**

It has long been acknowledged that COCs greatly reduce the incidence of functional ovarian cysts.26 Originally this observation led to it being inferred that COCs could be used to treat functional ovarian cysts; however, randomized controlled trials as summarized in a recent review have shown that COCs do not hasten the resolution of functional ovarian cysts.3 There are two types of functional ovarian cysts: follicular and luteal. Follicular cysts arise from follicles that fail to rupture at the time of ovulation and which can continue to grow; they can reach a diameter of up to 5 cm. After ovulation, the corpus luteum can be transformed into a mostly hemorrhagic corpus luteum cyst. In both cases, acute complications due to torsion or rupture can occur. Because COCs suppress ovulation, it is evident that the occurrence of luteal cysts will be prevented through COC use. The degree of prevention of follicular cysts will depend on the type of COC: high-dose pills will be more effective than low-dose pills. Because follicles start growing in the pill-free interval, the continuous use of COCs will also be more effective in preventing follicular cysts than the usual 21-/28-day regimen.

**Endometriosis**

Although the precise etiopathology of endometriosis is unknown, reflux of endometrial cells at the time of menstruation is generally considered to be the initiating event. Extra-uterine implantation and growth of endometrial cells is further promoted by the cyclic production of estrogens. COCs could prevent the initiation or extension of endometriosis by two mechanisms: the volume of menstrual flow is reduced and progestogens, either directly or by their anti-estrogenic effect, prevent implantation and growth of endometrial cells. A number of case-control and cohort studies have shown that the risk of endometriosis is reduced in pill users.31 However, studies on the favorable effect of COCs on the risk of endometriosis may be somewhat biased: the suppression of symptoms, including potential subfertility, frequently postpones diagnostic evaluation. The question of whether COCs are instrumental in the primary prevention of endometriosis remains to be answered.

**Uterine leiomyomas**

The occurrence of uterine leiomyomas or fibroids is determined by genetic factors and exposure to estrogens. Therefore, reproductive events impact on the risk of developing fibroids. For instance, there is an inverse relationship between the incidence of fibroids and the number of term pregnancies; an inverse relationship can also be found between the incidence of fibroids and smoking. Due to the anti-estrogenic activity of progestogens, COCs could have a protective effect on the development of fibroids. Indeed, the Oxford Family Planning Association found that the risk of fibroids was reduced by about 31% in women who had used OCs for 10 years and that it also decreased consistently with an increasing duration of OC use.32

**Benign breast disease**

Benign breast disease is a collective term referring to a number of benign breast conditions such as fibrocystic breast disease, fibroadenoma, and undefined breast lumps. Various risk factors for benign breast disease have been assessed by analysis of data obtained from a multicenter cohort study of contraceptive use among women in the United Kingdom.33 An inverse association was found between use of OCs and the risk of fibroadenoma, chronic cystic disease, and breast lumps. Current users of the pill had the lowest risk, particularly when the use was for an extended period. In contrast,
past users demonstrated no reduction in risk. Because this study comprised mainly women on COCs containing estrogen of 50 µg or more, the analysis was recently updated to include a much larger number of cases and also a substantial number of women taking low-dose COCs. It was concluded that all types of COCs appear to reduce the incidence of benign breast disease. All observational studies on the relationship between COC use and diseases are subject to different kinds of biases (eg, prescription and selection bias) and confounding factors, and therefore conclusions on presumed benefits of COCs should be approached with caution. However, the fact that a protective effect was also reported in a large prospective cohort study confirms the contention that COCs indeed reduce the incidence of benign breast disease.

**Iron-deficiency anemia**

It is well known that COCs reduce menstrual blood loss by about 50%, both in quantity and in duration. This applies not only to normally menstruating women but also to women suffering from heavy menstrual blood loss. About 10% of menstruating women suffer from heavy menstrual bleeding (defined as a menstrual blood loss of more than 80 mL). It is particularly in those women that COCs are able to prevent iron-deficiency anemia. In normally menstruating women, no difference was observed in the biomarkers of iron deficiency between users and nonusers of COCs.

**Pelvic inflammatory disease**

Earlier studies have shown that COCs may protect against acute episodes of pelvic inflammatory disease. However, a meta-analysis of prospective and case-control studies found an odds ratio (OR) of 1.93 (95% CI: 1.77–2.11) for the risk of chlamydial infection for COC users. In a study among commercial sex workers in Mombasa, Kenya, the use of hormonal contraception by HIV-1-infected women was associated with an increased risk of cervicitis and cervical Chlamydia infection. It may be concluded that COCs enhance the risk of acquiring sexually transmitted infections, presumably by their effect on the cervical epithelium. These findings do not necessarily contradict previous reports on the reduced risk of acute pelvic inflammatory disease, but they indicate that COCs are at least ineffective in preventing the transmission of venereal diseases.

**Rheumatoid arthritis**

There have been many studies on the role of COCs in rheumatoid arthritis (RA). The majority of studies have found that past or current use of COCs has a protective effect against RA development. In a recent case-control study, Berglin et al reported a decreased risk for development of RA in women who had been using COCs for 7 years or more (OR: 0.37; 95% CI: 0.15–0.93). In the Norfolk Arthritis Register, which is a primary care-based cohort of patients with recent-onset inflammatory polyarthritis, it was found that COC users have a better functional outcome than nonusers. COC use at baseline and before onset of symptoms appeared to have the most consistent benefit.

**Noncontraceptive therapeutic indications for COCs**

**Heavy menstrual bleeding**

COCs are associated with a decreased menstrual flow by limiting endometrial proliferation. Although COCs are widely used as a first-line treatment for heavy menstrual bleeding, it is remarkable that until very recently there was a lack of published randomized trial data to definitely prove the efficacy of COCs for this treatment. One small nonrandomized crossover trial (n = 45) showed that COCs were effective in modulating blood loss, on average providing a 40%–50% decrease, along with a decrease in the occurrence of dysmenorrhea. Because of the lack of solid proof of efficacy, Farquhar and Brown concluded in a recent Cochrane review that there were not enough trial data to recommend COCs for treatment of abnormal uterine bleeding. It should be remembered that lack of evidence does not necessarily mean that COCs cannot be effective in reducing blood loss in women with heavy menstrual bleeding. Several decades of clinical experience attests to the place of COCs in the treatment of heavy menstrual bleeding. Recently, two randomized trials of an OC containing estradiol valerate and dienogest provided solid proof of the efficacy of COCs for this treatment. The reduction of blood loss in the study group varied from 60% to 70% compared with the placebo group. Less-frequent menses or amenorrhea can be achieved with extended estrogen–progestogen COC regimens; however, there are no studies to prove that this mode of administration is superior to the cyclic use of COCs for treating heavy menstrual bleeding.

**Dysmenorrhea**

Dysmenorrhea or painful menstruation is associated with ovulatory cycles. Headaches, nausea, and vomiting can be accompanying symptoms. With the withdrawal of progesterone and estradiol at the end of the ovulatory cycle, a cascade of endometrial events begins, including the production and release of prostaglandins, which are thought to be the main factor in painful uterine contractions. As COCs suppress
ovulation and reduce the proliferation of the endometrium (and therefore also reduce the production of prosta
glandins), they could be effective in reducing the symptoms
dysmenorrhea. A recent Cochrane review concluded that preparations of COCs with doses less than 35 µg were
effective and should be the preparation of choice.54 Two recent randomized trials showed that COCs are effective
for the treatment of primary dysmenorrhea55 as well as for
dysmenorrhea due to endometriosis.56 Even better results can be obtained by COCs used in a continuous fash-
ion. Headaches, genital irritation, tiredness, bloating, and menstrual pain were significantly reduced in the extended
cycles.57

Premenstrual syndrome

“Premenstrual syndrome (PMS) is a psychological and
somatic disorder of unknown etiology. The symptoms of
PMS regularly occur during the luteal phase of the men-
strual cycle and resolve by the end of menstruation.”58 It
is estimated that 5% of all women of fertile age suffer
from severe PMS.59 COCs prevent ovulation and should be
effective for the treatment of PMS. However, evidence
from the limited studies available does not support the
efficacy of OC agents containing progestogens derived from 19-nortestosterone.60 The combination of estrogen
and progestogen may produce symptoms similar to PMS,
such as water retention and irritability. The introduction of an OC pill containing low-dose ethinyl estradiol and
a new progestogen, drospirenone, has offered clinical
efficacy for PMS.61 Drospirenone is a spironolactone
derivative with antimineralocorticoid and anti-androgenic
activity. Drospirenone’s anti-androgenic activity makes it
also effective in the reduction of acne and seborrhea. The
antimineralocorticoid activity helps to reduce some of the
bothersome symptoms (such as swelling) associated with
the premenstrual phase of the menstrual cycle. Therefore,
this pill has the potential to improve women’s quality of
life. There is some evidence that triphasic OCs are more
effective for some of the symptoms of PMS.62 In a study by
Graham and Sherwin,63 premenstrual breast pain and bloating
were found to be significantly reduced with a triphasic
OC; however, there were no beneficial effects for any of the
mood symptoms. Continuous oral contraception provides
greater suppression of the ovary and endometrium and it
avoids the cyclic interruption of the hormonal exposure that
may trigger some symptoms associated with PMS. It has
been shown that this mode of oral contraception is associ-
ated with improved patient symptomatology.57,64

Endometriosis

Medical therapy is an important alternative or complement to
surgery for symptomatic endometriosis. Because endometrio-
sis is an estrogen-dependent disease, medical treatments are
based on their systemic or local anti-estrogenic effects. Both
progestogens and COCs are as effective as more sophisticated
and expensive drugs such as gonadotropin-releasing
hormone analogs or aromatase inhibitors.65 “COCs also
reduce the rate of postoperative endometrioma recurrence
and should now be considered an essential part of long-term
therapeutic strategies in order to limit further damage to
future fertility”.65

Acne

Acne is a common skin disorder that occurs in both sexes
and particularly affects teenagers (when androgens start
stimulating the sebaceous glands to increase production of
sebum). Although the etiopathology of acne is complex,
reduction of androgen production or antagonizing their effect
on the sebaceous glands is one of the pillars of a successful
treatment. COCs reduce the steroid production by the
ovaries: the estrogenic component increases the production
of sex hormone-binding globulin whereas the progestogenic
component can interact to varying degrees with the androgen
receptors. Newer synthetic progestogens, such as the third-
generation gonanes desogestrel and norgestimate, have less
activity at the androgen receptor and more specificity for the
progestogen receptor, and therefore the androgenic effects
are minimized. “Cyproterone acetate is a synthetic derivative
of 17-hydroxyprogesterone; it is approved in Europe for the
treatment of acne, hirsutism, and alopecia but it is not avail-
able in the United States”.66 Cyproterone acetate may be used
as a sole agent or in combination with ethinyl estradiol. In
the latter case it is prescribed as an OC particularly for the
treatment of acne (Diane-35®). Drospirenone is a relatively
new fourth-generation progestogen that partially blocks
endogenous androgens from binding the androgen receptor.
A recent Cochrane review provided a comprehensive assess-
ment of the efficacy of COCs for the treatment of acne in
women.67 It was found that all types of COCs were effective
for the treatment of acne and that in this respect only subtle
differences existed between COCs with different types of
progestogens. This proves that the effect of COCs on the
androgen level is the most important factor.

Perimenopausal symptoms

The years of fluctuating ovarian function leading up
to the final cessation of menstruation are termed the
perimenopause. This commonly lasts between 2 to 3 years, usually in a woman’s late forties or early fifties. During the perimenopause, menstrual bleeding typically becomes irregular and menopausal symptoms may be experienced. Although fertility is low, most perimenopausal women are anxious to avoid any risk of pregnancy. Vasomotor symptoms are experienced by up to 80% of women during the menopausal transition. Hot flushes, night sweats, and palpitations may significantly affect daily life and interfere with sleep, reducing quality of life for perimenopausal women. Estrogen-containing hormonal regimens offer effective treatment for vasomotor symptoms and remain the treatment of choice if symptoms are severe. For perimenopausal women with irregular, anovulatory cycles, COCs regulate the menstrual bleeding pattern, reducing both bleeding and pain. In healthy older women, these very significant menstrual benefits may well outweigh any small risks associated with COC use. These risks need to be evaluated in the context of each woman’s individual risk profile and weighed against the potential benefits: effective contraception, predictable bleeding patterns that are less heavy and less painful, reduction in vasomotor symptoms, maintenance of bone mineral density, and protection against ovarian and endometrial cancer.60

Conclusion
Not only are OCs one of the most effective methods of contraception but also they confer a number of health benefits, either by prevention of some diseases or through their use in the treatment of some gynecological disorders or discomfort related to the menstrual cycle. Besides a proven substantial reduction in the risk of ovarian and endometrial cancer, preventive effects on benign breast disease, endometriosis, fibroids, RA, and colon cancer are less pronounced, and in certain cases not unequivocally proven. Since the birth of the pill some 50 years ago, numerous changes in dosage and composition have been introduced with the general aim, apart from some commercial motives, to reduce side effects without affecting the contraceptive efficacy. The estrogen and progestogen dosage has been reduced, new progestogens have been added, alternative modes (24-day cycles, extended use of COCs) and routes of administration (transdermal, vaginal) are now offered, and, more recently, ethinyl estradiol has been replaced by natural estradiol combined with a selective progestogenic compound. Randomized studies on all these new formulations have mainly focused on contraceptive efficacy, cycle control, and biochemical variables as a substitute for potential adverse health effects.

Imitation of the natural cycle is sometimes put forward as a positive argument in the promotion of new brands of OCs. However, the restoration of a menstrual cycle is not necessarily associated with long-term beneficial side effects. Repeated and year-long menstruation is a rather recent phenomenon in human history; in fact, it is associated with the increase in some diseases such as ovarian, endometrial, and colon cancer.60 New formulations of OCs should also be evaluated with respect to their beneficial noncontraceptive side effects.

Disclosure
The author reports no conflicts of interest in this work.

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