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Oral Contraceptives

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Oral Contraceptives 1994

A report by the
Special Advisory Committee on
Reproductive Physiology
to the Drugs Directorate
Health Protection Branch
Health Canada

The views expressed in this publication are those of the Special Advisory Committee on Reproductive Physiology and do not necessarily reflect those of Health Canada.

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1. Introduction

Among women under the age of 30, oral contraceptives remain the most popular form of contraception. Health Canada has distributed information on oral contraceptives to health professionals in Canada since 1970. The Special Advisory Committee on Reproductive Physiology to the Health Protection Branch prepared major reports in 1970, 1975 and 1985. In the past, these reports have focused mainly on the risks of oral contraceptives, prompted by reaction to legal actions involving oral contraceptives in this country. In the 1985 report, the Committee recommended lowering the estrogen dose to 35 micrograms or less, and since 1985, the vast majority of oral contraceptives prescribed have been low dose, between 30 and 35 micrograms of ethinyl estradiol. Data accumulated up to now suggest that these new low-dose oral contraceptives have reduced adverse effects. The present report reflects the safety of modern oral contraceptives. This new emphasis on safety is seen in the removal of an upper age limit for use of oral contraceptives for healthy nonsmoking women and in the addition of a chapter to this document (Chapter 6) on the non-contraceptive health benefits of oral contraceptives.

For the first time, during the preparation of this report, a draft of the instructions on labelling for physicians and for patients was sent for comment to national medical societies, provincial medical associations, pharmaceutical companies, planned parenthood groups and individual physicians who expressed an interest in contraception. The Committee very much appreciated the recommendations it received from these varied sources and, where possible, it incorporated them into the text of the report. Therefore, the final report reflects not only the views of the members of the Special Advisory Committee on Reproductive Physiology to the Health Protection Branch, but also as much input as possible from interested parties across the country.

Other new recommendations by the Committee that are incorporated into this report are 1) that emphasis be placed on the use of latex condoms in conjunction with oral contraceptives for prevention of sexually transmitted diseases, especially in view of the critical human immunodeficiency virus (HIV) problem, 2) that the use of oral contraceptives is acceptable beyond the age of 35 in healthy, nonsmoking women, and 3) that the patient package insert be rewritten in language easily understood by patients.

The members of the Special Advisory Committee anticipate that the present report will provide much-needed new information to health professionals across the country and will serve as a frequently used reference.

2. Hormonal Methods of Contraception

It is well established that oral contraceptives (OCs) containing estrogen and progestin affect hypothalamic, pituitary and ovarian function. They may alter many other physiological systems. Although the exact mechanisms of action are incompletely understood, there is universal agreement that the inhibition of the "ovulatory peak" of luteinizing hormone (LH) is a constant factor. OCs may exert their contraceptive action in at least four ways:

- by inhibiting ovulation;
- by causing endometrial changes hindering implantation;
- by altering the physical and chemical properties of the cervical mucus, thereby inhibiting sperm penetration; and
- by causing subtle changes in the hypothalamic-pituitary-ovarian axis and possibly altering corpus luteum function. The steroid profiles quite often show either insufficient or an absence of luteal activity, or a significant and gradual decrease in several indices of luteal function.

Probably none of these factors alone accounts for the high degree of anti-fertility effect of any OC. They may all play a part in the production of effective contraception.

OCs were developed to prevent unwanted pregnancies. The first generation of OCs contained the progestins norethynodrel or norethindrone. Their efficacy was related to suppression of ovulation that was attributed primarily to these progestins. To decrease the cost and adverse effects of these OCs, investigators and drug companies reduced the amount of progestin. In studies by Eckstein *et al.*[1] and Mears[2] using 2.5 mg of norethynodrel and 36 µg of mestranol, contraceptive efficacy was reduced from 100 to 71 per cent. This result emphasized the fact that ovulation suppression was related not only to the progestin dosage but also to estrogen and to the ratio between the estrogen and the progestin component. Eckstein suggested that when the dosage of norethynodrel is lowered, the concentration of estrogen becomes critical; excessive reduction of the estrogen dosage impairs the contraceptive efficacy of these preparations.

Combination Oral Contraceptives

A new generation of combination OCs containing a reduced dosage of progestin and a higher concentration of estrogen was approved following extensive clinical trials. The new combinations containing either ethinyl estradiol or mestranol as the estrogen and a progestin (either norethindrone, norethindrone acetate, norethynodrel, ethynodiol diacetate, dl-norgestrel, levonorgestrel, norgestimate or desogestrel) were shown to be virtually 100 per cent effective when the preparations were taken properly, even at a dosage of 30 to 35 µg of the estrogen. Since thromboembolic phenomena are considered to be related most often to

estrogen dosages exceeding 50 µg/day, it is currently agreed that dosages of 30 to 35 µg/day of an appropriate estrogen are optimal with respect to contraceptive efficacy, patient compliance, and the lowest risk of thromboembolism and other estrogen-related side effects.

Sequential Oral Contraceptives

Sequential OCs were introduced for a short period. The ovulation-suppressing effect of estrogen was used in association with a progestin, which was added in the latter part of the cycle primarily to maintain cycle control. The main disadvantage of these preparations was that they required a higher dosage of the estrogen to be effective. Even then, their efficacy was lower than that of the combination preparations although still higher than non-hormonal methods of contraception. In 1976, sequential OCs were withdrawn from the Canadian market due to the suggestion that one of these preparations might predispose users to the development of endometrial carcinoma.

Continuous Low-Dose Progestins (the Mini-Pill)

Oral contraceptive preparations containing progestin only (mini-pills) were introduced in the early 1970s. Elimination of the estrogen altered, in part, the mode of action and consequently lowered the efficacy of these OCs. There is a wide variation in the pregnancy rates for compounds that have been studied. For the product that is available in Canada, which contains norethindrone, the pregnancy rate is approximately 1.0 to 2.0 per 100 women-years. This compound is indicated mostly for a limited patient population in which the use of estrogen or a higher dosage of progestin would be undesirable. Some doctors recommended the use of these preparations for nursing mothers (see section on Resuming Oral Contraception After Parturition or Abortion). The main problem associated with the use of continuous low-dose progestins as contraceptive agents is the high incidence of poor cycle control resulting in unpredictable bleeding or spotting. Because of the possibility of missed intrauterine pathology (organic disease), serious consideration should be given to discontinuing this medication if irregular bleeding or spotting persists.

Biphasic and Triphasic Oral Contraceptives

The next step in OC development was the introduction of biphasic and triphasic combination formulations. In biphasics, the dosage of the estrogen remains constant while the dosage of the progestin is increased in the latter part of the cycle. In triphasics, the dosage of the progestin (C19 steroid derivatives) is varied between three different segments of the cycle. The dosage of the estrogen in some preparations is increased slightly during mid-cycle and then reduced in the latter part of the cycle. These alterations in the estrogen and progestin ratio result in a

low incidence of breakthrough bleeding and spotting, good tolerance and a high level of efficacy. Alterations in carbohydrate and lipid metabolism and other progestin-related side effects can theoretically be reduced by lowering the total progestin intake to a minimum.

Injectable Progestins

There are no long-acting injectable progestins approved for contraception in Canada. However, one or more are approved in many countries.

An example of an injectable contraceptive is depot medroxyprogesterone acetate (DMPA), a C21 progestin.[3-6] The absence of estrogenic and androgenic activities could be considered for women in whom estrogens (as in OCs) are contraindicated but who desire a highly effective contraceptive method. The estimated mortality rate for DMPA is lower than that estimated for intrauterine devices, OCs or childbirth. This method requires an injection every three months, which permits close contact with health care providers and brings a reduction in menstrual bleeding, premenstrual tension, cramping, bloating and iron deficiency anemia. Pregnancy rates are comparable to those reported for OCs, ranging from 0.0 to 1.2 per 100 women-years, using 150 mg DMPA intramuscularly every 90 days.

However, more frequent side effects such as menstrual disturbance (irregular bleeding and spotting), weight gain, headache and a delay in the return to fertility may render the use of DMPA less desirable for some patients.[7]

There has also been concern regarding a possible increased risk of breast cancer after short-term use of DMPA.[8] Moreover, long-term use of DMPA has been associated with significant reductions in bone density in the lumbar spine and femoral neck, and could be considered a potential risk factor for osteoporosis.[9] These risks form the basis for the decision of Health Canada to refuse the application for use of this compound as a contraceptive agent.

In spite of the above concerns, this Committee believes there may be specific clinical situations where the advantages of depot medroxyprogesterone acetate outweigh the potential risks. DMPA may be useful in those women:

- who are at risk of cardiovascular problems, despite age and smoking habits;
- who have had repeated failures due to poor compliance when using other methods; and
- for whom amenorrhea would provide relief from severe premenstrual syndrome or dysmenorrhea due to endometriosis.

Subdermal Implants

Recently, a subdermal contraceptive implant system (Norplant®) was introduced in Canada. It consists of a series of six silastic capsules, each 2.4 mm × 34 mm, and each containing 36 mg of levonorgestrel (LNG) implanted subdermally in the volar surface of the upper arm. Insertion requires a minor surgical procedure –

one 3 to 5 mm incision through the skin at the insertion site. This is a simple office procedure once physicians are trained in insertion techniques. All six implants are inserted at the same sitting.

Once the capsules are implanted, the progestin (levonorgestrel) contained within them is released into the circulation. At first, it is released at a rate of 70 µg/day. This level decreases gradually and stabilizes after one year to a level of 30 µg/day. This method provides effective contraception for five years. In one study, the effectiveness of this subdermal implant system was shown to be very high. A yearly pregnancy rate of 0.4/100 women using this method was reported compared to a rate of 1.6/100 women in a group employing the Copper T 200 IUD. Contraindications and side effects associated with this method of contraception are similar to those for any progestin-only contraceptive. Contraceptive efficacy is achieved to a lesser degree via ovulation suppression with this method compared to combination oral contraceptives. Endometrial and cervical effects are therefore very important in achieving contraceptive efficacy.

Drug interactions involving the progestin component of combination oral contraceptives (see section on Oral Contraceptives and Drug Interactions) apply to the progestin in these implants as well.

The subdermal implant progestin-only contraceptive system provides long-term reversible contraception for those women who are not candidates for oral contraception because of estrogen intolerance or a contraindication to estrogen, but who still wish to use steroidal contraception.

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3. Non-Hormonal Methods of Contraception

"In the Canadian National Fertility Survey (1984) the most popular method of birth control cited by women aged 18 to 29 was OCs. Women 30 years or older were more likely to choose permanent sterilization, increasing with age from 36 to 67 per cent. Likewise, male sterilization increased with age 30 to 49 years, from 16 to 22 percent.[1] A recent American survey (Ortho 1991) suggests that OCs (28 per cent) and condoms (16 per cent) are the methods used most frequently by women aged 15 to 50 years.[2] No recent Canadian data are available."

Latex condoms and vaginal barriers used in conjunction with spermicidal agents are known to reduce the incidence of human immunodeficiency virus (HIV) infections and the transmission of sexually transmitted diseases (STD). Women at greater risk for HIV/STD infection are those who use OCs or sterilization alone as their method of contraception.[3] Although the use of condoms by unmarried women has doubled or tripled in the last decade, only 7 to 18 per cent of women say they use condoms as a backup for STD prevention.[2,4]

More recently, contraceptive promotion and educational programs are reinforcing the concurrent use of two methods that both lower the risk of accidental pregnancy and provide HIV/STD protection.

Efficacy

The failure rates cited in the literature often reflect the bias of "perfect" user compliance with a chosen method; that is, the behaviour of a consistent user. "Typical" failure rates – those that reflect the behaviour of an average user – provide more likely outcomes for the contraceptive methods currently available.

Effectiveness rates are modified by the following variables:

- efficacy of the method when used correctly and consistently;
- technical attributes of the method that ease or interfere with use;
- characteristics of the user; and
- competence of the investigational instrument.[5]

Actual effectiveness rates measure contraceptive failure rates against chance pregnancy in couples not using contraception.

Failure rates reflect accidental pregnancies in a population using a particular method within the first year of use, and with maintenance of use over time. Method failure rates refer to pregnancies attributed to contraceptive method or device failure in "perfect" users. User failure rates refer to user technique and/or compliance failure. The simultaneous use of two methods dramatically reduces the risk of accidental pregnancy, provided they are used consistently.

Post-Coital Douches

The post-coital douche only slightly reduces the chance of conception. It is by far the least effective method of contraception since sperm enter the cervical glands and upper genital tract within minutes after intercourse. Also, its use should be discouraged because trauma may result from poor technique. It offers no protection from STD, hepatitis B or C, or HIV infection.

The Rhythm Method and Natural Methods

The rhythm method ranges from periodic abstinence to various methods of ovulation charting. Periodic abstinence has a 20 per cent pregnancy rate in the first year of use[3] with rates ranging from 10 to 14 per cent with ovulation methods. This lower rate is dependent upon the chosen method being correctly taught, understood, and consistently practised with measurements of basal body temperature and monitoring of the cervical mucus. Again, it does not offer protection against STD, hepatitis B or C, or HIV infection.

Coitus Interruptus

This practice may be more widespread than acknowledged by the medical profession given that the Canadian National Fertility Study cited 23 per cent of couples not using an identified contraceptive method.[8] Five per cent of women mention withdrawal as the contraceptive practice used with their partners. The pregnancy rate in the first year of use is 18 per cent and the lowest reported rate is 6.7 per cent in documented trials. Like the previous two methods, this technique provides a questionable reduction in STD, hepatitis B or C, or HIV transmission.

Spermicides

Spermicides such as jellies, creams and foams are more effective if they are used with vaginal barrier techniques or condoms. The pregnancy rate for spermicides alone in the first year of use is 21 per cent. When used alone, the effectiveness of spermicides is low because patient motivation varies and instructions for use may be improperly followed. Factors that seem to reduce efficacy include failure to insert the spermicide high enough into the vagina to cover the cervix, failure to apply the product before each coital act and failure to wait until the spermicide is totally dispersed before coitus begins. Spermicidal agents contribute somewhat to the prevention of HIV/STD transmission. The vaginal spermicidal sponge must be moistened before insertion to activate the spermicide.

Barrier Methods – Female

Currently there are three female barrier methods: the diaphragm, the cervical cap and the spermicidal sponge. A review of the literature on these methods suggests single, nulliparous women having less frequent sexual intercourse have the best compliance and user effectiveness.[5] These methods are twice as likely to fail in parous women with at least one prior birth than in nulliparous women, despite no significant user difference in technique.[5-7]

The advantage of the barrier method is STD reduction. The diaphragm and contraceptive sponge produce a 40 to 80 per cent reduction in chlamydial, gonorrheal and trichomonal infections.[8] Use of a barrier method with a spermicidal agent also reduces the risk of HIV transmission.

Vaginal Diaphragm

If used properly and consistently, the diaphragm offers a level of protection reflected by a first-year pregnancy rate of 30.2 per cent among multiparous women, and 14.9 per cent in nulliparous users.[9] Increased frequency of intercourse and parity lead to higher failure rates. Well-educated women aged 30 to 34 tend to have the highest incidence of use – 75 per cent for two years or more and 43 per cent for five years or more.[7]

Vaginal Sponge

The sponge is a polyurethane foam or polyvinyl cup. The polyurethane sponge is impregnated with the spermicide nonoxynol-9. It may be left in place up to 24 hours (30 hours maximum), requires adequate hydration with tap water before insertion, and should remain in place for six hours after the last coitus.

The manufacturer of the polyurethane sponge cites a pregnancy rate of 17.0 per cent based on method effectiveness.[10] There is a differential between nulliparous and parous women, with pregnancy rates in the first year of use being 18 per cent and 28 per cent respectively.[5,9] Allergy to nonoxynol-9 or a history of Toxic Shock Syndrome are contraindications to the use of the contraceptive vaginal sponge. This technique provides reduction in HIV/STD transmission.

Cervical Cap

This is a barrier method employing a rubber conical device that forms a vacuum seal over the cervix. It may be used for 48 to 72 hours with a spermicidal agent.

An 18-centre Canadian trial with 613 women showed a continuation rate of 58.2 per cent by seven months and 35.0 per cent by one year. In both Canadian and American studies, single, nulliparous women aged 20 to 25 years, with reliable method compliance, had the best outcomes with pregnancy rates of 15.3 per cent. Women having a prior pregnancy within a year of use, or parity of two or more, had the highest pregnancy rate – 29.9 per cent.[7,11] In the Canadian

trial, there was a cumulative pregnancy rate of 19.2 per cent – 34 per cent of this being attributed to method failure, 35.6 per cent to compliance failure, and 30.5 per cent to unknown causes.[11]

As the spermicidal agent is housed in the dome, it offers little vaginal protection against HIV infection unless spermicide is introduced vaginally as well.

Vaginal Condom

This is a loose-fitting polyurethane vaginal sheath with two flexible polyurethane rings. One ring encloses the cervix as an internal retention mechanism, the other remains external to the vaginal introitus protecting the external genitalia from direct contact with the base of the penis. Preventions of HIV/STD transmission and female control of contraception are advantages. This method is currently under review for use in North America. This device is superior to the male condom in method reliability as slippage and leakage are less likely. Failure rates are cited at 0.06 per cent in European studies.

Barrier Methods – Male

Condoms

Compliance in the use of the condom, timing of application, and proper application technique are factors in method efficacy. Failure is related to a tear, leak or slippage. The rate of accidental pregnancy in the first year of consistent use is 12 per cent, with the lowest reported rate at 4.2 per cent.[5] Used with a spermicidal agent, the consistent user pregnancy rate is 4 to 8 per cent. The condom was the primary contraceptive choice for 9 per cent of Canadian couples (Canada, 1984), and for 16 per cent of American couples (U.S., 1987, 1990). It is now the second most popular contraceptive method (after OCs) for single, sexually active women aged 18 to 29 years. There is a trend to the increasing acceptability of the condom in women of all age groups. Latex condom use reduces the risk of HIV, hepatitis B or C, and STD transmission. Users of oral contraceptive pills should be counselled in safer sex practices, with the use of condoms or barrier techniques recommended as backup methods in sexual practices with identified risk factors.

Intra-uterine Contraceptive Devices (IUDs)

The IUD has shown a decline in use in North America from the 12 to 13 per cent of Canadian women aged 25 to 34 years who selected the IUD in 1984 (Canadian National Fertility Survey). Users of non-medicated IUDs have a pregnancy rate of 3 per cent in the first year of use.[5] Reported rates are as low as 0.5 per cent[12] in copper-bearing or progestin-enhanced (medicated) IUDs.

The risk of a woman developing pelvic inflammatory disease (PID) increases as her number of sexual partners increases. Women with an increased risk of PID are not good candidates for IUD use. This is especially true in the very young,

who often claim to have a single sexual partner at the time of consulting for contraception but frequently turn out to be serially monogamous. A history of PID is also a contraindication to IUD use. Some case-control and other studies[3,4] have confirmed an association between IUD usage and the risk of PID. This risk is greatest in the first few weeks following insertion. The risk in those studies was lowest for women using progestin-enhanced IUDs and highest for those using non-medicated IUDs. Other studies confirm a much lower risk for PID in an ideal group of multiparous women each having one sexual partner.

Enlarged, deformed or very small uteri tend to accommodate IUDs poorly; small uteri are associated with a higher incidence of expulsion. The nulliparous woman also has been shown to have higher risks of expulsion, cramping and inter-menstrual bleeding. IUD use is ideal for women wanting to space out the birth of their children or to limit the size of their family. In time, most IUD-wearing family limiters tend to opt for sterilization of either partner.

Women with excessively heavy menses also tend to be poor candidates for IUD use since menstrual blood loss may be increased with IUD use. This is less of a problem with newer IUDs that are smaller and more flexible. The device should be inserted only after the benefits and risks of this method of contraception have been fully explained to the woman.

Only medicated IUDs (copper-bearing and progestin-enhanced) are available in Canada now. A new generation of IUDs has been designed with modifications to reduce the incidence of expulsion, uterine cramping and menstrual blood loss. These IUDs contain either copper or progestin, are smaller and more flexible, and tend to be easier to insert. Tailless IUDs also have been investigated, in an attempt to remove any communication between the vaginal pool and the uterine cavity. The levonorgestrel device (LNG-IUD) may reduce PID because levonorgestrel helps to thicken cervical mucus, which acts as a barrier to bacteria.[13] IUDs offer small protection against HIV/STD infection.

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4. Post-Coital Interception

Post-coital interception (also called post-coital contraception) remains a relatively new, but incompletely understood therapy.[1] There is evidence that the administration of high-dose estrogen or a lower dose estrogen/progestin combination preparation within 72 hours of unprotected intercourse may have a definite interceptive effect. The limitations of this approach must be clearly understood. It should be considered only for emergencies where unprotected or inadequately protected intercourse has occurred or when there is a failure of a method (e.g. condom breakage or leakage, displacement of a diaphragm or cervical cap, etc.). It is therefore not an acceptable ongoing method of fertility control.

High-dose estrogen-only therapy, using diethylstilbestrol (DES) or ethinyl estradiol (EE), has no advantage over the combination estrogen/progestin method, which is employed widely. The disadvantage of the estrogen-only preparations is the high incidence of nausea and vomiting, headache and breast tenderness associated with their use. Also, the prolonged course of therapy recommended (five days) often leads to noncompliance because of side effects. Such compliance failures are associated with an increased risk of method failure. The dosage of EE (5 mg for five days: 25 mg total) is equivalent to the amount of estrogen ingested over two years using a 50 μg combination oral contraceptive. The estrogen/progestin combination therapy for post-coital interception seems to have the advantage of being simpler and equally effective, and has a high degree of patient acceptability. The most commonly employed regimen is the administration of four tablets, each containing levonorgestrel (0.5 mg) combined with ethinyl estradiol (50 μg). Two tablets are administered immediately, followed by the final two tablets 12 hours later. Treatment should be administered within 72 hours of coital exposure.[2] Failure rates of 0 to 1.6 per cent have been reported.[3] An anti-emetic may be administered simultaneously with each of the two doses to reduce the risk of nausea and vomiting.

Several mechanisms of action have been postulated for the combination estrogen/progestin interceptive method. These include:

- total suppression or a significant delay of the LH peak (when treatment is administered immediately prior to or at the LH surge);
- a variable luteal phase dysfunction (luteolytic);
- establishment of an endometrium that is out of phase and development with respect to the menstrual cycle day (and thus inappropriate for implantation); and
- possibly disordered tubal transport of the fertilized ovum.[4]

There is no clinical or experimental evidence of an abortifacient effect of any post-coital interceptive method since abortion implies disruption of an already implanted embryo or pre-embryo.

The question of the potential teratogenic effects of both the high-dose estrogen and the estrogen/progestin preparations has been considered. No teratogenicity has been reported when these preparations failed as post-coital interceptive agents. The congenital anomalies associated with the administration of diethylstilbestrol (DES) seem related to a very specific time of administration in early fetal development. No congenital anomalies have been reported in cases of DES failure as a post-coital interceptive agent. Nevertheless, it is prudent to avoid both high dosages of DES and ethinyl estradiol for post-coital interception when the estrogen/progestin methods seem equally effective and use much lower dosages of estrogen.

Insertion of a copper-bearing IUD has been effective for post-coital interception.[5] This method serves the added purpose of providing continuing fertility control. However, the IUD should be not be used by women having a high risk of sexually transmitted disease at the time, such as rape victims, women with a recent history of pelvic inflammatory disease or women with multiple sexual partners. The advantage of this method is that post-coital contraceptive efficacy has been shown up to seven days following unprotected intercourse. As a result, if the IUD is selected as a post-coital interceptive method, appropriate cervical swabs should be obtained simultaneously. This method is not ideal for the nulliparous patient since insertion is often difficult. However, the IUD often remains the only post-coital interceptive choice when exposure has occurred more than 72 hours before medical consultation (beyond established efficacy for the combination estrogen/progestin method) but fewer than seven days prior to insertion.

Other methods of post-coital interception have been investigated including prostaglandins, gonadotropin releasing hormone (GnRH) agonists and, most recently, RU 486 (mifepristone). The latter, the first true anti-progesterone preparation, is also an effective early abortifacient. Its efficacy as a post-coital agent has recently been shown in two comparative trials.[6,7] RU 486 is not currently available in North America.

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5. Patient Selection

OCs are the safest and most efficient reversible method of birth control when used by well-motivated women who have no evidence of conditions that preclude their use or effectiveness. Patient selection cannot be stated simply. It requires a dialogue between patient and physician. The physician needs information concerning the patient's physical and mental health, family and personal history, and the woman's needs for protection against pregnancy. During the initial visit, the patient should participate in a full discussion of the benefits and risks of oral contraception, as well as of other contraceptive methods, so that when the use of an OC is appropriate, she will feel that she has selected the best contraceptive method for her. The time spent on preliminary counselling is reflected in an increase in patient compliance.

Well-recognized contraindications to the use of OCs exist as follows:

- history of/or actual thrombophlebitis or thromboembolic disorders;
- history of/or actual cerebrovascular disorders;
- history of/or actual myocardial infarction or coronary arterial disease;
- active liver disease or history of/or actual benign or malignant liver tumours;
- known or suspected carcinoma of the breast;
- known or suspected estrogen-dependent neoplasia;
- undiagnosed abnormal vaginal bleeding;
- any ocular lesion arising from ophthalmic vascular disease, such as partial or complete loss of vision or defect in visual fields; or
- suspected or diagnosed pregnancy.

The majority of women deciding to use OCs will be young and healthy, and will have no evidence of conditions that preclude their use. The history should include all obstetrical and gynecological information with special emphasis on estrogen-dependent malignancies, diabetes, thromboembolic disorders, depressive reactions, hypertension, classical migraine headaches and jaundice.

Before oral contraceptives are used, a thorough physical examination should be performed, including a blood pressure determination. Breasts, liver, extremities and pelvic organs should be examined. A Papanicolaou smear should be taken if the patient has been sexually active.

The first follow-up visit should be done three months after oral contraceptives are prescribed. Thereafter, examinations should be performed at least once a year or more frequently if indicated. During each annual visit, examination should include those procedures that were done during the initial visit as outlined above or as per recommendations of the Canadian Task Force on the Periodic Health Examination.

6. Non-Contraceptive Benefits of Oral Contraceptives

Besides the contraceptive efficacy of oral contraceptives, many non-contraceptive benefits, both gynecologic and non-gynecologic, have been identified. These are related to alterations in the hormonal milieu affecting not only the reproductive tract (uterus and ovaries), but also other hormone-sensitive target organs including the breast. Details concerning these non-contraceptive benefits are included throughout the body of this report.

Effects on Menses

- increased menstrual cycle regularity
- decreased menstrual blood loss
- decreased incidence of iron deficiency anemia secondary to reduced menstrual blood loss
- decreased incidence of dysmenorrhea

Effects Related to Ovulation Inhibition

- decreased incidence of functional ovarian cysts
- decreased incidence of ectopic pregnancy

Effects on Other Organs of the Reproductive Tract

- decreased incidence of acute salpingitis
- decreased incidence of endometrial cancer (50 per cent)
- decreased incidence of ovarian cancer (40 per cent)
- potential beneficial effects on endometriosis

Effects on Breasts

- decreased incidence of benign breast disease (fibroadenomas and fibrocystic breast disease)
- decreased incidence of breast biopsies

The non-contraceptive benefits of oral contraceptives should be considered in addition to the efficacy of these preparations when counselling patients regarding contraceptive method selection.

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7. Selection of the Oral Contraceptive

Table 1:
Oral Contraceptives Available in Canada[1]

Product	Manufacturer	Estrogen	µg/ Tablet	Progestin	µg/ Tablet
20, 30 and 35 µg Estrogen				(days in brackets for biphasics and triphasics)	
Minestrin 1/20	Parke-Davis	Ethinyl Estradiol	20	Norethindrone Acetate	1000
Marvelon	Organon	Ethinyl Estradiol	30	Desogestrel	150
Ortho-Cept	Ortho	Ethinyl Estradiol	30	Desogestrel	150
Min-Ovral	Wyeth	Ethinyl Estradiol	30	Levonorgestrel	150
Loestrin 1.5/30	Parke-Davis	Ethinyl Estradiol	30	Norethindrone Acetate	1500
Demulen 30	Searle	Ethinyl Estradiol	30	Ethynodiol Diacetate	2000
Cyclen	Ortho	Ethinyl Estradiol	35	Norgestimate	25
Ortho 0.5/35	Ortho	Ethinyl Estradiol	35	Norethindrone	500
Ortho 1/35	Ortho	Ethinyl Estradiol	35	Norethindrone	1000
Brevicon 0.5/35	Syntex	Ethinyl Estradiol	35	Norethindrone	500
Brevicon 1/35	Syntex	Ethinyl Estradiol	35	Norethindrone	1000
Synphasic[3,4]	Syntex	Ethinyl Estradiol	35(21)	Norethindrone	500(7) 1000(9) 500(5)
Ortho 10/11[2,4]	Ortho	Ethinyl Estradiol	35(21)	Norethindrone	500(10) 1000(11)
Ortho 7/7/7[3,4]	Ortho	Ethinyl Estradiol	35(21)	Norethindrone	500(7) 750(7) 1000(7)
Tri-Cyclen[3,4]	Ortho	Ethinyl Estradiol	35(21)	Norgestimate	180(7) 215(7) 250(7)
Triphasil[3,4]	Wyeth	Ethinyl Estradiol	30(6) 40(5) 30(10)	Levonorgestrel	50(6) 75(5) 125(10)
Triquilar[3,4]	Berlex	Ethinyl Estradiol	30(6) 40(5) 30(10)	Levonorgestrel	50(6) 75(5) 125(10)

1 Most of the estrogen-progestin combination products listed in this table are also available with inert tablets that permit uninterrupted 28-day cycles of therapy.
2 Biphasic product.
3 Triphasic product.
4 The number of days each dosage of estrogen and progestin is to be taken is shown in brackets in the dosage columns.

Table 1:
Oral Contraceptives Available in Canada (concluded)[1]

Product	Manufacturer	Estrogen	µg/ Tablet	Progestin	µg/ Tablet
50 µg Estrogen – For conception control only when lower dosage estrogen formulations prove to be unsatisfactory.					
Ovral	Wyeth	Ethinyl Estradiol	50	Levonorgestrel	250
Norlestrin 1/50	Parke-Davis	Ethinyl Estradiol	50	Norethindrone Acetate	1000
Demulen 50	Searle	Ethinyl Estradiol	50	Ethynodiol Diacetate	1000
Ortho-Novum 1/50	Ortho	Mestranol	50	Norethindrone	1000
Norinyl 1/50	Syntex	Mestranol	50	Norethindrone	1000
Estrogen Free					
Micronor	Ortho			Norethindrone	350

1 Most of the estrogen-progestin combination products listed in this table are also available with inert tablets that permit uninterrupted 28-day cycles of therapy.

8. Specific Problems Associated with Contraceptive Use

Contraception in Teenagers

Teenagers present a unique challenge: they are sporadic rather than consistent contraceptive users. The Committee recommends that OCs may be prescribed, but teenagers should be given full information, including details on the side effects and efficacy of other contraceptive methods such as vaginal creams, foams, and inserts; the diaphragm and condom; and the "morning-after pill". Most of these are more easily obtainable on short notice than OCs. Those teenagers who are contemplating or are already engaged in sexual activity must be offered protection against the risk of pregnancy. There is no reason to contraindicate OCs in these young women. The adverse consequences of an unwanted pregnancy in a teenager younger than age 17 far outweigh any physiological effects associated with the inhibition of gonadotropin production by OCs. There is no contraindication to continuing on the oral contraceptive pill, if a teenager is sexually active. There is no indication for discontinuing the use of OCs for a "rest" as has been the practice in some areas. This only results in an increased incidence of unwanted pregnancy. To enhance patient compliance, teenagers should be seen at more frequent intervals. A visit at the end of the first three cycles of therapy is advantageous since problems associated with side effects and compliance can be dealt with early.

Sexually active adolescents are at a higher risk of developing sexually transmitted diseases than other groups since they are more likely to have multiple sexual partners. Teenagers often tend to be serially monogamous. Although the oral contraceptive has been shown to have some protective effect against the development of pelvic inflammatory disease (see section on Non-contraceptive Benefits of Oral Contraceptives), it is still wise to recommend the use of a latex condom with OCs. The combination of the two provides not only the most effective method of birth control, but also increased protection against sexually transmitted diseases.

Contraception in Women Older than 35

There is probably more anxiety in women older than age 35 about getting pregnant than in women of almost any other age. This anxiety is very understandable and often leads to the question of when a woman should discontinue contraception, if she is near or at the menopause. Fertility decreases with age, particularly in the late thirties, but the risk of pregnancy continues until the menopause as long as a woman is menstruating, even irregularly.

Therefore, a woman older than 35 should continue to use some method of contraception. It is probably safe to allow her to discontinue contraception one year after the clinical onset of the menopause or six months following two gonadotropin estimations three months apart, both showing menopausal levels of serum follicle stimulating hormone (FSH) levels (>40 IU/L).

Many women older than 35 will have opted for a permanent method of sterilization for themselves or their partner, or will be using a reversible contraceptive method to which they have become accustomed, which they have used successfully and which they may wish to continue to use. This method may include oral contraceptives. Data continue to accumulate in support of the safety of low-dose oral contraceptives among women older than 35 who have no contraindications to their use and are otherwise in good health. Smoking remains the major risk factor for women older than 35. Women who smoke should not use oral contraceptives beyond the age of 35. Current scientific opinion holds that the relative safety of low-dose OCs, combined with the well-established non-contraceptive benefits of these pills for women beyond the age of 35 who do not smoke and are in otherwise good health, often outweighs the potential risks. An increased risk of cardiovascular disease that may be attributed to oral contraceptive use remains a possibility in this population. However, it may be a lower risk than that associated with pregnancy and attendant surgical and medical procedures that may be needed. The lowest possible dose formulation compatible with a high level of efficacy, a low incidence of side effects and good cycle control should be prescribed.

In summary then, although there are many alternatives to OC use in women older than 35, including barrier methods, IUDs and permanent contraception (sterilization of the male or female partner), low-dose oral contraceptives should be included among choices for those women who are potential candidates (non-smokers in good health with no medical contraindications). OCs may continue to be prescribed to these potential candidates following appropriate counselling. Continued follow-up of these women is recommended as described in Chapter 5. Screening procedures (lipid profiles, Pap smears, etc.) should be performed according to the recommendations proposed for each test, based upon the patient's age, medical history and other co-existing risk factors.

Oral Contraceptives and Smoking

Using 1982 data from the U.S., it was estimated that 86 per cent of deaths associated with oral contraceptive use result from the combination of OC use and smoking by women aged 35 and older. Epidemiologic studies suggested that the approximately 50 deaths in the U.S. attributable to OC use each year could be reduced to about seven if no OC users smoked and none took the pill after their 35th birthday. If no OC users smoked, the estimated number of deaths attributable to OC use would be reduced to about 20 per year.[1]

However, these studies relate to higher dosage preparations containing 50 μg of the estrogen component or more. Studies with the lower dose preparations do not support such large numbers of OC-related deaths among nonsmoking women taking lower dose preparations (35 μg of estrogen or less).

Heavy smoking (more than 15 cigarettes per day) seems to be a very important risk factor in the development of vascular disease in users of OCs. An increased incidence of myocardial infarction, stroke and arterial thromboembolism has been observed in several studies.[2,3] The risk of myocardial infarction in OC users increases with the number of cigarettes smoked per day.[3]

Mortality rates per 100,000 women who smoked were 10.2 among OC users versus 2.6 among non-users aged 30 to 39. Among women older than 40 who smoked, the mortality rate was 62.0 among users compared to 15.9 among non-users.[4]

Smoking also increases the relative risk of hemorrhagic stroke. OCs increase this risk to 1.2 among nonsmokers, whereas heavy smokers who are also OC users have a relative risk of 6.1 to 7.6.[5]

Overall, heavy smoking increases the risk of major types of vascular disease. Indeed, it is the most significant risk factor. When combined with one or more other risk factors such as hypertension, increasing age over 30 years, diabetes, obesity and hyperlipoproteinemia, smoking has a very significant synergistic effect. It is recommended that women should be counselled to stop smoking.

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Resuming Oral Contraception After Parturition or Abortion

After the delivery of a baby, non-nursing women can expect menstruation to resume in about six weeks. Therefore, OCs may be given four weeks after delivery. OC-enhanced thrombotic episodes are minimal at this time.

In normal breast-feeding mothers, ovulation resumes approximately five months after delivery.[1] If a woman is breast-feeding, low-dose OCs do not interfere with continuation of lactation.[2,3] The hormones contained in these products are excreted in the breast milk in small quantities, but do not alter its quality or

volume provided they are not given until lactation is well established.[4] The long-term effects of the small amount of hormones transmitted to the neonate are not known. Therefore, both the benefits and possible risks of OCs must be considered by the patient and her physician, and these should be weighed against the benefits and risks of alternate methods of contraception. There is no evidence that the low-dose progestin-only preparation (mini-pill) has any clinical advantage over the low-dose combination (estrogen and progestin) preparations in these situations.

Following a first-trimester spontaneous or induced abortion, ovulation will often precede the first menses (two to four weeks). Thus, for women who wish to start using OCs after a first-trimester abortion, OCs may be given immediately after the abortion.

Following a mid-trimester abortion, ovulation is not expected before the first menses or approximately six weeks. OCs may be started two weeks after the abortion, by which time coagulation mechanisms should have returned to normal.

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Oral Contraceptives and Drug Interactions

Since the introduction of oral contraceptives more than 30 years ago, there have been many reports of drug interactions with these agents. Some are well documented and of clinical significance but others are less so and are of questionable or unknown clinical relevance. There are two major types of interactions between OCs and concomitant drugs. First, the efficacy of OCs may be altered (usually decreased) by interacting agents. Second, OCs may alter the efficacy, or alter the adverse effects, of other drugs.

The potential for drug interactions with OCs seems more likely today, and the occurrence perhaps more frequent, due to the expanding use of low-dose estrogen OCs. Confounding factors make the actual incidence and therapeutic significance of these interactions difficult to determine. It is well accepted that approximately one per cent of women will experience contraceptive failure while taking OCs. Failure may occur because of improper use of the OC (i.e. not taking OCs at the same time each day, missing pills, etc.). The efficacy of OCs also may be diminished in women with certain diseases (e.g. persistent diarrhea).

Contraceptive failure also could be due to concomitant drug therapy. Most of the information concerning drug interactions with OCs comes from case reports and data reported retrospectively. Clinical trials have not been done because of the large numbers of patients that would need to be recruited and the ethical considerations of conducting such trials. Therefore, clinicians must rely on the information available and interpret it carefully.

Several mechanisms are thought to be responsible for altering the efficacy of OCs:

- interference with absorption of the OCs from the GI tract;
- increased levels of plasma sex hormone binding globulin (SHBG) leading to decreased levels of active steroid;
- competition between the OCs and interacting drug for the same metabolizing enzyme;
- microsomal enzyme induction (or inhibition) in the liver, which may increase (or decrease) the metabolism of the OC; and
- interference with the enterohepatic recirculation of steroid metabolites.

Unexpected spotting or breakthrough bleeding may suggest reduced contraceptive efficacy. If the efficacy of the OC is reduced sufficiently, pregnancy may result.

The proposed mechanisms of known and suspected drug interactions that have been reported with OCs are reviewed in Tables 2 and 3 at the end of this section. Table 2 lists those drugs that interfere with the efficacy of OCs. Most anti-convulsant agents, including phenobarbital, phenytoin, primidone, carbamazepine and ethosuximide, have been implicated in contraceptive failure with OCs. These agents induce hepatic microsomal enzymes responsible for the metabolism of OCs, leading to increased metabolism and lower effective levels of steroids. It also has been reported that an increase in SHBG leads to lower free progesterone levels. As these anticonvulsants are often prescribed to women of childbearing age, it is generally recommended that an alternative method of contraception be used. Some experts suggest using an OC with 50 μg or more of ethinyl estradiol. The benefits of this approach must be weighed against the increased risk of adverse effects such as thromboembolic disorders. No reports of an interaction between valproic acid and OCs could be found.

Anti-infective agents also have been implicated in the failure of OCs. Rifampin was the first drug reported to interfere with OCs. Like the anticonvulsants, rifampin is a hepatic microsomal enzyme inducer, and can effectively reduce steroid levels. Griseofulvin, an antifungal agent, may also interact with OCs in a similar way. Women receiving OCs and rifampin or griseofulvin should be counselled about the possible interaction and be advised about alternative methods of birth control.

Perhaps more controversial is the proposed interaction between OCs and broad-spectrum antibiotics. This interaction may be mediated through some of the mechanisms mentioned above. Some anti-infectives may cause hepatic microsomal enzyme induction (as seen with rifampin and griseofulvin). Adverse

effects of antibiotics, such as diarrhea, may speed transit time through the gastrointestinal tract and decrease absorption of the OC. In addition, antibiotics may alter gut bacterial flora. It is known that approximately 60 per cent of ethinyl estradiol is metabolized on its first pass through the liver, and the conjugates are excreted in the bile. Bacteria in the gut hydrolyse the conjugates back to active ethinyl estradiol, which is then reabsorbed. Antibiotic-induced alterations in gut bacteria could reduce this enterohepatic recirculation of ethinyl estradiol.

There have been several well-documented case reports of pregnancy occurring while women, correctly using OCs, were taking antibiotics, especially ampicillin and tetracycline. Contraceptive failures have also been reported with chloramphenicol, isoniazid, neomycin, nitrofurantoin, penicillin V, sulfonamides, erythromycin and cotrimoxazole. The number of case reports is small compared to the number of women receiving OCs. However, that fact does not diminish the clinical implications of the interaction, even if it occurs only in a few women. As many women on OCs are likely to be prescribed antibiotics sometime, the controversy expands to how to counsel these patients. Some experts believe that an alternative form of birth control should not be recommended during a short course of antibiotic therapy. Others believe that because of the potential risk of interaction, and the inability to predict those who are likely to experience interaction, all women should be advised of the risk, and additional methods of contraception should be recommended. Women to be placed on long-term antibiotic therapy, such as tetracycline for acne, should also be advised of the interaction.

There are a few drugs and classes of drugs in Table 2 for which the evidence of reduced OC efficacy is questionable. The most recent evidence concerning the interaction between OCs and clofibrate indicates that OCs probably have more of an effect on reducing the efficacy of clofibrate than the opposite (see Table 3 under Cholesterol Lowering Agents). The same is probably true for analgesics in that OCs actually reduce the efficacy of ASA and acetaminophen (see Table 3 under Antipyretics). It has been reported that long-term use of OCs and phenylbutazone may result in an increased incidence of breakthrough bleeding. Although it has been reported that antihistamines may reduce OC efficacy, this was not supported by the results of a pharmacokinetic study with OCs, doxylamine and diphenhydramine. The antimigraine preparations in Table 2 refer primarily to ergotamine preparations that also contain barbiturates. As mentioned previously with the anticonvulsants, barbiturates can increase the metabolism of OCs, leading to reduced efficacy.

It should be mentioned that there are a few drugs that may actually increase the action and/or plasma concentration of OCs. There is little information in the literature on these types of interactions, possibly because the interaction is likely to increase the efficacy of the OC. However, there is also the possibility of increased risk of toxicity with the OCs. There are two potential interactions worth noting. When vitamin C and OCs are given concurrently, there is an increase in plasma ethinyl estradiol levels. This should not be of concern unless a person stops intake of regular vitamin C which may cause a drop in steroid plasma

levels. Acetaminophen can also increase ethinyl estradiol levels by decreasing its metabolism during absorption. Again, this should not be clinically significant unless a person stops taking regular high doses of acetaminophen abruptly. If patients are on OCs and either vitamin C or acetaminophen, it is recommended that they be slowly tapered off these agents if they are to be stopped.

As shown in Table 3, OCs can interfere with the efficacy of other drugs. OCs may increase the levels of some clotting factors and reduce antithrombin III levels, diminishing the effect of anticoagulants. Paradoxically, OCs also may enhance the effects of anticoagulants. It is probably best to avoid concomitant use of these drugs. OCs also can affect the blood levels of theophylline. When these drugs are used together, the clearance of theophylline is decreased by up to 30 to 40 per cent, due to decreased oxidation via cytochrome P-450 and P-448 systems. This effect is greater in smokers because of the induction of theophylline metabolism. Smoking itself can lead to an increased risk of cardiovascular effects due to OCs. Alcohol too, is affected by OC use. Ethanol is eliminated at a slower rate in OC users because up to 25 per cent of ethanol undergoes metabolism via hepatic microsomal enzymes. It is recommended that women using OCs should not increase their consumption of alcohol.

In conclusion, OCs are among the most commonly used drugs in the world, with approximately 60 to 70 million women using them. Although they are extremely safe compounds, OCs have potential interactions with many drugs, which could possibly lead to contraceptive failure. When one considers the possibility of multiple drug regimens, the perplexing pharmacologic nature of OCs and their failure rate of about one per cent, the situation only becomes more complex.

Physicians and pharmacists clearly have a role to play in providing accurate information to the patient, discussing the potential ramifications with her and listening to her concerns. Drug and disease histories of the patient should be gathered and blood levels of the interacting drugs may have to be monitored. With the uncertainty of many of these drug interactions, individualized patient therapy is very important.

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Table 2*:
Drugs that May Decrease the Efficacy of Oral Contraceptives

Class of Compound	Drug	Proposed Mechanism	Suggested Management
Anticonvulsants	Carbamazepine Ethosuximide Phenobarbital Phenytoin Primidone	Induction of hepatic microsomal enzymes. Rapid metabolism of estrogen and increased binding of progestin and ethinyl estradiol to SHBG.	Use higher dose OCs (50 μg ethinyl estradiol), another drug or another method.
Antibiotics	Ampicillin Cotrimoxazole Penicillin	Enterohepatic circulation disturbance, intestinal hurry.	For short course, use additional method or use another drug. For long course, use another method.
	Rifampin	Increased metabolism of progestins. Suspected acceleration of estrogen metabolism.	Use another method.
	Chloramphenicol Metronidazole Neomycin Nitrofurantoin Sulfonamides Tetracyclines	Induction of hepatic microsomal enzymes. Also disturbance of enterohepatic circulation.	For short course, use additional method or use another drug. For long course, use another method.
	Troleandomycin	May retard metabolism of OCs, increasing the risk of cholestatic jaundice.	
Antifungals	Griseofulvin	Stimulation of hepatic metabolism of contraceptive steroids may occur.	Use another method.
Cholesterol Lowering Agents	Clofibrate	Reduces elevated serum triglycerides and cholesterol; this reduces OC efficacy.	Use another method.
Sedatives and Hypnotics	Benzodiazepines Barbiturates Chloral Hydrate Glutethimide Meprobamate	Induction of hepatic microsomal enzymes.	For short course, use additional method or another drug. For long course, use another method or higher dose OCs.
Antacids		Decreased intestinal absorption of progestins.	Dose two hours apart.
Other Drugs	**Phenylbutazone **Antihistamines **Analgesics **Antimigraine **Preparations Vitamin E	Reduced OC efficacy has been reported. Remains to be confirmed.	

* Adapted from Dickey, R.P., ed.: *Managing Contraceptive Pill Patients*, 5th edition, Creative Informatics Inc., Durant, OK, 1987.

** Refer to previous text on page 31.

Table 3*:
Modification of Other Drug Action by Oral Contraceptives

Class of Compound	Drug	Modification of Drug Action	Suggested Management
Alcohol		Possible increased levels of ethanol or acetaldehyde.	Use with caution.
Alpha-II Adrenoreceptor Agents	Clonidine	Sedation effect increased.	Use with caution.
Anticoagulants	All	OCs increase clotting factors, decrease efficacy. However, OCs may potentiate action in some patients.	Use another method.
Anticonvulsants	All	Fluid retention may increase risk of seizures.	Use another method.
Antidiabetic Drugs	Oral Hypoglycemics and Insulin	OCs may impair glucose tolerance and increase blood glucose.	Use low-dose estrogen and progestin OC or another method. Monitor blood glucose.
Antihypertensive Agents	Guanethidine and Methyldopa	Estrogen component causes sodium retention, progestin has no effect.	Use low-dose estrogen OC or use another method.
	Beta Blockers	Increased drug effect (decreased metabolism).	Adjust dose of drug if necessary. Monitor cardiovascular status.
Antipyretics	Acetaminophen	Increased metabolism and renal clearance.	Dose of drug may have to be increased.
	Antipyrine	Impaired metabolism.	Decrease dose of drug.
	ASA	Effects of ASA may be decreased by the short-term use of OCs.	Patients on chronic ASA therapy may require an increase in ASA dosage.
Aminocaproic Acid		Theoretically, a hypercoagulable state may occur because OCs augment clotting factors.	Avoid concomitant use.
Betamimetic Agents	Isoproterenol	Estrogen causes decreased response to these drugs.	Adjust dose of drug as necessary. Discontinuing OCs can result in excessive drug activity.

* Adapted from Dickey, R.P., ed.: *Managing Contraceptive Pill Patients*, 5th edition, Creative Informatics Inc., Durant, OK, 1987.

Table 3 (concluded): Modification of Other Drug Action by Oral Contraceptives

Class of Compound	Drug	Modification of Drug Action	Suggested Management
Caffeine		The actions of caffeine may be enhanced as OCs may impair the hepatic metabolism of caffeine.	Use with caution.
Cholesterol Lowering Agents	Clofibrate	Their action may be antagonized by OCs. OCs may also increase metabolism of clofibrate.	May need to increase dose of clofibrate.
Corticosteroids	Prednisone	Markedly increased serum levels.	Possible need for decrease in dose.
Cyclosporine		May lead to an increase in cyclosporine levels and hepatotoxicity.	Monitor hepatic function. The cyclosporine dose may have to be decreased.
Folic Acid		OCs have been reported to impair folate metabolism.	May need to increase dietary intake, or supplement.
Meperidine		Possible increased analgesia and CNS depression due to decreased metabolism of meperidine.	Use combination with caution.
Phenothiazine Tranquilizers	All Phenothiazines, Reserpine and similar drugs	Estrogen potentiates the hyper-prolactinemia effect of these drugs.	Use other drugs or lower dose OCs. If galactorrhea or hyper-prolactinemia occurs, use other method.
Sedatives and Hypnotics	Chlordiazepoxide Lorazepam Oxazepam Diazepam	Increased effect (increased metabolism).	Use with caution.
Theophylline	All	Decreased oxidation, leading to possible toxicity.	Use with caution. Monitor theophylline levels.
Tricyclic Antidepressants	Clomipramine (possibly others)	Increased side effects: i.e., depression.	Use with caution.
Vitamin B_{12}		OCs have been reported to reduce serum levels of Vitamin B_{12}.	May need to increase dietary intake, or supplement.

9. Complications of Oral Contraceptive Therapy

The material contained in the following sections is not meant to be a comprehensive review of the adverse effects associated with the use of OCs. Current knowledge is presented in areas of major concern, such as cardiovascular system effects and possible relationships between OCs and the development of cancer. Other subjects of continuing interest are also discussed. It is hoped that this information will prove useful to physicians and their patients.

Oral Contraceptives and Cardiovascular System Effects

Myocardial Infarction

Older evidence, examining data for the use of OCs mainly containing 50 μg or more of estrogen, suggested that there were important additional risk factors for vascular disease among women receiving OCs.[1-3] Many of these studies, however, did not correct for smoking as a confounding factor. Even in the older studies, there was no correlation between the incidence of arterial disease and the duration of use of OCs.[1]

Newer studies are now available that suggest that there is no increased risk of myocardial infarction related to low-dose combination OC use.[4-6] Rosenberg *et al.*[5] and Thorogood *et al.*[6], in two hospital-based case control studies, determined that both current and past use of low-dose oral contraceptives did not increase the relative risk of myocardial infarction compared to non-users. However, in the study of Thorogood *et al.*[6], smoking and OC use did increase the risk of myocardial infarction.

Cerebrovascular Disease

There appears to be a small increased risk of thrombotic and hemorrhagic stroke in women using OCs and this risk is further increased by smoking. For current users of OCs, the relative risk of stroke was found to be 3.2. For former users it was 4.5. In addition, 71 per cent of the ever-users and 67 per cent of the controls who died of subarachnoid hemorrhage were smokers, compared to 48 per cent of all ever-users and 40 per cent of all controls who were nonsmokers.[7]

Women who present with unexplained central nervous system symptoms, which might indicate thrombotic or hemorrhagic events, should discontinue the use of OCs. These warning symptoms may include transient numbness at the side of the tongue, speech defects, loss of vision, periodic weakness of a limb, a change in the character of a migrainous attack or major symptoms of a stroke. The use

of OCs in patients with recognized risk factors for cerebrovascular disease, especially in older women or in those who are heavy smokers, is not recommended.

Mechanism of Risk

It is likely that the increased risk of cardiovascular morbidity and mortality outlined above is related to the increased thrombogenic tendency in OC users, likely as a result of the pharmacologic levels of synthetic estrogen in these preparations. The obligatory first-pass hepatic effect results in increased coagulation factor production and decreased fibrinolytic activity. In contrast, OC use may actually protect against atherogenesis, as suggested by the studies in cynomolgus monkeys by Clarkson and Adams.[8-10] In these studies, monkeys fed an atherogenic diet and exposed to contraceptive levels of estrogen and progestin had reduced atherosclerotic plaque formation despite significantly reduced HDL-cholesterol levels.[8,9] The mechanism for this protective effect may be a direct action of estrogen, at the level of the blood vessel wall, to block LDL-cholesterol deposition.[10]

Venous Thromboembolism

Women who use OCs have an increased risk of developing superficial thrombophlebitis, deep venous thrombosis and pulmonary embolism. There is a two to four times increased risk in users but the opportunity for detection bias when clinical diagnosis is used alone suggests that even this increased risk may be overestimated.[11]

There is no correlation between venous thromboembolism and total duration of use or previous use of OCs. The presence of varicose veins in the absence of previous deep venous thrombosis also is not a risk factor.[11]

The discontinuation of the use of OCs in a woman who is to have major elective surgery should be planned four weeks prior to admission to the hospital. If this is not feasible, minimum precautions should include the discontinuation of the use of OCs as soon as possible and the administration of prophylactic heparin subcutaneously during the hospital stay. In the absence of complications, OCs may be restarted two weeks after discharge from the hospital.

Hypertension

Many observers have pointed out that the use of OCs is associated with a modest but definite rise in blood pressure, especially systolic blood pressure, which is related to the patient's age and the duration of use.[12,13] Hypertension does not appear until after three to nine months of OC use. All women who are given OCs should, therefore, have blood pressure recordings taken at regular intervals during the first year of medication and during every subsequent visit. They also should be instructed to report any abrupt increase in weight, which is an indication of sodium and water retention and sometimes accompanies an increase in blood

pressure. If a significant elevation of blood pressure occurs (20 mm Hg systolic and/or 10 mm Hg diastolic), the OC should be withdrawn and an alternate method of contraception prescribed. In young, healthy patients, the blood pressure will usually return to normal within three months. Oral contraception may be cautiously resumed, but with very careful monitoring. If the blood pressure does not return to normal, or if it increases again on resumption of medication, this method of contraception might contribute to the early development of hypertensive vascular disease and therefore should not be used.

Notwithstanding the above, OCs may be prescribed for young, healthy women who have mild, stable hypertension, provided that frequent monitoring of blood pressure is performed. The Committee does not recommend OCs for patients who have moderate or severe hypertension.

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Oral Contraceptives and Carcinogenesis

Introduction

The possible relationship between OCs and carcinogenesis is difficult to evaluate for several reasons. Cancers often have latent periods of 5 to 30 years between exposure to a carcinogen and detection of the disease. Estrogens and progestins have different effects upon different tissues. These effects may vary from one person to another and with the age of the patient.

Breast cancer and cervical neoplasia are common. Many subgroups of patients of different ages, family histories and fertility patterns can be studied. Some relationships that appear may seem statistically significant, but are due only to chance.

The association between oral contraceptives (OCs) and neoplasia has been under investigation for the past 30 years. The first report on steroid contraception and neoplasia was formulated by a WHO Scientific Group in 1978 that recognized the important and complex nature of this problem. It recommended further population-based research, predominantly case-control and follow-up studies.[1] Following this recommendation, many epidemiological studies were carried out, but no consistent findings were achieved due to methodological difficulties involved in the carcinogenesis of oral contraceptives. These difficulties are due to the large numbers of variables that have to be controlled to avoid study biases and to achieve significant results. Despite these difficulties, progress has been made. The most consistent observation has been that combination oral contraceptives reduce the risk of epithelial ovarian cancer and endometrial cancer. Other observations include the following: no consistent increase in the risk of invasive cervical carcinoma, a small increase in the risk of breast cancer after prolonged use in women under the age of 35, a strong relationship between oral contraceptive users and the risk of hepatic adenoma, and an increased risk of liver carcinoma.

In light of the above, the investigation of the relationship between oral contraceptives and neoplasia should take into account certain considerations:

- There is a long latent period between exposure to a carcinogen and the onset of neoplasia.
- Different effects of estrogens and progestins on various tissues are compounded by the multitude of preparations of those two hormones in varying doses.
- The formulations have changed over the years and patient recollection of preparations prescribed several years earlier can be unreliable.
- Besides duration of use, the timing of use in relation to events such as menarche, pregnancies and menopause may be critical.
- As steroid hormones are likely to be promoters, not initiators, of carcinogenesis, the timing of oral contraceptive use may be important.
- In view of the likely multiple causes of any specific neoplasia, studies should take into account the interaction of the various risk factors.

Cervix

Many epidemiological studies have investigated the relative risk OC users face of developing cervical neoplasia, and the possibility of a positive carcinogenic interaction with human papilloma virus (HPV).[2-5] The results of many of these studies are inconclusive.[2] According to a group of Spanish researchers, which evaluated 49 epidemiological studies, there are many methodological difficulties in this area of research. Many variables are difficult to measure (e.g. sexual behaviour) and this problem can cause significant biases responsible for inconsistent findings.[3] Many studies have failed to reveal an etiologic association between OC use and cervical neoplasia.[2] However, some studies suggest slightly increased risk with long-term usage.[6,7]

Research on the correlation between OC use and cervical intraepithelial neoplasia shows conflicting results. Some studies show no increase in risk[8,9], others are inconclusive.[10,11] The hypothesis that OCs significantly increase the risk for cervical adenocarcinoma was tested in several studies and the results have been inconsistent.[1] The report of a recent study from the University of Alberta does not support the idea that OCs direct the differentiation of cervical neoplasia towards an adenocarcinoma of the endocervix.[12] It has been reported that HPV infected women do not have an increased risk of developing cervical neoplasia when using OCs.[4]

In summary, there are distinct differences in the pathogenesis of squamous cell carcinoma and adenocarcinoma of the cervix. Lacking reliable data, there is no conclusive evidence concerning any possible relationship between oral contraceptives and adenocarcinoma of the cervix. As risk factors for cervical cancer encompass psychosocial and behavioral patterns that are also associated with oral contraceptive use, there are methodological difficulties in adjusting for the interaction of those potentially confounding risk factors in the interpretation of studies. This limitation is specially relevant in view of the role of sexually transmitted infections in the etiology of squamous carcinoma of the cervix.

Endometrium

The major risk factor for endometrial cancer is considered to be prolonged hyperestrogenism associated with a lack of cyclic exposure to progesterone.[13] Fourteen epidemiological studies reported to date investigated the relative risk of endometrial cancer in women taking OCs. Most of the studies showed a protective effect of combination oral contraceptives against endometrial cancer.[14] The strongest effect was in women younger than age 60.[14] This protective effect is long lasting and persists even 15 years or more after discontinuation of OCs.[14] The results of two large U.S. studies[15,16] show that the protective effect of OCs is similar for different formulations. Associations between oral contraceptives and complex (adenomatous) hyperplasia of the endometrium and uterine leiomyomata were inconclusive.[17,18]

In summary, OCs offer substantial, long-lasting protection against endometrial carcinoma in women younger than 60.

Ovary

The large body of epidemiological literature on OCs in relation to primary ovarian cancer was analyzed by Stanford from the Fred Hutchinson Cancer Research Center.[19] After reviewing many studies, he concluded that women who have ever used OCs have about a 30 per cent reduction in the risk of developing epithelial ovarian cancer. Five or more years of use are associated with a 50 per cent reduction in risk. These findings were similar for malignant and low malignant potential (borderline) ovarian epithelial tumours and for all major histologic subtypes. The protective effect persists for 10 or more years after OC use is discontinued. All women from developed and developing countries benefit from the reduced risk. These findings do not include non-epithelial ovarian tumours or benign ovarian tumours including teratoma and cystadenoma. A reduction in risk is seen for all formulations.

In summary, there is no conclusive evidence of any possible relationship between OCs and either benign ovarian tumours or non-epithelial ovarian cancers. A protective effect for ever-users of oral contraceptives has been shown in relation to epithelial ovarian cancer.

Liver

The introduction of oral contraceptives has been followed by case reports of benign hepatic tumours in young women.[20] These reports and data of two case-control studies suggest a strong relationship between OCs and hepatocellular adenoma.[21] There have also been suggestions, based on sporadic case reports, that OC users can be at increased risk for focal nodular hyperplasia.[22] In the last decade, many case reports of malignant liver tumours in young women who use OCs were published. Subsequently, many case-control studies investigated this association. An excellent overview of these studies was published by Rosenberg.[21] The author concluded that, in low-risk populations (e.g. in North America and Western Europe), there is a strong positive association between hepatocellular carcinoma and OC use, and the risk rises proportionally to the duration of use. Since this increased risk occurs in the low-prevalence populations, the incidence of primary liver cancer attributable to OCs is likely to be low also. In countries with a high incidence of liver cancer, there is no association between short-term OC use and a risk of hepatocellular carcinoma, and there is no risk of cholangiocarcinoma.

In summary, there is a strong positive association between OC use and the incidence of hepatic adenoma. Many epidemiological studies show an increased risk of primary liver cancer with OC use, particularly long-term use. The highest risk of developing primary liver cancer is found in low-risk populations. Therefore, the number of cases in Canada that are attributable to OC use is probably small because liver cancer is extremely rare. At present, the relationship between focal nodular hyperplasia and OC use is not fully documented.

Breast

Endogenous hormones are necessary for the development of the normal breast. The introduction of oral contraceptives was followed by concern about a potential link between exogenous hormones and a risk of breast cancer.[1] In the last 20 years, about 50 epidemiological studies have investigated this hypothesis. Recently, a few excellent critical epidemiological reviews of these studies were published.[23-26] The authors separately tabulated results of case-control and cohort studies in relation to many different variables in calculating the relative risk for breast carcinoma in OC users.[23-25] These studies were characterized by predominantly large population samples, and different age groups and OC exposures, and were carried out in developed and developing countries.

Several important conclusions can be derived from the analysis of this large body of epidemiological literature. There is general agreement that most studies revealed no increase in the risk of breast cancer for women from developed countries who had ever used oral contraceptives, even with long duration of use or a long time after exposure.[1,23] However, there are suggestions that oral contraceptives can increase the risk of breast cancer for women in developing countries and for young women with benign breast lesions. Also, data derived from several studies reveal statistically significant increases in the risk of breast cancer for young, premenopausal women exposed to long-term use of OCs.[23,24] The risk of breast cancer is not altered by different formulations of OCs.[1]

Whereas almost all studies have not associated OCs with an overall increased risk of breast cancer, subgroup analyses have uncovered an increased risk for the development of breast cancer in women younger than 45. The relative risk, which is about 1.5, worsens with increasing duration of use. This increased risk is modest in size, and does not relate to the majority of cases of breast cancer, which occur after age 50.

Inconsistent conclusions have resulted from studies investigating the role of OC use in relation to either the user's age while taking OCs or age during first full-term pregnancy. Furthermore, studies investigating the role of OCs in the etiology of breast cancer have been inconclusive regarding well-recognized risk factors such as family history, nulliparity and early menarche. Studies have also failed to link the development of cancer to specific components of OCs and no specific formulation of OCs has been incriminated.

Other Sites

Although there have been reports of a link between OCs and other neoplasia such as malignant melanoma, colorectal cancer, gallbladder cancer and pituitary tumours, there is no evidence to suggest that OCs lead to an increased risk.

Summary

In summary, the most consistent observation has been the fact that combination oral contraceptives reduce the risk of epithelial ovarian cancer and endometrial cancer. Other observations include the following: no increase in the risk of invasive cervical carcinoma, a small increase in the risk of breast carcinoma after long-term use, a strong relationship between oral contraceptive use and the risk of hepatic adenoma, and a slightly increased risk of liver carcinoma.

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Oral Contraceptives, Pregnancy and Fetal Anomalies

The risk of pregnancy complications resulting from ingestion of female sex hormones was a very controversial issue in the 1970s.[1,2] Female sex hormones have been used in the treatment of several conditions, such as habitual or threatened abortion, premature labour, infertility and dysmenorrhea. However, they are most widely used as OCs.

In considering the risks associated with the use of OCs, it is necessary to distinguish between (a) pregnancy that occurs immediately after discontinuing the use of the contraceptive and (b) use of the pill during a conception cycle and after conception, because of method failure.

Pregnancy Immediately After Discontinuing Oral Contraceptive Use

Following the discontinuation of OCs, there may be a delay of several months in the re-establishment of normal ovulatory cycles. OC use does not lead to permanent infertility. A pregnancy that occurs immediately after discontinuing the use of OCs raises the possibility of a "carry over" effect that may interfere with physiological function and so influence oocyte maturation or the quality of the endometrium.

Assays of plasma protein and steroid hormones suggest that while most women ovulate during the first cycle after ceasing to use OCs, the LH peak or surge that results in the rupture of the follicle and release of the oocyte in this cycle is slightly delayed. The first cycle, therefore, may be longer than usual, even up to six weeks.

It is advisable for those discontinuing OC use to wait one cycle before trying to conceive. This delay will enable (a) blood levels of various chemicals (such as enzymes, vitamins, minerals and elements) to return to normal levels and (b) easier calculation of gestational age using the date of onset of the last menstrual period. It is also opportune for those women to have their rubella immunity status checked before the discontinuation of OCs. Women should make sure that their dietary intake of folic acid is adequate prior to conception because of the known association between folic acid deficiency and neural tube defects.

Conception occurring soon after the discontinuation of OCs is not associated with an increased risk of spontaneous abortion.[3] Abortions that do occur do not have an increased incidence of chromosomal abnormalities[3-5] despite earlier findings of an excess of lethal triploidy.[6] A prospective study of about 33,000 pregnancies has shown that there is no increased risk of congenital malformation in infants conceived within one month of the discontinuation of OCs.[7]

In summary, women who discontinue the use of OCs immediately before conception seem to impose no increased risk on the fetus.[8]

Oral Contraceptive Use During and After the Cycle of Conception

In 1981, a scientific committee of the World Health Organization (WHO) concluded that the evidence for an increased risk of congenital malformations due to OC use during and after the cycle of conception is not clear and that, if such risk exists, it is very small and likely to be related to malformations of the heart and limbs.[8] Since then, large prospective studies have shown that there is no increased risk of limb reduction defects[9,10] or congenital heart defects.[10] There is some evidence that the risk of a major congenital malformation is three times higher in women who smoke than in nonsmokers.[7]

The large prospective study of about 33,000 pregnancies, referred to earlier in this section, also showed that there was no increased risk of chromosomal abnormalities[11] when oral contraceptives were either discontinued immediately before conception or used during the cycle of conception.

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Oral Contraceptives and the Endocrine System

Gonadotropins, Ovarian Sex Steroids and Sex Hormone Binding Globulin (SHBG)

OCs exert their effect by interfering with the normal reproductive cycle. There is a suppression of follicular maturation and of cyclical development of the endometrium, the latter becoming thinner and less glandular. Cervical mucus is also altered, becoming thick and tacky and much less penetrable to sperm.

Although contraceptive steroids interfere with the reproductive process at all of these levels, the primary site of action is at the level of the hypothalamus. Pituitary LH and FSH are suppressed and consequently ovulation is inhibited. There is also a decrease in ovarian steroidogenesis. With combination OC steroids containing 50 µg or less of estrogen, irregular LH peaks can be observed throughout the treatment cycle.[1] There is evidence, however, that the pituitary reserve of gonadotropins is depleted by OCs. The pituitary response to gonadotropin releasing hormone (GnRH) stimulation is significantly depressed in OC users, even after GnRH priming, as compared to controls following ingestion of OC formulations containing both high- and low-dose synthetic estrogens.[2] Studies using low doses of ethinyl estradiol (EE ≤ 35 µg) and any of the new progestins show a significant decrease in LH and FSH and a profound inhibition of serum estradiol.[3,4] Recent studies also prove that low-dose OCs can effectively decrease serum testosterone and androstenedione.[3]

With the decreased progestin content of the newer oral contraceptive formulations, and with the introduction of new progestins that possess less or no androgenic activity and even some anti-androgenic activity, the changes

associated with these OCs reflect their estrogen content, not their progestin activity. Estrogen, in a dose-dependent fashion, affects the levels of transport globulins such as sex hormone binding globulin (SHBG), cortisol binding globulin (CBG) and thyroxine binding globulin (TBG). In the presence of combination oral contraceptives, these globulins are thus sensitive to the estrogenicity of the steroid components of the combination OCs. Several reports have noted a marked increase in SHBG associated with the intake of low-dose OCs.[4-7] The newer progestins are associated with a doubling or tripling of SHBG levels, suggesting more of an estrogenic effect or less of an androgenic effect than the older progestins. Since SHBG is the main protein responsible for the binding of testosterone in the serum, there is a marked decrease in free and bioavailable testosterone associated with these oral contraceptive preparations. In fact, a low-dose triphasic OC has been found effective in attenuating the mild hyperandrogenic activity in post-pubertal acne.[5] New OCs containing a progestin that has anti-androgenic properties also have been found effective in counteracting hyperandrogenic states in women having hirsutism[6] and polycystic ovary syndrome.[7]

ACTH, Adrenal Steroids and Cortisol Binding Globulin (CBG)

The effects of estrogens and/or progestins on ACTH secretion have not been examined extensively. An early study reported mean daily plasma concentrations of ACTH significantly lower in women treated with a high-dose OC compared to untreated ovulatory women.[8] Initial and current studies also show reduced secretion of dehydroepiandrosterone sulphate (DHEA-S) in women taking OCs.[5-7,9] A more recent study described an increased adrenocortical responsiveness to exogenous ACTH in low-dose oral contraceptive users.[10] There is no evidence, however, of an association between adrenocortical insufficiency and OC use, and the pituitary-adrenal response to stress seems unaffected.

Interestingly, several studies have reported a significant elevation of total plasma cortisol in OC users.[10] In all likelihood, the major impact of the combination OC is due to an increase in the protein-bound cortisol fraction that is not hormonally active.[11,12] An early study suggested that levels of both free and active cortisol are elevated by combination OCs.[13] Both components of oral contraceptives (estrogen and progestin) would be involved in the increase of free cortisol: estrogen reduces the ability of the liver to metabolize cortisol and progestin can displace cortisol from CBG. Although there are no data available for free cortisol with new OCs, the situation probably would be similar. The increase in free cortisol would explain the diminution of ACTH by negative feedback of the unbound cortisol. On the other hand, there are no clinical signs of increased glucocorticoid activity noted during the administration of OCs.

The influence of estrogen-progestin combinations on adrenal mineralocorticoid function has been recently reviewed by Lemay *et al.*[11] The effect of OCs on aldosterone seems to result essentially from the action of estrogens on the reninangiotensin system. There is no direct action on the adrenal. Aldosterone is weakly bound to CBG.

TSH and Thyroid Hormones

Thyroid hormones circulate as both thyroxine (T_4) and triiodothyronine (T_3). Most of the circulating thyroid hormone is bound to TBG, whereas less than 0.1 per cent circulates in the unbound or free form. As noted above, ingestion of synthetic estrogens stimulates the hepatic production of globular proteins, including TBG. Therefore, total T_4 levels are elevated with OC use. However, the levels of free T_4 are unaffected by estrogen ingestion and, together with measurement of TSH, provide an accurate assessment of a patient's thyroid state.

Although OCs may cause alteration in certain thyroid function tests, there is no significant alteration in the clinical thyroid state of users. It is, however, very important for the clinician to understand and be aware of the effects of OCs upon test results when investigating patients who are under treatment.

The reason that OCs are not involved in the induction of hyperthyroidism or hypothyroidism is likely because the estrogen component causes an increase in the protein fraction, but does not increase the free (hormonally active) thyroxine level. This increase in the protein fraction also results in the inverse effect seen in the T_3 resin uptake test.

Depending upon the estrogen/progestin content of the OC, serum levels of total T_4 can go up by some 20 per cent and, reciprocally, the T_3 resin uptake can go down by some 10 per cent. The free thyroxine index and the real free T_4 do not change. These changes are similar to those seen in early pregnancy.

When the medication is withdrawn, these changes may require 6 to 10 weeks to revert to the original levels of thyroid hormones. Serum TSH and T_3 radioimmunoassays are unchanged or show a slight increase.

Prolactin, Growth Hormone and Pituitary Adenomas

It is well known that estrogens stimulate prolactin (PRL) secretion. However, the effect of progestins on circulating PRL has not been well appreciated. It was found that in 42 cases of histologically verified pituitary adenomas, 74 per cent of the patients developed amenorrhea and/or galactorrhea in immediate association with the use or discontinuation of oral contraceptives, or postpartum.[15] There is also evidence that about 10 per cent of the general population have small pituitary tumours. Several studies have tried to evaluate the effects of oral contraceptives on circulating PRL. Initial studies with OC preparations containing 50 µg of ethinyl estradiol reported an increased incidence of hyperprolactinemia.[16] In more recent studies with OCs containing 35 µg or less of EE, PRL was not elevated or only episodically elevated.[17-19]

The possible association between the use of oral contraceptives and PRL secreting adenomas has been reviewed recently by Milne and Vessey.[20] Animal studies, knowledge of the actions of estrogen on PRL secreting cells in the normal pituitary gland and in pituitary tumours, and uncontrolled clinical studies

all suggest that OCs may have an impact on pituitary tumours, causing their development or accelerating their growth. However, there is little evidence of a real increase in incidence and neither case-control nor cohort studies have supported the hypothesis of such an association.[21]

It is reasonable to state at this time that there is no evidence of an etiological relationship between OC use and pituitary prolactinomas. However, amenorrhea, which is a common presenting symptom of such disease, will be masked by the usual withdrawal bleeding induced by an OC. The Committee does suggest that the appearance of galactorrhea while on OCs merits investigation.

Estrogen treatment is also well known to stimulate growth hormone (GH) secretion in both men and women. Even a very low dose of EE results in a significant augmentation of pulsatile GH activity in prepubertal girls with Turner's syndrome.[22] A recent study using a low-dose OC showed a change in GH secretion towards a pattern of smaller peaks at a higher frequency.[23] A sex steroid-induced change in GH secretion may be relevant for certain metabolic effects of oral contraceptives, mainly effects on the liver. Certain hepatic effects of oral contraceptives – i.e. on the synthesis of substrate, high-density and low-density lipoproteins, various coagulation factors and antithrombin III – may be related to a sex steroid-induced change in GH secretion during treatment rather than consequences of a direct steroid action on hepatic cells. Currently, however, there is virtually no information on the influence of various progestins on GH secretion.

Amenorrhea During Oral Contraceptive Use

Physiologically, the low-dose combination OC, which includes a daily dose of progestin, restricts the build-up of the endometrium. Ordinarily, this results simply in a reduction of menstrual bleeding. However, in a few patients, the endometrial suppression is of such magnitude that no withdrawal bleeding may occur. In this situation, the possibility of pregnancy must be excluded soon. This can be aided considerably by a beta human chorionic gonadotropin (ßhCG) pregnancy test performed either on a first morning urine sample or, preferably, on a blood specimen.

It is obviously important to resume contraception quickly if there is no evidence of pregnancy. This harmless form of amenorrhea has no relationship or association with development of either the condition known as post-pill amenorrhea or with future fertility. Having excluded pregnancy initially, there is also no evidence of an increased risk of becoming pregnant under these circumstances, assuming the patient continues to take the oral contraceptives as directed.

In situations where a woman is disturbed emotionally by the continued amenorrhea, it may be necessary to switch to a more estrogen-dominant type of OC.

Post-Pill Amenorrhea

The incidence of amenorrhea that lasts more than three months after a woman discontinues the use of OCs has been reported to be one per cent or less. This is very similar to the incidence of spontaneous amenorrhea in non-users of OCs.[24]

Women who have a history of menstrual abnormalities such as oligomenorrhea, or extreme variations in body weight, are much more prone to develop post-pill amenorrhea. Most reports in the literature agree that spontaneous amenorrhea and post-pill amenorrhea are the same condition; full investigation is necessary if amenorrhea has lasted more than six months.[25,26] The probability of amenorrhea developing after cessation of therapy with OCs does not appear to be related to the duration of use of these products. It is recommended, therefore, that a history of menstrual disturbance should not be considered a contraindication to oral contraceptive use. When amenorrhea arises, it is unfortunate that so many women develop feelings of extreme guilt concerning their fertility because of oral contraceptive use. One should attempt to dispel these feelings by assuring them that, with therapy, their prognosis is no different than if they had never taken OCs; these compounds were a coincidental factor rather than a causative agent in the fertility problem.

Amenorrhea and galactorrhea may occur after discontinuing the use of OCs. These demand a thorough investigation to identify the cause before starting any treatment.

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Oral Contraceptives and Infections

General Considerations

The use of OCs appears to affect the cervical flora. Among healthy women, more aerobes and significantly more anaerobes have been isolated from the cervix of women using OCs.[1] A predominance of anaerobes in the cervical flora may be related to sexual activity or to a change in the cervical milieu in OC users. This should be regarded as a normal finding in healthy sexually active women.

Multiple bacteria have been recovered from the endometrium of healthy asymptomatic women. The use of OCs does not seem to modify the endometrial flora.[2]

Candida Albicans

The incidence of Candida albicans infection has nearly doubled over the last decade in the United States, along with a significant increase in non-albicans Candida infection.[3] However, the relationship between OC use and mycotic vaginitis is not easy to establish. It is likely that OCs do not lead to an increased risk of Candida, which is considered a secondary opportunist organism.[4,5] Among the various publications on the subject, the conclusion differs depending on how the information was obtained.

In ovulating women, Candida infection is most prevalent in the luteal phase, when adherence of Candida to the vaginal epithelial cells is greater.[6] The hormonal status may influence the pathogenicity of Candida by modulating the immune response.[6] Progesterone per se does not seem to have an influence on Candida, but this hormone may suppress the cell-mediated immune response, which is the natural defense against Candida.[6-8] Progesterone suppresses the anti-candidal activity of T-lymphocytes, promoting Candida germination and causing an asymptomatic carrier to become symptomatic.[7,8] Recurrent vaginal candidiasis may be the first symptom in HIV-positive women.

Women on OCs do not show a marked fluctuation in progesterone and estrogen levels. However, any situation causing a localized immunosuppression in the vagina may increase the risk of promoting clinical infection in susceptible subjects.

Chlamydia Trachomatis

Genital chlamydial infection is a disease of major importance in Canada. Statistics from 1990 show high rates of infection in young adults, on the order of 3,000/100,000 for females 15 to 19 years of age.[9] These rates are three times higher than those for gonorrhea, and are probably underestimated because reporting is not compulsory.

In women using OCs, several studies show a significantly greater risk of becoming infected with Chlamydia trachomatis.[10-12] There is at least a doubling of the risk.[13] The association between OCs and Chlamydia trachomatis seems to be related to the presence of cervical ectopy, which is prevalent in OC users.[12] Chlamydia trachomatis has great affinity for the columnar epithelium of the endocervical canal. It has been postulated that exposing this epithelium to Chlamydia makes it more likely that the genital infection will occur. Indeed, before becoming active, Chlamydia must attach itself to this epithelium. This increased risk of cervical infection is generally believed to be related to an increased risk of chlamydial pelvic inflammatory disease (PID). However, because of inadequate or insufficient data, other authors question whether OC users have an increased risk of acquiring Chlamydia.

One recent study comes to a different conclusion and proposes that OCs may have a protective role against PID in women infected with Chlamydia trachomatis.[15] This conclusion has been criticized, however, because of insufficient data; the possibility has been raised that OCs might lower the incidence of clinical PID, but not of asymptomatic infection.[16]

The prevalence of Chlamydia trachomatis infection in OC users should draw attention to the relevance of a selective screening program in the population at risk.[17] To prevent the spread of disease, it is important to treat all sexual contacts of infected persons.

Human Immunodeficiency Virus

Throughout the world, the HIV/AIDS virus is spread more often through heterosexual transmission than through any other means. The transmission rate from the infected to the non-infected partner is quite variable, ranging from 9 to 50 per cent. However, it also seems to be affected by several associated conditions, including OC use and genital ulcers.[18,19]

A study in a high-risk population has shown that women using OCs became seropositive at a higher rate than women not using OCs, the risk of infection being greater in those using OCs continuously throughout the study.[20] The same data showed an independent association between OC use, genital ulcers and seroconversion. The proposed mechanism is related to the frequency of cervical ectopy associated with OC use. The cervical columnar epithelium may be disrupted easily during sexual activity, causing mucosal discontinuity and a greater risk of acquiring HIV infection. This greater risk is also associated with the presence of Chlamydia trachomatis infection of the cervix and other STDs, which seem to facilitate the acquisition of HIV infection. The use of condoms completely removes the risk associated with genital ulcers.

The observations from the previous study must be interpreted with caution, and may not be applicable to the general population. More studies are needed on the subject. However, to obtain adequate protection from HIV and other STDs, and to provide effective contraception, it is strongly recommended to use condoms with other contraceptive methods, including OCs.

Human Papilloma Virus

HPV infections, particularly type 16 and 18, have been implicated as a causative agent in cervical cancer. Whether they are associated with OC use is a matter of debate. Some studies have reported a strong association between HPV infection of the cervix and OC use.[21,22] OCs may act as promoters of other risk factors such as HPV infection, or as co-carcinogens. They may change the hormonal milieu and modify the immune response to HPV.[21]

Other authors question an association between OCs and HPV because of insufficient data or evidence.[23] The relationship between OC use and cervical cancer deserves more evaluation. Meanwhile, the actual data do not require a change in the recommendations for OC use in patients with abnormal Pap smears.

Neisseria Gonorrhoeae

The rate of genital infection with Neisserria gonorrhoeae has been decreasing constantly over the last decade in Canada.[24] However, the resistance to treatment is increasing, as more and more Neisseria isolates show a resistance to penicillin and tetracycline.[25]

Previous studies have shown a reduced incidence of acute gonococcal salpingitis among OC users compared to non-users.[26,11] One study suggests that teenagers who use OCs are not at increased risk of acquiring cervical infection with Neisseria gonorrhoeae.[27] However, a recent publication has failed to establish an association between the use of OCs and PID in women presenting with gonococcal cervicitis, and has concluded that OC use does not protect against gonococcal salpingitis.[16] In contrast, other authors propose that OC use may increase the risk of cervical infection with Neisseria gonorrhoeae, but the mechanism involved here would not be related to the cervical ectopy.[13]

Neisseria gonorrhoeae remains present in the young sexually active population, and demands appropriate investigation that also should be carried out for other STDs, especially Chlamydia trachomatis.

Bacterial Vaginosis

Bacterial vaginosis is now the most prevalent vaginal infection in the U.S.[3] OC use does not seem to affect its incidence.[4] OCs even may have a protective effect on the presence of hydrogen peroxide-producing lactobacilli, maintaining an acidic pH in the vagina.[3]

Trichomonas Vaginalis

Vaginal infection with trichomonas has declined by approximately 40 per cent over the last 20 years.[3] The influence of OCs on trichomonas infection is beneficial. OCs have a protective effect, probably because of the acidic pH of the vagina related to the presence of the lactobacillus, which is maintained by OC use.

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Oral Contraceptives and Ocular Effects

Many reports of adverse ocular effects associated with the use of OCs have appeared in the medical literature.[1,2] Intolerance to the use of contact lenses, manifested by subjective discomfort and change in visual acuity, is due to edema of the cornea from fluid retention. With the use of low-dose OCs and the fitting of soft contact lenses, this side effect is becoming less common.

Ophthalmic migraine is very rare. Loss of vision may be due to cerebral ischemia or retinal vascular occlusive episodes such as hemorrhage, thrombosis and arterial spasm. Further OC use is contraindicated in those conditions and in focal migraine associated with abnormalities in the visual field.[3]

Patients who complain of contact lens intolerance should be instructed to discontinue using these lenses and to undergo full ophthalmologic assessment. Refitting of the lenses may be necessary. Migraine patients using OCs who develop increasing frequency and severity of associated eye symptoms should be examined ophthalmologically for evidence of retinal, vascular and/or neurological changes. Sudden changes in visual acuity or field of vision in OC users should be assessed for evidence of occlusion of the central retinal artery or vein, or branches thereof, and appropriate referral and treatment should be given. OC use should be discontinued if there is evidence of any of these conditions.

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Oral Contraceptives and Migraine

The following observations suggest that female sex hormones play an important role in the etiology of migraine, and estrogen has been incriminated:[1]

- Whereas there is a female-to-male ratio of 1:1 for migraine cases before puberty, that ratio is 3:1 among adults.
- Most women suffering from migraine have those episodes during menstruation. True menstrual migraine occurs exclusively during menstruation and accounts for approximately 15 per cent of all migraine cases in women of reproductive age.
- Although migraine can worsen early in pregnancy, it often improves later during pregnancy.
- Migraine can either improve or worsen around the menopause.

Headaches are a frequent complaint of OC users and may be of sufficient severity to cause cessation of pill taking.[2] Studies on known migraine sufferers have shown an increase in both the frequency and severity of the migrainous attacks when the contraceptive pill is taken.[3] It is imperative to distinguish between true migraine and headache due to another cause. The mechanism by which OCs can exacerbate migrainous symptoms is not known; however, the increase in frequency or severity of symptoms should cease when the medication is discontinued if they were truly OC-related.

In OC users, migraine occurs around the time of the withdrawal bleeding on the days when OCs are not being ingested. There is still a debate on the link between OCs and migraine:[1] neurologists tend to report an adverse effect whereas other doctors either fail to demonstrate any effect or report an improvement.[4]

Women who have had migrainous symptoms in the past may be prescribed OCs since not all patients will experience an exacerbation of symptoms. If the pill is prescribed to a migraine sufferer, careful note should be made of any increase in the severity of symptoms. If this occurs, the medication should be discontinued.

There are isolated case reports linking the use of OCs with both exacerbation of migrainous symptoms and development of retinal and cerebral artery insufficiency. The Collaborative Group for the Study of Stroke in Young Women[5] felt that migraine increases the risk for stroke irrespective of OC use. Severe migraine and focal migraine accompanied by symptoms of cerebral ischemia should be considered as relative contraindications to OC use.

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Oral Contraceptives and Depression

The randomized double-blind study of Cullberg[1] and the prospective cohort study of the Royal College of General Practitioners[2] suggest a 10- to 15-per-cent increase in depression among women using OCs compared to women not using them. However, more recent studies fail to show an association between OC use and depression.[3] This may be due to the decrease in the hormonal content of the currently prescribed OCs (30 to 35 µg estrogen).

Chang *et al.*[4] point out that oral contraceptive depression is not characterized by recognized symptoms of other types of depression such as guilt, low self-esteem, hopelessness and sadness. The emotional disturbances, cited as depression, may be better characterized as dissatisfaction. This dissatisfaction is expressed as anger and frustration at physical side effects, such as bleeding, weight gain and headache, and emotional effects such as annoyance at having to take a pill every day, or anxieties about the possible dangers of the pill.

There is as yet no clear consensus about which component of the oral contraceptive pill is associated with depression. Progesterone in large dosage produces a sedative effect. Estrogen, on the other hand, can decrease the production of serotonin through a functional vitamin B_6 deficiency.

Whether one considers estrogen, the progestin or both as the operative component, there is much less emphasis on the complaint of depression these days. There is some evidence that this is due to the gradual reduction in the amount of both steroids in newer OCs currently on the market. In the Royal College of General Practitioners' Oral Contraception Study, the relative risk of neurotic depression in women taking OCs increased with increasing dosage of estrogen.[5] In this study, the possible influence of the accompanying progestins contained in the various OCs could not be properly evaluated or eliminated.

Because depression, mood change and dissatisfaction are common conditions, they also may be expected to occur independent of OC use in some women who may be predisposed to depression, fatigue and premenstrual irritability. OCs are not thought to influence the occurrence of premenstrual symptoms,[6] whereas libido tends to improve with the protection against conception.

Women who appear emotionally disturbed or who have a history of psychosis or depression may be prescribed OCs in light of the above association between depression and hormonal steroids. They should be monitored closely so as to base the decision regarding further prescription on their individual response.

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Oral Contraceptives, Some Changes in Metabolism and Alterations in Clinical Laboratory Tests

Carbohydrate Metabolism

Glucose is a source of energy in normal healthy individuals. Changes in glucose and insulin levels have been implicated in the development of atherosclerosis and diabetes, and are associated with an increased incidence of coronary heart disease and vascular disorders in women of childbearing age. Variations in carbohydrate metabolism, with changes in serum insulin and growth hormone levels, have been observed in women using OCs. An increased incidence of impaired and diabetic glucose tolerance has been reported but it rarely leads to overt diabetes. Low-dose combination oral contraceptives may induce changes in measures of carbohydrate metabolism such as elevated plasma glucose and insulin concentrations. The magnitude of these changes depends on the dose and type of progestin.[1]

Some researchers have found that glucose tolerance deteriorates in some women using oral contraceptives but the clinical importance of such changes is not certain. The Royal College of General Practitioners study[2] found no increased risk for clinical diabetes mellitus among current users, former users and long-term users of oral contraceptives.

Ovarian steroid hormones have been known to modify carbohydrate metabolism. In animal studies, estrogens have an effect upon carbohydrate metabolism, but to a degree that apparently is dependent upon the type of estrogen, the dosage schedule and the carbohydrate status of the animal under treatment. According to human data, estrogens do not have a consistent effect upon glucose tolerance and insulin secretion. The fasting plasma glucose may fall, gluconeogenesis may be impaired, liver glycogen may be increased and glycogenolysis may be reduced. Progesterone and progestins increase the secretion of insulin and enhance pancreatic response.

As suggested by animal work, the inconsistencies observed in human studies may be explained by variations in the chemical nature of the OC, the dosage of the ingredients, the individual's sensitivity to the metabolic action of the steroids and the carbohydrate status of the individual. In 1963, Waine and colleagues[3] reported that OCs decreased oral glucose tolerance. Various authors have observed as much as a 25-per-cent increase in fasting blood sugar and a decreased glucose tolerance in 18 to 77 per cent of treated subjects. Alterations in glucose tolerance were more pronounced in the oral test than in the intravenous test. Longitudinal studies of normal women taking low-dose oral contraceptives have shown an increase in incremental area under the oral glucose tolerance test, glucose concentration profile of 0 to 418 per cent. Most of these percentage differences are highly significant, even after standardization for age, weight, cigarette smoking, alcohol intake, exercise habits, and family history of diabetes and heart disease. There is a consistent effect of progestin dose on the glucose and insulin response. Higher progestin dosages have the greatest impact. The c-peptide concentration responses confirm the relative difference in insulin response, and show that underlying the elevated insulin levels are increases in pancreatic insulin secretion.[1]

Although large epidemiologic studies show no difference in the frequency of diabetes mellitus in non-users and ever-users of high-dose combination oral contraceptives, other studies have shown an increased risk of impaired glucose tolerance in current users, which is estimated to be roughly twice as frequent as that in non-users.

Women at risk of developing impaired glucose tolerance while receiving high-dose oral contraceptives either have previous gestational diabetes mellitus or a positive family history of diabetes mellitus, or are older or obese. The tendency to decreased glucose tolerance seems related to the dosage and clinical structure of the progestin used in oral contraceptives. The use of low-dose oral contraceptive preparations, particularly with reduced progestin content as in triphasic OCs and newer progestins, is accompanied by a low risk of impaired glucose tolerance even in previous gestational diabetics.[4]

In some studies with norgestimate, gestodene and desogestrel, slight changes in fasting blood glucose level, glucose responses to oral challenges and increases in blood insulin concentrations have been reported. However, these changes tend to disappear with continuing oral contraceptive use.[5]

Investigators have measured insulin levels and glucose tolerance in subjects taking OCs. The consensus is that insulin levels are elevated in such patients. In patients receiving OCs, the fasting plasma insulin level is higher and the increase observed after oral glucose is greater and more sustained, even after an oral sulfonylurea test.[6] Thus, there seems to be a change in carbohydrate metabolism whereby an initial elevation of blood glucose and insulin levels is followed by a depression of the blood glucose and persistent or further increase in the plasma insulin. Intake of ethinyl estradiol in combination with desogestrel or gestodene may be accompanied by increased insulin resistance, especially a hyperinsulinemic response to a glucose challenge, despite unchanged glucose values

compared to a baseline test. This reaction is similar to earlier observations made with norgestrel and norethindrone. It is conceivable that the diabetogenic effects of the progestins are caused by an increase in the insulin-binding receptor affinity, or fewer insulin receptors, or a post-receptor defect in cellular insulin action.[6] The apparent increase in the plasma insulin could be explained by relative insulin resistance. The following mechanisms have been described to explain insulin resistance:

- a decreased affinity of insulin receptors;
- a reduction in the number of receptors;
- significant changes in intracellular insulin metabolism;
- diversion from the liver of gluconeogenic precursors; and
- a change in metabolic clearance rate.[7]

The combination OCs are responsible for increased insulin resistance, impairment of glucose tolerance, increased plasma insulin and growth hormone, and elevation of non-esterified fatty acids (NEFA).[8]

Plasma growth hormone is increased by combination OCs.[9] Normally, growth hormone levels decrease with increasing levels of blood glucose. Combination OCs seem to act on the hypothalamus, causing an increase in human growth hormone releasing factor which, in turn, stimulates the secretion of growth hormone from the anterior pituitary gland. Human growth hormone has an initial antagonizing action on glucose usage that leads to an elevation of peripheral glucose levels. In turn, the increased glucose stimulates the pancreas to release more insulin. This pattern has been observed in the first two or three cycles of OC administration. The pancreas of the normal individual can compensate for increased growth hormone, and the resultant elevation of circulating insulin causes the blood sugar to return to normal or perhaps subnormal levels. This compensatory mechanism is observed about three months after one begins to use OCs. Over long periods, some women may develop decompensation of the islet cells.[11]

It is important to note that following the discontinuation of OC use there is usually a rapid and spontaneous resolution of abnormal glucose tolerance.[10]

Pre-diabetic and Diabetic Patients and Oral Contraceptives

Few studies have been conducted on diabetic, gestational diabetic or non-insulin-dependent diabetic patients. Spellacy[12] observed an improvement of the oral glucose tolerance after six months of 0.4 mg of norethindrone and 35 µg of ethinyl estradiol in four out of five women with borderline abnormal oral glucose tolerance. Skouby[7,13] found no deterioration of glucose tolerance in non-insulin-dependent diabetics taking norgestrel.[14] The levonorgestrel triphasic has been used in gestational diabetics and insulin-dependent diabetics. No change in glucose tolerance in the former and no increased difficulty in control in the latter has been found.[13] However, there was a significant increase in insulin levels in these patients. Radberg[15] found that OCs may interfere with dietary treatment of

diabetes by increasing hunger and craving for carbohydrates. Therefore, it may be appropriate to consider an alternate method of contraception in diabetic or even pre-diabetic patients provided the benefits of such alternate methods outweigh the contraceptive and non-contraceptive benefits of OCs.

Lipid Metabolism

Water-insoluble lipids are carried in the plasma as lipoproteins. These lipoproteins are a mixture of triglycerides, cholesterol, phospholipids and a protein component. Based on centrifugation, lipids can be classified into three major components: very low density lipoproteins (VLDL), low density lipoproteins (LDL), and high density lipoproteins (HDL). High density lipoproteins are subdivided into HDL_2 and HDL_3.[16] Most cholesterol is associated with LDL and shows a positive association with atherosclerosis. High density lipoproteins, in particular HDL_2, are associated with premature atherosclerosis when decreased, and are protective against the development of atherosclerosis when elevated.

The estrogenic and progestogenic components of OCs have very different effects upon triglyceride and cholesterol levels, and upon the levels and proportions of the various lipoprotein fractions.[16,17] Estrogens alone tend to cause a moderate rise in triglycerides, a mild rise in cholesterol (particularly the cholesterol associated with high density lipoproteins) and a concomitant decrease in low density lipoprotein cholesterol. These effects are potentially protective against the development of atherosclerosis. Progestins, on the other hand, tend to cause very little change or even a decrease in triglyceride levels, a decrease in high density lipoprotein cholesterol and an increase in low density lipoprotein cholesterol. On balance, these latter effects should be atherogenic. The lipid effects of progestins are dependent upon the dosage and type of progestin and the dosage of the associated estrogen.

The net effect of any oral contraceptive pill on serum lipids is related to the types and relative amounts of estrogen and progestin. However, it has not been shown clinically that any one OC is associated with a higher incidence of atherosclerosis or premature cardiovascular disease.

The development of atherosclerosis is multifactorial and is dependent upon a complex interaction of age, heredity, blood lipid levels, diet, hypertension, smoking, obesity, diabetes mellitus and lifestyle. Changes in lifestyle factors such as smoking, alcohol consumption, body weight and pattern of exercise can cause alterations in lipid levels that are outside acceptable, normal ranges.[18,19]

There are many reports of changes in levels of lipids associated with the use of OCs.[16,17,20-23] Some authors have suggested that combination OCs may be atherogenic. Others have engaged in comparisons of progestin potency, which this Committee does not consider scientifically valid because the effects of one progestin cannot be directly compared with those of another. However, most of these reports, particularly those that studied the low-dose combination OCs, or desogestrel, norgestimate and gestodene compounds, suggest a lipid neutrality

with little or no changes from normal concentrations of high density lipoprotein, low density lipoprotein or cholesterol, and an increase in triglyceride levels.[5,24]

Although distinctions cannot be made among the various combination OCs concerning possible increased or decreased risk of atherosclerosis, it is always prudent to use the lowest dosage of any given progestin in a combination OC that is consistent with effectiveness and good cycle control. It is also wise to carefully observe patients with a family history of hyperlipidemia or who have other predisposing factors for the development of abnormal serum lipid levels. Women who have excessively high levels of triglycerides or LDL cholesterol, or who develop these for whatever reason while taking OCs, should be considered for alternate methods of contraception.

Protein Metabolism

The influence of oral contraceptives on protein metabolism can be observed on the coagulation system and the level of transport globulins. In OC users, levels of ceruloplasmin, ferritin, thyroid binding globulin, transcortin and sex hormone binding globulin are all increased. They are influenced by both estrogen and progestins, sometimes in opposing fashion. For example, levels of sex hormone binding globulin increased by two fold or less with a levonorgestrel triphasic[25] by cycle six. They doubled with gestodene[25] and tripled with both norgestimate and desogestrel preparations.

In the coagulation system, epidemiologic evidence has established that oral contraceptives increase the risk of both arterial and venous thromboembolic diseases. The hypercoagulability in oral contraceptive users is mainly related to platelets.[26] The hypercoagulability is dose-related for arterial and venous events in the case of estrogen,[27] and only for arterial events in the case of progestins. Moreover, estrogen causes an increase in various clotting factors and a reduction in fibrinolytic system activity while progestins tend to increase fibrinolytic activity. With estrogen, factor VIIc, factor XIIc, antithrombin III, and proteins C and S are elevated.

Progestins influence the magnitude of changes and enhance fibrinolysis by increasing plasminogen 30 to 40 per cent, decreasing histidine-rich glycoprotein 15 to 26 per cent, increasing tissue plasminogen activator activity by more than 150 per cent, and decreasing tissue plasminogen activator inhibition 30 to 40 per cent while decreasing tissue plasminogen activator antigen level by 15 to 20 per cent.[27] The newer progestins – norgestimate, desogestrel and gestodene – have been associated with similar changes.[28,29] There is no dramatic change in any coagulation or fibrinolytic parameter although individual extreme values could be altered substantially, therefore playing a role in individual thromboembolic risk.[30]

Folic Acid Metabolism

Folate deficiency in women taking OCs is rare but OCs have been incriminated in its occurrence. Several researchers have reported contrary findings. Spray[31], McLean[32], Castren[33] and Pritchard[34] all failed to observe either a significant fall

in serum folic acid, or an effect on folate metabolism in patients taking OCs. The type of contraceptive and the length of use, short or long, did not seem to have a significant effect. In contrast, Sojania[35-37] observed a decrease in both serum and red cell folate. These alterations promptly disappeared after discontinuation of the contraceptive medication. Streiff[38] has described a folate deficiency anemia in some OC users, this being explained by a 50 per cent decrease in the absorption of polyglutamic folate. Holmes[39] reported that OCs are an unlikely cause of the megaloblastic anemia he observed in some patients; they should be regarded as a factor in women who have occult malabsorption.

Liver Function

Jaundice has been reported in women using OCs. Impairment in the function of the bile secretory-excretory apparatus, sufficient to cause jaundice, is estimated to occur in a maximum of 1 in 10,000 women taking OCs. With certain exceptions, the clinical course is benign, and there have been no reported fatalities in uncomplicated cases. The jaundice usually subsides when the medication is discontinued. A history of other liver disease, including cholestatic jaundice of pregnancy,[40,41] primary biliary cirrhosis, recurrent pruritus of pregnancy and porphyria,[42] is thought to confer added risks.

The liver is the site of biotransformation and inactivation of steroids. Constituents of oral contraceptive tablets are steroidal agents that affect the production of plasma proteins, the degree of effect depending upon the type of protein, and the type of OC and its dosage. In large doses, estrogens have a catabolic effect; in low doses they are anabolic. Progestins themselves are not anabolic but may potentiate the anabolic effect of estrogens. Some oral contraceptives increase blood levels of thyroxine, corticosteroids and lipids by increasing carrier proteins without an elevation of the free, active form of the substances carried.[43]

Biochemical and obstructive abnormalities in the liver

The significance of the changes in levels of bromsulphthalein (BSP) in women using OCs is uncertain. In normal women, there is cyclical variation of bromsulphthalein retention; higher levels are noted during the luteal phase.[44] Also, healthy premenopausal women older than 40 may show increased BSP retention.[45]

The cause of changes in hepatic function in women using OCs is not known, but it may be related partly to an impairment in the excretion of conjugated bilirubin into the canaliculi, and also to reversible parenchymal hepatocellular changes. Animal experiments suggest that those steroids bearing a C17 alpha-alkyl group do impair the excretion of conjugated bilirubin into the canaliculi. The degree of impairment is at least partly dose-related.[46] Progestins alone, in the dosages normally used in oral contraceptives, are less likely to produce this effect. However, it is seen when progestins are used in combination with estrogens.

Elevations of serum transaminase and alkaline phosphatase have also been reported with the use of OCs[47] and are generally considered due to

intracanalicular obstruction. Usually, these abnormalities revert to normal when oral contraception is discontinued.[48] Persistence of treatment is sometimes followed by a gradual return of the levels to a normal range.[42]

Parenchymal abnormalities

In women treated with OCs, changes in the endoplasmic reticulum and the mitochondria have been seen in liver biopsies examined by electron microscopy.[49] These changes are less marked in patients using combination OCs as opposed to sequentials, and are minimal and far less frequent when the subjects are given low-dose progestins alone.[50]

In animals, progesterone causes increases in liver weight, hepatic demethylation, hepatic microsomal protein content and urinary excretion of ascorbic acid.[51] Estrogen and diethylstilbestrol significantly reduce hepatic demethylation.[52]

The jaundice reported to occur in women using OCs resembles cholestatic jaundice of pregnancy, being relatively benign and transient, and showing similar biochemical changes. There is general agreement that most of the clinical and biochemical changes described are rapidly reversible, probably due to the generous reserve capacity of the liver.

Alterations in Common Clinical Laboratory Tests

The oral contraceptive pill causes alterations in some common clinical laboratory tests. Allowance for these effects must be made when interpreting results.

Liver function tests

Bromsulphthalein Retention Test (BSP)	Moderate increase
AST (SGOT) and GGT	Minor increase
Alkaline Phosphatase	Variable increase
Serum Bilirubin	Increased, particularly in conditions predisposing to or associated with hyperbilirubinemia

Thyroid function tests

Protein-bound Iodine (PBI)	Increased
Total Serum Thyroxine (T_4)	Increased
Thyroid Stimulating Hormone (TSH)	Unchanged

Adrenocortical function tests

Plasma Cortisol	Increased

Coagulation tests

Factors II, VII, IX, X, XII and XIII	Increased
Factor VIII	Mild increase

Platelet aggregation and adhesiveness	Mild increase in response to common aggregating agents
Fibrinogen	Increased
Plasminogen	Mild increase
Antithrombin III	Mild decrease
Prothrombin Time	Increased

Miscellaneous tests

Serum Folate	Occasionally decreased
Glucose Tolerance Test	Variable increase with return to normal after 6 to 12 months
Insulin Response	Mild to moderate increase
c-Peptide Response	Mild to moderate increase

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10. Premenstrual Syndrome and Oral Contraceptive Use

Premenstrual syndrome (PMS) has been defined as the recurrence, in the luteal phase of the menstrual cycle, of a combination of psychological and physical symptoms of sufficient severity to interfere with interpersonal relationships or normal activities.[1] PMS may represent more than one entity. Its etiology remains unclear; proposed factors include psychological bases, progesterone deficiency, prolactin excess, thyroid hypofunction, renin-angiotensin alterations, antidiuretic hormone excess, decreased colloid osmotic pressure, endorphin activity alterations, serotonin metabolism alterations, prostaglandin action and vitamin deficiency.[2-4]

Surveys of women in their reproductive years show the prevalence of reported PMS symptoms varies between 30 and 70 per cent.[2,4] Of these women, only 7 to 10 per cent seek medical attention, primarily for symptoms related to impaired social functioning and depression.[4-6]

The symptom complexes attributed to PMS are extensive yet can be divided into two groups, somatic and psychologic. Abraham and Hargrove [6] divided PMS into four groups according to the predominant symptom: anxiety/irritability, appetite changes, fluid retention and mastalgia, and depression. Reid and Yen [2] developed four patterns based on the timing of symptoms in relationship to phases of the menstrual cycle.

To simplify diagnosis, several inventory scales have been developed. The only reliable method to show cyclicity and evaluate the nature of symptoms is to use a prospective rating scale for at least two consecutive months.[7,8] There are as yet no screening or diagnostic physiologic markers available.

The use of oral contraceptives may modify or eliminate ovarian cyclicity. Whether OCs have a role in PMS treatment is questionable. Early studies on OCs containing estrogen in excess of 50 μg showed no benefit over placebo [9,10] but low-dose monophasic or multiphasic agents have not been fully evaluated. Oral contraceptives have shown a wide variation in effect from relief of mild symptoms, limitation of symptoms and no change, to worsening of symptoms.[11,12]

Graham and Sherwin at McGill studied 250 women aged 18 to 45 years to assess the degree and type of premenstrual changes reported by OC users and non-users. The Premenstrual Assessment Form (PAF), a 95-item retrospective questionnaire, was administered to women attending general health and gynecology clinics. Women using low-dose OCs had similar symptoms and severity of symptoms compared to non-users, but the OC group reported a shorter duration of symptoms with changes beginning closer to the onset of menses. Scores in PAF

subscales of premenstrual anxiety, fatigue, low mood, water retention and impaired social functioning were significantly lower for OC users.[5]

Patterns of menstrual cycle-related changes were compared in three groups of women using either triphasic OCs, monophasic OCs or non-hormonal contraception. Most of the women studied had mild to moderate symptoms. The monophasic group showed a tendency to "menstrual" instead of "premenstrual" symptoms. This group also reported significantly less breast tenderness than the other two groups.[13] There is evidence to suggest that women with severe PMS may receive no benefit from OCs[3] or may be more susceptible to adverse reactions.[14]

A low-dose oral contraceptive, monophasic or triphasic, may be prescribed for mild to moderate PMS; the duration of symptoms is usually reduced. However, in women with severe PMS, OCs seem to have no effect or to worsen symptoms. Medical and surgical modalities, other than OCs, are available for amelioration of moderate to severe PMS.[15-22]

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Appendix

Methods of Assessing the Efficacy and Undesirable Effects of Oral Contraceptives

Contraceptive methods can be assessed and compared in three ways:

1. Analysis of fertility, morbidity and mortality rates in different populations in relation to the use of various contraceptives.

These methods are often inconclusive because of the many confounding variables and the absence of accurate estimates of contraceptive usage.

2. Cohort studies in which the fertility, morbidity and mortality rates of large groups in relation to the use of various contraceptives are studied.

This approach has been used in the assessment of the efficacy of contraceptive techniques for several decades. The traditional method of estimating failure rates has been to use the Pearl Index:

Pregnancy rate per 100 women-years = $P \times 1{,}200/M$

where P = number of pregnancies
M = aggregate of all months of exposure by couples included in the investigation

One flaw in this formula is that it takes no account of the change in risk with duration of use of the contraceptive.[1] It tacitly assumes that the experience of 100 women observed for one year can be compared with that of 50 women observed for two years or 200 women observed for six months. This is unlikely to be true. The type of woman who abandons a particular contraceptive method after a few months is likely to experience a higher failure rate than one who uses the technique consistently for several years.

Alternate, more valid methods of analysis of cohort data are based upon life-table techniques.[2] These methods can be applied in various ways to assess the risk of failure for different reasons, either as single risks (gross) or competing risks (net).[3] Clinical trials of contraceptives have shown a close agreement between the Pearl Index and a cumulative 12-month life-table pregnancy rate. In the early stages of these clinical trials, the Pearl Index seemed superior to the short-term life-table.[4]

The chief disadvantage of the cohort approach is the large number of women required in the study to obtain precise estimates. For the assessment of efficacy, this is not an overriding disadvantage, but for estimating the risk of rare life-threatening side effects, the numbers required are impracticable. The problem of confounding factors is often acute in cohort studies where the necessary data may not always be collected.

3. Case-control studies.

These are often used as a substitute for the more precise cohort studies when the latter are not feasible.[5] Case-control studies are valuable for the study of rare events, which is often the case when examining side effects of oral contraceptives. In the context of contraception, the method involves recording the number of patients with the side effect in question and comparing with matched controls. The proportion of each group, cases and controls, that has used a particular contraceptive is determined.

The risk of the side effect among users compared to non-users is estimated by:

$$R = \frac{\text{(cases: users)} \times \text{(controls: non-users)}}{\text{(cases: non-users)} \times \text{(controls: users)}}$$

Assume, for example, that 200 affected patients had used the contraceptive method believed to be a factor, and that 150 had not done so, while 35 controls had used the method, and 315 had not. The relative risk is then:

$$R = \frac{200 \times 315}{150 \times 35} = 12$$

The major advantage of this method is that relatively small numbers of patients and controls can provide significant results. The chief difficulty with the case-control method is the choice of controls. However, in modern case-control studies, considerable care is taken to collect data on confounding variables, and therefore confounding is often better handled than in cohort designs.[6,7]

Most studies of the comparative efficacy and side effects of contraceptives are necessarily of the observational type where the choice of contraceptive technique for a particular woman has involved conscious selection by the physician and/or the woman herself. It is seldom feasible to mount an experiment in which women are assigned at random to one of two or more contraceptive methods. Lacking such random allocations, the interpretation of observed differences must always be cautious, and the effect of known selective factors allowed for in the analysis wherever possible.

Since it is very difficult to distinguish between so-called "method failure" and "patient failure", the assessment of efficacy should be based upon the total pregnancy rate. In designing comparative studies, the numbers of patients included should be sufficient to detect clinically important differences in efficacy or the incidence of side effects at conventional levels of statistical significance. The required sample size must be calculated in advance for any given study.

Summary

The most efficient method of assessing the efficacy and side effects of a contraceptive is a cohort study analyzed by life-table techniques. For rare side effects, where cohort studies are impracticable, a case-control comparison provides a feasible alternative. Whatever method is used, the numbers studied should be sufficiently large to detect important differences with reasonable confidence. Particularly without random treatment, consideration must be given, in both design and analysis, to variables other than treatment that may confound the result.

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Drugs Directorate Guidelines

Directions for Use of Estrogen-Progestin Combination Oral Contraceptives (OCs)

Patient Package Insert for Patients Using Oral Contraceptives (Birth Control Pills)

Supplementary Information Booklet for Patients Considering the Use of Oral Contraceptives (Birth Control Pills)

These guidelines were derived from a report (*Oral Contraceptives 1994*) prepared by the Special Advisory Committee on Reproductive Physiology to the Health Protection Branch. They have been prepared for manufacturers of oral contraceptives. The guidelines are not intended to be exhaustive or inflexible. Within the framework provided, appropriate adaptation may be made according to the type of drug product and the data available.

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Directions for Use of Estrogen-Progestin Combination Oral Contraceptives (OCs)

1 Indications

"Prevention of Pregnancy" or "Conception Control" – for low dose products containing less than 50 µg of estrogen.

For products containing 50 µg of estrogen, the indication should be limited to the statement "For conception control in circumstances where low-dose estrogen formulations prove to be unacceptable", such as breakthrough bleeding or concurrent medication that may alter OC metabolism or absorption.

For products containing more than 50 µg of estrogen, the indications should be limited to uses other than contraception such as dysfunctional uterine bleeding.

2 Contraindications

1. History of or actual thrombophlebitis or thromboembolic disorders.
2. History of or actual cerebrovascular disorders.
3. History of or actual myocardial infarction or coronary arterial disease.
4. Active liver disease or history of or actual benign or malignant liver tumours.
5. Known or suspected carcinoma of the breast.
6. Known or suspected estrogen- dependent neoplasia.
7. Undiagnosed abnormal vaginal bleeding.
8. Any ocular lesion arising from ophthalmic vascular disease, such as partial or complete loss of vision or defect in visual fields.
9. When pregnancy is suspected or diagnosed.

3 Warnings

3.1 Predisposing Factors for Coronary Artery Disease

Cigarette smoking increases the risk of serious cardiovascular side effects and mortality. Birth control pills increase this risk, especially with increasing age. Convincing data are available to support an upper age limit of 35 years for oral contraceptive use by women who smoke.

Other women who are independently at high risk for cardiovascular disease include those with diabetes, hypertension, abnormal lipid profile, or a family history of these. Whether OCs accentuate this risk is unclear.

In low-risk, non-smoking women of any age, the benefits of oral contraceptive use outweigh the possible cardiovascular risks associated with low-dose formulations. Consequently, oral contraceptives may be prescribed for these women up to the age of menopause.

Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels. This risk increases with age and becomes significant in OC users older than 35 years of age. Women should be counselled not to smoke.

3.2 Discontinue Medication at the Earliest Manifestation of the following:

3.2.1 Thromboembolic and Cardiovascular Disorders such as Thrombophlebitis, pulmonary embolism, cerebrovascular disorders, myocardial ischemia, mesenteric thrombosis, and retinal thrombosis.

3.2.2 Conditions that Predispose to Venous Stasis and to Vascular Thrombosis (e.g. immobilization after accidents or confinement to bed during long-term illness). Other non-hormonal methods of contraception should be used until regular activities are resumed. For use of oral contraceptives when surgery is contemplated, see **PRECAUTIONS** (page 79).

3.2.3 Visual Defects – Partial or Complete

3.2.4 Papilledema or Ophthalmic Vascular Lesions

3.2.5 Severe Headache of Unknown Etiology or Worsening of Pre-existing Migraine Headache

4 Precautions

4.1 Physical Examination and Follow-up

Before oral contraceptives are used, a thorough history and physical examination should be performed, including a blood pressure determination. Breasts, liver, extremities and pelvic organs should be examined and a Papanicolaou smear should be taken if the patient has been sexually active.

The first follow-up visit should be three months after oral contraceptives are prescribed. Thereafter, examinations should be performed at least once a year or more frequently if indicated. At each annual visit, examination should include those procedures that were done at the initial visit as outlined above or per recommendations of the Canadian Workshop on Screening for Cancer of the Cervix. Their suggestion was that, for women who had two consecutive negative Pap smears, screening could be continued every three years to the age of 69.

4.2 Pregnancy

Oral contraceptives should not be taken by pregnant women. However, if conception accidentally occurs while taking the pill, there is no conclusive evidence that the estrogen and progestin contained in the oral contraceptive will damage the developing child.

4.3 Breast-feeding

In breast-feeding women, the use of oral contraceptives results in the hormonal components being excreted in breast milk and may reduce its quantity and quality. If the use of oral contraceptives is initiated after the establishment of lactation, there does not appear to be any effect on the quantity and quality of the milk. There is no evidence that low-dose OCs are harmful to the nursing infant.

4.4 Hepatic Function

Patients who have had jaundice, including a history of cholestatic jaundice during pregnancy, should be given oral contraceptives with great care and under close observation.

The development of severe generalized pruritus or icterus requires that the medication be withdrawn until the problem is resolved.

If a patient develops jaundice that proves to be cholestatic in type, the use of oral contraceptives should not be resumed. In patients taking oral contraceptives, changes in the composition of the bile may occur and an increased incidence of gallstones has been reported.

Hepatic nodules (adenoma and focal nodular hyperplasia) have been reported, particularly in long-term users of oral contraceptives. Although these lesions are extremely rare, they have caused fatal intra-abdominal hemorrhage and should be considered in women with an abdominal mass, acute abdominal pain, or evidence of intra-abdominal bleeding.

4.5 Hypertension

Patients with essential hypertension whose blood pressure is well-controlled may be given oral contraceptives but only under close supervision. If a significant elevation of blood pressure in previously normotensive or hypertensive subjects occurs at any time during the administration of the drug, cessation of medication is necessary.

4.6 Migraine and Headache

The onset or exacerbation of migraine or the development of headache of a new pattern that is recurrent, persistent or severe, requires discontinuation of oral contraceptives and evaluation of the cause.

4.7 Diabetes

Current low-dose OCs exert minimal impact on glucose metabolism. Diabetic patients, or those with a family history of diabetes, should be observed closely to detect any worsening of carbohydrate metabolism. Patients predisposed to diabetes who can be kept under close supervision may be given oral contraceptives. Young diabetic patients whose disease is of recent origin, well-controlled, and not associated with hypertension or other signs of vascular disease such as ocular fundal changes, should be monitored more frequently while using oral contraceptives.

4.8 Ocular Disease

Patients who are pregnant or are taking oral contraceptives, may experience corneal edema that may cause visual disturbances and changes in tolerance to contact lenses, especially of the rigid type. Soft contact lenses usually do not cause disturbances. If visual changes or alterations in tolerance to contact lenses occur, temporary or permanent cessation of wear may be advised.

4.9 Breasts

Increasing age and a strong family history are the most significant risk factors for the development of breast cancer. Other established risk factors include obesity, nulliparity and late age for first full-term pregnancy. The identified groups of women that may be at increased risk of developing breast cancer before menopause are long-term users of oral contraceptives (more than eight years) and

starters at early age. In a few women, the use of oral contraceptives may accelerate the growth of an existing but undiagnosed breast cancer. Since any potential increased risk related to oral contraceptive use is small, there is no reason to change prescribing habits at present.

Women receiving oral contraceptives should be instructed in self-examination of their breasts. Their physicians should be notified whenever any masses are detected. A yearly clinical breast examination is also recommended because, if a breast cancer should develop, drugs that contain estrogen may cause a rapid progression.

4.10 Vaginal Bleeding

Persistent irregular vaginal bleeding requires assessment to exclude underlying pathology.

4.11 Fibroids

Patients with fibroids (leiomyomata) should be carefully observed. Sudden enlargement, pain, or tenderness requires discontinuation of the use of OCs.

4.12 Emotional Disorders

Patients with a history of emotional disturbances, especially the depressive type, may be more prone to have a recurrence of depression while taking oral contraceptives. In cases of a serious recurrence, a trial of an alternate method of contraception should be made, which may help to clarify the possible relationship. Women with premenstrual syndrome (PMS) may have a varied response to oral contraceptives, ranging from symptomatic improvement to worsening of the condition.

4.13 Laboratory Tests

Results of laboratory tests should be interpreted in the light that the patient is on OCs. The following laboratory tests are modified.

4.13.1 Liver Function Tests

Bromsulphthalein Retention Test (BSP)	Moderate increase
AST (SGOT) and GGT	Minor increase
Alkaline Phosphatase	Variable increase
Serum Bilirubin	Increased, particularly in conditions predisposing to or associated with hyperbilirubinemia

4.13.2 Coagulation Tests

Factors II, VII, IX, X, XII and XIII	Increased
Factor VIII	Mild increase
Platelet aggregation and adhesiveness	Mild increase in response to common aggregating agents
Fibrinogen	Increased
Plasminogen	Mild increase
Antithrombin III	Mild decrease
Prothrombin Time	Increased

4.13.3 Thyroid Function Tests

Protein-bound Iodine (PBI)	Increased
Total Serum Thyroxine (T_4)	Increased
Thyroid Stimulating Hormone (TSH)	Unchanged

4.13.4 Adrenocortical function tests

Plasma Cortisol	Increased

4.13.5 Miscellaneous Tests

Serum Folate	Occasionally decreased
Glucose Tolerance Test	Variable increase with return to normal after 6 to 12 months
Insulin Response	Mild to moderate increase
c-Peptide Response	Mild to moderate increase

4.14 Tissue Specimens

Pathologists should be advised of oral contraceptive therapy when specimens obtained from surgical procedures and Pap smears are submitted for examination.

4.15 Return to Fertility

After discontinuing oral contraceptive therapy, the patient should delay pregnancy until at least one normal spontaneous cycle has occurred in order to date the pregnancy. An alternate contraceptive method should be used during this time.

4.16 Amenorrhea

Women having a history of oligomenorrhea, secondary amenorrhea, or irregular cycles may remain anovulatory or become amenorrheic following discontinuation of estrogen-progestin combination therapy.

Amenorrhea, especially if associated with breast secretion, that continues for six months or more after withdrawal, warrants a careful assessment of hypothalamic-pituitary function.

4.17 *Thromboembolic Complications – Post-surgery*

There is an increased risk of thromboembolic complications in oral contraceptive users after major surgery. If feasible, oral contraceptives should be discontinued and an alternative method substituted at least one month prior to **major** elective surgery. Oral contraceptive use should not be resumed until the first menstrual period after hospital discharge following surgery.

4.18 *Drug Interactions*

The concurrent administration of oral contraceptives with other drugs may result in an altered response to either agent. Reduced effectiveness of the oral contraceptive, should it occur, is more likely with the low-dose formulations. It is important to ascertain all drugs that a patient is taking, both prescription and non-prescription, before oral contraceptives are prescribed.

Refer to *Oral Contraceptives 1994* (Chapter 8), Health Canada, for possible drug interactions with OCs.

Table *:
Drugs that May Decrease the Efficacy of Oral Contraceptives

Class of Compound	Drug	Proposed Mechanism	Suggested Management
Anticonvulsants	Carbamazepine Ethosuximide Phenobarbital Phenytoin Primidone	Induction of hepatic microsomal enzymes. Rapid metabolism of estrogen and increased binding of progestin and ethinyl estradiol to SHBG.	Use higher dose OCs (50 µg ethinyl estradiol), another drug or another method.
Antibiotics	Ampicillin Cotrimoxazole Penicillin	Enterohepatic circulation disturbance, intestinal hurry.	For short course, use additional method or use another drug. For long course, use another method.
	Rifampin	Increased metabolism of progestins. Suspected acceleration of estrogen metabolism.	Use another method.
	Chloramphenicol Metronidazole Neomycin Nitrofurantoin Sulfonamides Tetracyclines	Induction of hepatic microsomal enzymes. Also disturbance of enterohepatic circulation.	For short course, use additional method or use another drug. For long course, use another method.
	Troleandomycin	May retard metabolism of OCs, increasing the risk of cholestatic jaundice.	
Antifungals	Griseofulvin	Stimulation of hepatic metabolism of contraceptive steroids may occur.	Use another method.
Cholesterol Lowering Agents	Clofibrate	Reduces elevated serum triglycerides and cholesterol; this reduces OC efficacy.	Use another method.
Sedatives and Hypnotics	Benzodiazepines Barbiturates Chloral Hydrate Glutethimide Meprobamate	Induction of hepatic microsomal enzymes.	For short course, use additional method or another drug. For long course, use another method or higher dose OCs.
Antacids		Decreased intestinal absorption of progestins.	Dose two hours apart.
Other Drugs	**Phenylbutazone **Antihistamines **Analgesics **Antimigraine **Preparations Vitamin E	Reduced OC efficacy has been reported. Remains to be confirmed.	

* Adapted from Dickey, R.P., ed.: *Managing Contraceptive Pill Patients*, 5th edition Creative Informatics Inc., Durant, OK, 1987.
** Refer to previous text on page 31.

Table *:
Modification of Other Drug Action by Oral Contraceptives

Class of Compound	Drug	Modification of Drug Action	Suggested Management
Alcohol		Possible increased levels of ethanol or acetaldehyde.	Use with caution.
Alpha-II Adrenoreceptor Agents	Clonidine	Sedation effect increased.	Use with caution.
Anticoagulants	All	OCs increase clotting factors, decrease efficacy. However, OCs may potentiate action in some patients.	Use another method.
Anticonvulsants	All	Fluid retention may increase risk of seizures.	Use another method.
Antidiabetic Drugs	Oral Hypoglycemics and Insulin	OCs may impair glucose tolerance and increase blood glucose.	Use low-dose estrogen and progestin OC or another method. Monitor blood glucose.
Antihypertensive Agents	Guanethidine and Methyldopa	Estrogen component causes sodium retention, progestin has no effect.	Use low-dose estrogen OC or use another method.
	Beta Blockers	Increased drug effect (decreased metabolism).	Adjust dose of drug if necessary. Monitor cardiovascular status.
Antipyretics	Acetaminophen	Increased metabolism and renal clearance.	Dose of drug may have to be increased.
	Antipyrine	Impaired metabolism.	Decrease dose of drug.
	ASA	Effects of ASA may be decreased by the short-term use of OCs.	Patients on chronic ASA therapy may require an increase in ASA dosage.
Aminocaproic Acid		Theoretically, a hypercoagulable state may occur because OCs augment clotting factors.	Avoid concomitant use.
Betamimetic Agents	Isoproterenol	Estrogen causes decreased response to these drugs.	Adjust dose of drug as necessary. Discontinuing OCs can result in excessive drug activity.

* Adapted from Dickey, R.P., ed.: *Managing Contraceptive Pill Patients*, 5th edition, Creative Informatics Inc., Durant, OK, 1987.

Table (concluded): Modification of Other Drug Action by Oral Contraceptives

Class of Compound	Drug	Modification of Drug Action	Suggested Management
Caffeine		The actions of caffeine may be enhanced as OCs may impair the hepatic metabolism of caffeine.	Use with caution.
Cholesterol Lowering Agents	Clofibrate	Their action may be antagonized by OCs. OCs may also increase metabolism of clofibrate.	May need to increase dose of clofibrate.
Corticosteroids	Prednisone	Markedly increased serum levels.	Possible need for decrease in dose.
Cyclosporine		May lead to an increase in cyclosporine levels and hepatotoxicity.	Monitor hepatic function. The cyclosporine dose may have to be decreased.
Folic Acid		OCs have been reported to impair folate metabolism.	May need to increase dietary intake, or supplement.
Meperidine		Possible increased analgesia and CNS depression due to decreased metabolism of meperidine.	Use combination with caution.
Phenothiazine Tranquilizers	All Phenothiazines, Reserpine and similar drugs	Estrogen potentiates the hyper-prolactinemia effect of these drugs.	Use other drugs or lower dose OCs. If galactorrhea or hyper-prolactinemia occurs, use other method.
Sedatives and Hypnotics	Chlordiazepoxide Lorazepam Oxazepam Diazepam	Increased effect (increased metabolism).	Use with caution.
Theophylline	All	Decreased oxidation, leading to possible toxicity.	Use with caution. Monitor theophylline levels.
Tricyclic Antidepressants	Clomipramine (possibly others)	Increased side effects: i.e., depression.	Use with caution.
Vitamin B_{12}		OCs have been reported to reduce serum levels of Vitamin B_{12}.	May need to increase dietary intake, or supplement.

5 Non-Contraceptive Benefits of Oral Contraceptives

Several health advantages other than contraception have been reported.

- Combination oral contraceptives reduce the incidence of cancer of the endometrium and ovaries.
- Oral contraceptives reduce the likelihood of developing benign breast disease.
- Oral contraceptives reduce the likelihood of development of functional ovarian cysts.
- Pill users have less menstrual blood loss and have more regular cycles, thereby reducing the chance of developing iron-deficiency anemia.
- The use of oral contraceptives may decrease the severity of dysmenorrhea and premenstrual syndrome, and may improve acne vulgaris, hirsutism, and other androgen-mediated disorders.
- Other non-contraceptive benefits are outlined in *Oral Contraceptives 1994*, Health Canada.

Oral contraceptives **do not protect** against sexually transmitted diseases including HIV/AIDS. For protection against STDs, it is advisible to use latex condoms **in combination with** oral contraceptives.

6 Adverse Reactions

An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives:

- Thrombophlebitis
- Pulmonary embolism
- Mesenteric thrombosis
- Neuro-ocular lesions (e.g. retinal thrombosis)
- Myocardial infarction
- Cerebral thrombosis
- Cerebral hemorrhage
- Hypertension
- Benign hepatic tumours
- Gallbladder disease

The following adverse reactions also have been reported in patients receiving oral contraceptives:

Nausea and vomiting, usually the most common adverse reaction, occurs in approximately 10 per cent or fewer of patients during the first cycle. Other reactions, as a general rule, are seen less frequently or only occasionally.

Other adverse reactions are to be listed by the manufacturer.

Package Insert for Patients Using Oral Contraceptives (Birth Control Pills)

A supplementary information booklet that describes the benefits and risks of taking birth control pills (oral contraceptives) is available from your doctor or pharmacist. Be sure to obtain a copy and read it carefully before you start taking these pills.

(*Product Name*) is a birth control pill (oral contraceptive) that contains two female sex hormones *(give names and dosages)*. It has been shown to be highly effective in preventing pregnancy when taken as prescribed by your doctor. Pregnancy is always more risky than taking birth control pills, except in smokers older than age 35.

The birth control pill is not suitable for every woman. In a small number of women, serious side effects may occur. Your doctor can advise you if you have any conditions that would pose a risk to you. The use of the birth control pill always should be supervised by your doctor.

You should not use birth control pills if you have or have had any of the following conditions:

- unusual vaginal bleeding that has not yet been diagnosed;
- blood clots in the legs, lungs, eyes, or elsewhere;
- a stroke, heart attack, or chest pain (angina pectoris);
- known or suspected cancer of the breast or sex organs;
- a liver tumour associated with the use of the pill or other estrogen-containing products; and/or
- jaundice or liver disease if still present.

The pill should not be taken if you are pregnant or if pregnancy is suspected.

If you decide to take birth control pills

If you and your doctor decide that, for you, the benefits of birth control pills outweigh the risks, you should be aware of the following:

1. Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels. This risk increases with age and becomes significant in birth control pill users over 35 years of age. Women should not smoke.

2. Take the pills only on the advice of your doctor and carefully follow all directions given to you. You must take the pills exactly as prescribed. Otherwise, you may become pregnant.

3. Visit your doctor three months or sooner after the initial examination. Afterward, visit your doctor at least once a year.

4. Be alert for the following symptoms and signs of serious adverse effects. Call your doctor immediately if they occur:

- sharp pain in the chest, coughing blood, or sudden shortness of breath. These symptoms could indicate a possible blood clot in the lung;
- pain in the calf. This symptom could indicate a possible blood clot in the leg;
- crushing chest pain or heaviness. This symptom could indicate a possible heart attack;
- sudden severe or worsening headache or vomiting, dizziness or fainting, disturbance of vision or speech, or weakness or numbness in an arm or leg. These symptoms could indicate a possible stroke;
- sudden partial or complete loss of vision. This symptom could indicate a possible blood clot in the eye;
- severe pain or lump in the abdomen. These symptoms could indicate a possible tumour of the liver;
- severe depression;
- yellowing of the skin (jaundice);
- unusual swelling of the extremities; and/or
- breast lumps. **ASK YOUR DOCTOR FOR ADVICE AND INSTRUCTION ON REGULAR SELF-EXAMINATION OF YOUR BREASTS.**

5. Birth control pills should never be taken if you think you are pregnant. They will not prevent the pregnancy from continuing.

6. You will have a menstrual period when you stop taking birth control pills. You should delay pregnancy until another menstrual period occurs within four to six weeks. Contact your doctor for recommendations on alternative methods of contraception during this time.
7. Your doctor will advise you of the appropriate time to start the use of birth control pills after childbirth, miscarriage, or therapeutic abortion.
8. The hormones in birth control pills are known to appear in breast milk. These hormones may decrease the flow of breast milk. If birth control pills are not resumed until nursing is established, however, the quantity and quality of breast milk does not seem to be affected. There is no evidence that birth control pills are harmful to the nursing infant.
9. Should you require **MAJOR** surgery, inform your surgeon that you are using birth control pills.
10. **If you see a different doctor, inform him or her that you are taking birth control pills.** Tell the doctor that your birth control pills are *(Product Name).*

11. **Inform your doctor if you are taking or if you start to take other medications.** This applies to both prescription and non-prescription drugs. These medications may change the effectiveness and/or cycle control of your birth control pills. **You may need to use a back-up method of birth control.**

12. **THERE IS NO NEED TO STOP TAKING BIRTH CONTROL PILLS FOR A REST PERIOD.**

13. Birth control pills **DO NOT PROTECT** against sexually transmitted diseases (STDs), including HIV/AIDS. For protection against STDs, it is advisable to use latex condoms **IN COMBINATION WITH** birth control pills.

HOW TO TAKE BIRTH CONTROL PILLS

1. **READ THESE DIRECTIONS**
- before you start taking your pills, and
- any time you are not sure what to do.

2. **LOOK AT YOUR PILL PACK** to see if it has 21 or 28 pills:
- **21-Pill Pack:** 21 active pills (with hormones) taken daily for three weeks, and then no pills taken for one week or
- **28-Pill Pack:** 21 active pills (with hormones) taken daily for three weeks, and then seven "reminder" pills (no hormones) taken daily for one week.

ALSO CHECK: *Note to manufacturers: Place a picture of the pill pack here, showing: 1) where to start, 2) direction to take pills in, and 3) week numbers*

3. You may wish to use a second method of birth control (e.g. latex condoms and spermicidal foam or gel) for the first seven days of the first cycle of pill use. This will provide a back-up in case pills are forgotten while you are getting used to taking them.

4. **When receiving any medical treatment, be sure to tell your doctor that you are using birth control pills.**

5. **MANY WOMEN HAVE SPOTTING OR LIGHT BLEEDING, OR MAY FEEL SICK TO THEIR STOMACH DURING THE FIRST THREE MONTHS ON THE PILL.** If you do feel sick, do not stop taking the pill. The problem will usually go away. If it does not go away, check with your doctor or clinic.

6. **MISSING PILLS ALSO CAN CAUSE SOME SPOTTING OR LIGHT BLEEDING,** even if you make up the missed pills. You also could feel a little sick to your stomach on the days you take two pills to make up for missed pills.

7. **IF YOU MISS PILLS AT ANY TIME, YOU COULD GET PREGNANT. THE GREATEST RISKS FOR PREGNANCY ARE:**
- when you start a pack late, or
- when you miss pills at the beginning or at the very end of the pack.

8. **ALWAYS BE SURE YOU HAVE READY:**
- **ANOTHER KIND OF BIRTH CONTROL** (such as latex condoms and spermicidal foam or gel) to use as a back-up in case you miss pills, and
- **AN EXTRA, FULL PACK OF PILLS.**

9. **IF YOU EXPERIENCE VOMITING OR DIARRHEA, OR IF YOU TAKE CERTAIN MEDICINES,** such as antibiotics, your pills may not work as well. Use a back-up method, such as latex condoms and spermicidal foam or gel, until you can check with your doctor or clinic.

10. **IF YOU FORGET MORE THAN ONE PILL TWO MONTHS IN A ROW,** talk to your doctor or clinic about how to make pill-taking easier or about using another method of birth control.

11. **IF YOUR QUESTIONS ARE NOT ANSWERED HERE, CALL YOUR DOCTOR OR CLINIC.**

WHEN TO START THE *FIRST* PACK OF PILLS BE SURE TO READ THESE INSTRUCTIONS:

- before you start taking your pills, and
- any time you are not sure what to do.

Decide with your doctor or clinic what is the best day for you to start taking your first pack of pills. Your pills may be either a 21-day or a 28-day type.

Manufacturer's diagram here

A. 21-DAY COMBINATION

With this type of birth control pill, you are on pills for 21 days and off pills for seven days. You must not be off the pills for more than seven days in a row.

1. **THE FIRST DAY OF YOUR MENSTRUAL PERIOD (BLEEDING) IS DAY 1 OF YOUR CYCLE.** Your doctor may advise you to start taking the pills on Day 1, on Day 5, or on the first Sunday after your period begins. If your period starts on Sunday, start that same day.
2. Take one pill at approximately the same time every day for 21 days, **THEN TAKE NO PILLS FOR SEVEN DAYS.** Start a new pack on the eighth day. You will probably have a period during the seven days off the pill. (This bleeding may be lighter and shorter than your usual period.)

B. 28-DAY COMBINATION

With this type of birth control pill, you take 21 pills that contain hormones and seven pills that contain no hormones.

1. **THE FIRST DAY OF YOUR MENSTRUAL PERIOD (BLEEDING) IS DAY 1 OF YOUR CYCLE.** Your doctor may advise you to start taking the pills on Day 1, on Day 5, or on the first Sunday after your period begins. If your period starts on Sunday, start that same day.
2. Take one pill at approximately the same time every day for 28 days. Begin a new pack the next day, **NOT MISSING ANY DAYS.** Your period should occur during the last seven days of using that pill pack.

WHAT TO DO DURING THE MONTH

1. **TAKE A PILL AT APPROXIMATELY THE SAME TIME EVERY DAY UNTIL THE PACK IS EMPTY.**

- Try to associate taking your pill with some regular activity such as eating a meal or going to bed.
- Do not skip pills even if you have bleeding between monthly periods or feel sick to your stomach (nausea).
- Do not skip pills even if you do not have sex very often.

2. **WHEN YOU FINISH A PACK**

- **21 PILLS**
  WAIT SEVEN DAYS to start the next pack. You will have your period during that week.
- **28 PILLS**
  Start the next pack **ON THE NEXT DAY.** Take one pill every day. Do not wait any days between packs.

WHAT TO DO IF YOU MISS PILLS

The following outlines the actions you should take if you miss one or more of your birth control pills. Match the number of pills missed with the appropriate starting time for your type of pill pack.

SUNDAY START

Miss One Pill

Take it as soon as you remember and take the next pill at the usual time. This means that you might take two pills in one day.

Miss Two Pills in a Row

First two weeks

1. Take two pills the day you remember and two pills the next day.
2. Then take one pill a day until you finish the pack.
3. Use a back-up method of birth control if you have sex in the seven days after you miss the pills.

Third Week

1. Keep taking one pill a day until Sunday.
2. On Sunday, safely discard the rest of the pack and start a new pack that day.
3. Use a back-up method of birth control if you have sex in the seven days after you miss the pills.
4. You may not have a period this month.

If You Miss Two Periods in a Row, Call Your Doctor or Clinic.

Miss Three or More Pills in a Row

Anytime in the cycle

1. Keep taking one pill a day until Sunday.
2. On Sunday, safely discard the rest of the pack and start a new pack that day.
3. Use a back-up method of birth control if you have sex in the seven days after you miss the pills.
4. You may not have a period this month.

If You Miss Two Periods in a Row, Call Your Doctor or Clinic.

NOTE: 28-DAY PACK – If you forget any of the seven "reminder" pills (without hormones) in Week 4, just safely dispose of the pills you missed. Then keep taking one pill each day until the pack is empty. You do not need to use a back-up method.

OTHER THAN SUNDAY START

Miss One Pill

Take it as soon as you remember, and take the next pill at the usual time. This means that you might take two pills in one day.

Miss Two Pills in a Row

First two weeks

1. Take two pills the day you remember and two pills the next day.
2. Then take one pill a day until you finish the pack.
3. Use a back-up method of birth control if you have sex in the seven days after you miss the pills.

Third Week

1. Safely dispose of the rest of the pill pack and start a new pack that same day.
2. Use a back-up method of birth control if you have sex in the seven days after you miss the pills.
3. You may not have a period this month.

If You Miss Two Periods in a Row, Call Your Doctor or Clinic.

Miss Three or More Pills in a Row

Anytime in the cycle

1. Safely dispose of the rest of the pill pack and start a new pack that same day.
2. Use a back-up method of birth control if you have sex in the seven days after you miss the pills.
3. You may not have a period this month.

If You Miss Two Periods in a Row, Call Your Doctor or Clinic.

NOTE: 28-DAY PACK – If you forget any of the seven "reminder" pills (without hormones) in Week 4, just safely dispose of the pills you missed. Then keep taking one pill each day until the pack is empty. You do not need to use a back-up method.

Always be sure you have on hand
- a back-up method of birth control (such as latex condoms and spermicidal foam or gel) in case you miss pills, and
- an extra, full pack of pills.

IF YOU FORGET MORE THAN ONE PILL TWO MONTHS IN A ROW, TALK TO YOUR DOCTOR OR CLINIC about ways to make pill-taking easier or about using another method of birth control.

Supplementary Information Booklet for Patients Considering the Use of Oral Contraceptives (Birth Control Pills)

Introduction

This booklet will give you information to make an informed choice on the use of oral contraceptives. Oral contraceptives are also known as birth control pills or "the pill."

You should read this booklet if you are thinking about any method of birth control. If you have decided to take birth control pills, this booklet will help you understand both the risks and the benefits. It also will give you information on how to use birth control pills.

When taken as directed, birth control pills are a very effective way to prevent pregnancy. Only sterilization is more effective. The pill is convenient and has many benefits other than birth control. Most women do not develop serious and unpleasant side effects from using birth control pills.

The pill has important advantages over other methods of birth control. It also has certain risks that no other method has. Your doctor is the best person to explain the consequences of any possible risks.

You can help your doctor prescribe birth control pills as safely as possible. Tell your doctor about yourself, and be alert for the earliest signs of possible trouble.

Read this booklet carefully and discuss its contents with your doctor.

Types of birth control pills

There are two types of birth control pills:

1. The "combination pill" is the most common type. It contains two female sex hormones – an estrogen and a progestin. The amounts and types of estrogen and progestin differ from one preparation to another. The amount of estrogen is more important. The effectiveness and some dangers of birth control pills are related mainly to the amount of estrogen.
2. The "mini-pill" is the second type. It contains only one female sex hormone – a progestin.

How birth control pills work

Birth control pills work in two ways:

1. They inhibit the monthly release of an egg by the ovaries.
2. They change the mucus produced by the cervix. This slows the movement of the sperm through the mucus and through the uterus (womb).

Effectiveness of birth control pills

Combination birth control pills are more than 99 per cent effective in preventing pregnancy when

- the pill is **TAKEN AS DIRECTED**, and
- the amount of estrogen is 20 micrograms or more.

A 99 per cent effectiveness rate means that if 100 women used birth control pills for one year, one woman in the group would get pregnant.

The mini-pill (progestin only) is slightly less effective than combination birth control pills.

Other ways to prevent pregnancy

Other methods of birth control are available to you. They are usually less effective than birth control pills. Used properly, however, other methods of birth control are effective enough for many women.

The following table gives reported pregnancy rates for various forms of birth control, including no birth control. The reported rates represent the number of women out of 100 who would become pregnant in one year.

Reported Pregnancies per 100 Women per Year

Combination pill	less than 1 to 2
Intrauterine device (IUD)	less than 1 to 6
Condom with spermicidal foam or gel	1 to 6
Mini-pill	3 to 6
Condom	2 to 12
Diaphragm with spermicidal foam or gel	3 to 18
Spermicide	3 to 21
Sponge with spermicide	3 to 28
Cervical cap with spermicide	5 to 18
Periodic abstinence (rhythm), all types	2 to 20
No birth control	60 to 85

Pregnancy rates vary widely because people differ in how carefully and regularly they use each method. (This does not apply to IUDs since they are implanted in the uterus.) Regular users may achieve pregnancy rates in the lower ranges. Others may expect pregnancy rates more in the middle ranges.

The effective use of birth control methods other than birth control pills and IUDs requires more effort than taking a single pill every day. It is an effort that many couples undertake successfully.

Who should not use birth control pills

You should not use birth control pills if you have or have had any of the following conditions:

- unusual vaginal bleeding that has not yet been diagnosed;
- blood clots in the legs, lungs, eyes, or elsewhere;
- a stroke, heart attack or chest pain (angina pectoris);
- known or suspected cancer of the breast or sex organs;
- liver tumour associated with the use of birth control pills or other estrogen-containing products; and/or
- jaundice or liver disease if still present.

The pill should not be taken if you are pregnant or if pregnancy is suspected.

There are also conditions that your doctor will want to watch closely or that might cause your doctor to recommend a method of contraception other than birth control pills:

- breast conditions
  - a strong family history of breast cancer
  - breast disorders including pain, discharge from the nipples, thickenings, or lumps. In some circumstances, benefit may be derived from taking the pill; in other cases, adverse effects may follow.
- diabetes
- high blood pressure
- abnormal levels of fats in the bloodstream (high cholesterol or triglycerides)
- cigarette smoking
- migraine headaches
- heart or kidney disease
- epilepsy
- depression
- fibroid tumours of the uterus
- gallbladder or pancreatic disease
- plans for forthcoming surgery
- history of jaundice or other liver disease

You also should inform your doctor about a family history of blood clots, heart attacks or strokes.

The risks of birth control pills

1. *Circulatory disorders (including blood clots in legs, lungs, heart, eyes or brain)*

Blood clots are the most common serious side effect of birth control pills. Clots can occur in many areas of the body.

- In the brain, a clot can result in a stroke.
- In a blood vessel of the heart, a clot can result in a heart attack.
- In the legs and pelvis, a clot can break off and travel to the lung resulting in a pulmonary embolus.
- In a blood vessel leading to an arm or leg, a clot can result in damage to or loss of a limb.

Any of these conditions can cause death or disability. Clots also occur rarely in the blood vessels of the eye, resulting in blindness or impaired vision.

Women who use birth control pills have a higher incidence of blood clots. The risk of clotting seems to increase with higher estrogen doses. **It is important, therefore, to use as low a dosage of estrogen as possible.**

Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels. This risk increases with age and becomes significant in birth control pill users over 35 years of age. Women should not smoke.

2. *Breast cancer*

The most significant risk factors for breast cancer are increasing age and a strong history of breast cancer in the family (mother or sister). Other established risk factors include obesity, never having children, and having your first full-term pregnancy at a late age.

Some women who use birth control pills may be at increased risk of developing breast cancer before menopause, which occurs around age 50. These women may be long-term users of birth control pills (more than eight years) or women who start using birth control pills at an early age. In a few women, the use of birth control pills may accelerate the growth of an existing but undiagnosed breast cancer. Early diagnosis, however, can reduce the effect of breast cancer on a woman's life expectancy. The potential risks related to birth control pills seem to be small, however.

Women with the following conditions should be examined yearly by their doctors no matter what method of contraception they use:

- a strong history of breast cancer in the family;
- breast nodules or thickenings; and/or
- discharge from the nipple.

3. Dangers to developing child if birth control pills are used during pregnancy

Birth control pills should not be taken by pregnant women. There is no evidence, however, that the pill can damage a developing child.

There is also no evidence that the use of birth control pills immediately before a pregnancy will adversely affect a baby's development. When a woman stops taking birth control pills to become pregnant, however, her doctor may recommend a different method of contraception until she has a period on her own. In this way, the pregnancy can be more accurately dated.

4. Gallbladder disease and liver tumours

Users of birth control pills have a greater risk of developing gallbladder disease requiring surgery within the first year of use. The risk may double after four or five years of use.

The short and long-term use of birth control pills also has been linked with the growth of liver tumours. Such tumours are **EXTREMELY** rare.

5. Other side effects of birth control pills

Some users of birth control pills have unpleasant side effects. These side effects are temporary and are not hazardous to health.

There may be tenderness of the breasts, nausea and vomiting. Some users will experience weight gain or loss. Many of these side effects occurred with high-dose combination birth control pills. These side effects are less common with the low-dose pills prescribed today.

Unexpected vaginal bleeding or spotting and changes in the usual menstrual period may also occur. These side effects usually disappear after the first few cycles. They are **not** an indication to stop taking birth control pills. Unless more significant complications occur, a decision to stop using the pill or to change the brand of pill should be made only after three consecutive months of use. Occasionally, users develop high blood pressure that may require stopping the use of birth control pills.

Other side effects may include

- growth of pre-existing fibroid tumours of the uterus
- depression;
- liver problems with jaundice (yellowing of the skin);
- an increase or decrease in hair growth, sex drive and appetite;
- skin pigmentation;
- headaches;
- rash; and/or
- vaginal infections.

Infrequently, there is a need to change contact lens prescription or an inability to use contact lenses.

A woman's menstrual period may be delayed after stopping birth control pills. There is no evidence that the use of the pill leads to a decrease in fertility. As mentioned, it is wise to delay starting a pregnancy for one menstrual period after stopping birth control pills.

Non-contraceptive benefits of birth control pills

Several health advantages have been linked to the use of birth control pills.

- Combination estrogen and progestin birth control pills reduce the incidence of cancer of the uterus and ovaries.
- Birth control pills reduce the likelihood of developing benign (non-cancerous) breast disease and ovarian cysts.
- Users of birth control pills lose less menstrual blood and have more regular cycles. The risk of developing iron-deficiency anemia is thus reduced.
- There may be a decrease in painful menstruation and in premenstrual syndrome (PMS).
- Acne, excessive hair growth and male-hormone-related disorders also may be improved.

Birth control pills **DO NOT PROTECT** against sexually transmitted diseases (STDs), including HIV/AIDS. For protection against STDs, it is advisable to use latex condoms **IN COMBINATION WITH** birth control pills.

Periodic examination

A complete medical and family history is necessary before birth control pills are prescribed. A physical examination should include measuring blood pressure and examining the breasts, abdomen, pelvic organs, and limbs.

A second visit to your doctor should take place three months or sooner after starting birth control pills. During this visit, any side effects should be evaluated and your blood pressure checked again. Afterward, an annual examination similar to the first visit is recommended. A Pap smear is usually taken before starting birth control pills and then at intervals recommended by your doctor.

If you decide to take birth control pills

If you and your doctor decide that, for you, the benefits of birth control pills outweigh the risks, you should be aware of the following:

1. Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels. This risk increases with age and becomes significant in birth control pill users older than 35 years of age. Women should not smoke.

2. Take the pills only on the advice of your doctor and carefully follow all directions given to you. You must take the pills exactly as prescribed. Otherwise, you may become pregnant.

3. Visit your doctor three months or sooner after the initial examination. Afterward, visit your doctor at least once a year.

4. Be alert for the following symptoms and signs of serious adverse effects. Call your doctor immediately if they occur:

- sharp pain in the chest, coughing blood, or sudden shortness of breath. These symptoms could indicate a possible blood clot in the lung;
- pain in the calf. This symptom could indicate a possible blood clot in the leg;
- crushing chest pain or heaviness. This symptom could indicate a possible heart attack;
- sudden severe or worsening headache or vomiting, dizziness or fainting, disturbance of vision or speech, or weakness or numbness in an arm or leg. These symptoms could indicate a possible stroke;
- sudden partial or complete loss of vision. This symptom could indicate a possible blood clot in the eye;
- severe pain or lump in the abdomen. These symptoms could indicate a possible tumour of the liver;
- severe depression;
- yellowing of the skin (jaundice);
- unusual swelling of the extremities; and/or
- breast lumps. **ASK YOUR DOCTOR FOR ADVICE AND INSTRUCTION ON REGULAR SELF-EXAMINATION OF YOUR BREASTS.**

5. Birth control pills should never be taken if you think you are pregnant. They will not prevent the pregnancy from continuing.

6. You will have a menstrual period when you stop taking birth control pills. You should delay pregnancy until another menstrual period occurs within four to six weeks. Contact your doctor for recommendations on alternative methods of contraception during this time.

7. Your doctor will advise you of the appropriate time to start the use of birth control pills after childbirth, miscarriage, or therapeutic abortion.

8. The hormones in birth control pills are known to appear in breast milk. These hormones may decrease the flow of breast milk. If birth control pills are not resumed until nursing is established, however, the quantity and quality of breast milk does not seem to be affected. There is no evidence that birth control pills are harmful to the nursing infant.

9. Should you require **MAJOR** surgery, inform your surgeon that you are using birth control pills.

10. **If you see a different doctor, inform him or her that you are taking birth control pills.** Tell the doctor that your birth control pills are *(Product Name).*

11. **Inform your doctor if you are taking, or if you start to take, other medications.** This applies to both prescription and non-prescription drugs. These medications may change the effectiveness and/or cycle control of our birth control pills. **You may need to use a back-up method of birth control.**

12. **THERE IS NO NEED TO STOP TAKING BIRTH CONTROL PILLS FOR A REST PERIOD.**

13. Birth control pills **DO NOT PROTECT** against sexually transmitted diseases (STDs), including HIV/AIDS. For protection against STDs, it is advisable to use latex condoms **IN COMBINATION WITH** birth control pills.

HOW TO TAKE BIRTH CONTROL PILLS

1. **READ THESE DIRECTIONS**
- before you start taking your pills, and
- any time you are not sure what to do.

2. **LOOK AT YOUR PILL PACK** to see if it has 21 or 28 pills:
- **21-Pill Pack:** 21 active pills (with hormones) taken daily for three weeks, and then no pills taken for one week or
- **28-Pill Pack:** 21 active pills (with hormones) taken daily for three weeks, and then seven "reminder" pills (no hormones) taken daily for one week.

ALSO CHECK: *Note to manufacturers: Place a picture of the pill pack here, showing: 1) where to start, 2) direction to take pills in, and 3) week numbers*

3. You may wish to use a second method of birth control (e.g. latex condoms and spermicidal foam or gel) for the first seven days of the first cycle of pill use. This will provide a back-up in case pills are forgotten while you are getting used to taking them.

4. **When receiving any medical treatment, be sure to tell your doctor that you are using birth control pills.**

5. **MANY WOMEN HAVE SPOTTING OR LIGHT BLEEDING, OR MAY FEEL SICK TO THEIR STOMACH DURING THE FIRST THREE MONTHS ON THE PILL.** If you do feel sick, do not stop taking the pill. The problem will usually go away. If it does not go away, check with your doctor or clinic.

6. **MISSING PILLS ALSO CAN CAUSE SOME SPOTTING OR LIGHT BLEEDING,** even if you make up the missed pills. You also could feel a little sick to your stomach on the days you take two pills to make up for missed pills.

7. **IF YOU MISS PILLS AT ANY TIME, YOU COULD GET PREGNANT. THE GREATEST RISKS FOR PREGNANCY ARE:**
- when you start a pack late, or
- when you miss pills at the beginning or at the very end of the pack.

8. **ALWAYS BE SURE YOU HAVE READY:**
- **ANOTHER KIND OF BIRTH CONTROL** (such as latex condoms and spermicidal foam or gel) to use as a back-up in case you miss pills, and
- **AN EXTRA, FULL PACK OF PILLS.**

9. **IF YOU EXPERIENCE VOMITING OR DIARRHEA, OR IF YOU TAKE SOME MEDICINES,** such as antibiotics, your pills may not work as well. Use a back-up method, such as latex condoms and spermicidal foam or gel, until you can check with your doctor or clinic.

10. **IF YOU FORGET MORE THAN ONE PILL TWO MONTHS IN A ROW,** talk to your doctor or clinic about how to make pill-taking easier or about using another method of birth control.
11. **IF YOUR QUESTIONS ARE NOT ANSWERED HERE, CALL YOUR DOCTOR OR CLINIC.**

WHEN TO START THE *FIRST* PACK OF PILLS

Be Sure to Read these Instructions:

- before you start taking your pills, and
- any time you are not sure what to do.

Decide with your doctor or clinic what is the best day for you to start taking your first pack of pills. Your pills may be either a 21-day or a 28-day type.

Manufacturer's Diagram Here

A. 21-DAY COMBINATION

With this type of birth control pill, you are on pills for 21 days and off pills for seven days. You must not be off the pills for more than seven days in a row.

1. **THE FIRST DAY OF YOUR MENSTRUAL PERIOD (BLEEDING) IS DAY 1 OF YOUR CYCLE.** Your doctor may advise you to start taking the pills on Day 1, on Day 5, or on the first Sunday after your period begins. If your period starts on Sunday, start that same day.
2. Take one pill at approximately the same time every day for 21 days; **THEN TAKE NO PILLS FOR SEVEN DAYS.** Start a new pack on the eighth day. You will probably have a period during the seven days off the pill. (This bleeding may be lighter and shorter than your usual period.)

B. 28-DAY COMBINATION

With this type of birth control pill, you take 21 pills that contain hormones and seven pills that contain no hormones.

1. **THE FIRST DAY OF YOUR MENSTRUAL PERIOD (BLEEDING) IS DAY 1 OF YOUR CYCLE.** Your doctor may advise you to start taking the pills on Day 1, on Day 5, or on the first Sunday after your period begins. If your period starts on Sunday, start that same day.
2. Take one pill at approximately the same time every day for 28 days. Begin a new pack the next day, **NOT MISSING ANY DAYS**. Your period should occur during the last seven days of using that pill pack.

WHAT TO DO DURING THE MONTH

1. **TAKE A PILL AT APPROXIMATELY THE SAME TIME EVERY DAY UNTIL THE PACK IS EMPTY.**

- Try to associate taking your pill with some regular activity such as eating a meal or going to bed.
- Do not skip pills even if you have bleeding between monthly periods or feel sick to your stomach (nausea).
- Do not skip pills even if you do not have sex very often.

2. **WHEN YOU FINISH A PACK**

- **21 PILLS**
  WAIT SEVEN DAYS to start the next pack. You will have your period during that week.
- **28 PILLS**
  Start the next pack **ON THE NEXT DAY**. Take one pill every day. Do not wait any days between packs.

WHAT TO DO IF YOU MISS PILLS

The following outlines the actions you should take if you miss one or more of your birth control pills. Match the number of pills missed with the appropriate starting time for your type of pill pack.

SUNDAY START

Miss One Pill

Take it as soon as you remember and take the next pill at the usual time. This means that you might take two pills in one day.

Miss Two Pills in a Row

First two weeks

1. Take two pills the day you remember and two pills the next day.
2. Then take one pill a day until you finish the pack.
3. Use a back-up method of birth control if you have sex in the seven days after you miss the pills.

Third week

1. Keep taking one pill a day until Sunday.
2. On Sunday, safely discard the rest of the pack and start a new pack that day.
3. Use a back-up method of birth control if you have sex in the seven days after you miss the pills.
4. You may not have a period this month.

If You Miss Two Periods in a Row, Call Your Doctor or Clinic.

Miss Three or More Pills in a Row

Anytime in the cycle

1. Keep taking one pill a day until Sunday.
2. On Sunday, safely discard the rest of the pack and start a new pack that day.
3. Use a back-up method of birth control if you have sex in the seven days after you miss the pills.
4. You may not have a period this month.

If You Miss Two Periods in a Row, Call Your Doctor or Clinic.

NOTE: 28-DAY PACK – If you forget any of the seven "reminder" pills (without hormones) in Week 4, just safely dispose of the pills you missed. Then keep taking one pill each day until the pack is empty. You do not need to use a back-up method.

OTHER THAN SUNDAY START

Miss One Pill

Take it as soon as you remember and take the next pill at the usual time. This means that you might take two pills in one day.

Miss Two Pills in a Row

First two weeks

1. Take two pills the day you remember and two pills the next day.
2. Then take one pill a day until you finish the pack.
3. Use a back-up method of birth control if you have sex in the seven days after you miss the pills.

Third week

1. Safely dispose of the rest of the pill pack and start a new pack that same day.
2. Use a back-up method of birth control if you have sex in the seven days after you miss the pills.
3. You may not have a period this month.

If You Miss Two Periods in a Row, Call Your Doctor or Clinic.

Miss Three or More Pills in a Row

Anytime in the cycle

1. Safely dispose of the rest of the pill pack and start a new pack that same day.
2. Use a back-up method of birth control if you have sex in the seven days after you miss the pills.
3. You may not have a period this month.

If You Miss Two Periods in a Row, Call Your Doctor or Clinic.

NOTE: 28-DAY PACK – If you forget any of the seven "reminder" pills (without hormones) in Week 4, just safely dispose of the pills you missed. Then keep taking one pill each day until the pack is empty. You do not need to use a back-up method.

Always be sure you have on hand:

- a back-up method of birth control (such as latex condoms and spermicidal foam or gel) in case you miss pills, and
- an extra, full pack of pills.

IF YOU FORGET MORE THAN ONE PILL TWO MONTHS IN A ROW, TALK TO YOUR DOCTOR OR CLINIC about ways to make pill-taking easier or about using another method of birth control.

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