Abstract
Objective: To provide guidelines for health-care providers on the use of contraceptive methods to prevent pregnancy and sexually transmitted diseases.

Outcomes: Overall efficacy of cited contraceptive methods, assessing reduction in pregnancy rate, risk of infection, safety, ease of use, and side effects; the effect of cited contraceptive methods on sexual health and general well-being; and the cost and availability of cited contraceptive methods in Canada.

Evidence: Medline and the Cochrane Database were searched for articles in English on subjects related to contraception, sexuality, and sexual health from January 1988 to March 2003, in order to update the Report of the Consensus Committee on Contraception published in May-July 1998. Relevant Canadian Government publications and position papers from appropriate health and family planning organizations were also reviewed.

Values: The quality of the evidence is rated using the criteria described in the Report of the Canadian Task Force on the Periodic Health Examination. Recommendations for practice are ranked according to the method described in this Report.

Key Words
Contraception, statistics, Canada, sexuality, sexual health, hormonal contraception, emergency contraception, barrier methods of contraception, contraceptive sponge, female condoms, contraceptive diaphragm, cervical cap, spermicide, fertility awareness, abstinence, tubal ligation, vasectomy, sterilization, intrauterine devices

Recommendations:
Chapter 4: Combined Hormonal Contraception
1. A range of hormonal contraceptives should be available to ensure that the individual receives the preparation most suited for her needs. (Grade C)
2. Women using oral contraceptives should be counselled that antibiotic use does not appear to affect combined OC efficacy (except for griseofulvin and rifampin). (Grade B)

Chapter 5: Progestin-Only Hormonal Contraception
1. Progestin-only methods should be considered as contraceptive options for postpartum women, regardless of breastfeeding status, and may be introduced immediately after delivery. (Grade B)
2. Progestin-only methods should be considered as contraceptive options for women with a past history of venous thromboembolism (VTE), or for women who are at a higher risk of myocardial infarction or stroke. In women with a proven thrombophilia, progestin-only preparations should be used with caution. (Grade B)
3. Young women who use depot medroxyprogesterone acetate (DMPA) should be counselled about dietary and lifestyle factors that will affect their peak bone mass, such as smoking, exercise, and calcium intake. (Grade A)

Chapter 6: Special Considerations for Hormonal Contraception
1. All women who smoke should be counselled to stop. Women over 35 who smoke should be advised not to use combined oral contraceptives (OCs). (Grade A)
2. Women using combined OCs who are undergoing major surgery or surgery that will be followed by prolonged periods of immobility should receive peri-operative anti-thrombotic prophylaxis. (Grade A) Consideration may be given to discontinuing low-dose combined OCs 4 weeks prior to elective surgery. A reliable contraceptive method (e.g., progestin-only contraception) should be substituted when combined OCs are withdrawn. (Grade C)

Chapter 7: Intravascular Devices
1. Health-care professionals providing family planning services should be familiar with the use of the intravascular device (IUD). (Grade A)
2. Appropriately trained personnel in adequately equipped facilities should be available in order to ensure that women have access to the IUD if they desire this method of contraception. (Grade A)


CHAPTER 4: COMBINED HORMONAL CONTRACEPTION

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Combined hormonal contraception refers to contraceptive methods that contain both estrogen and a progestin. There are several forms of combined hormonal contraceptive methods, including the combined oral contraceptive pill, the transdermal contraceptive patch, the vaginal contraceptive ring, and the combined monthly injectable. At this time, only the combined oral contraceptive pill and the contraceptive patch are approved for use in Canada. Newer combined oral contraceptive pills and the vaginal contraceptive ring will hopefully be available in Canada in the future.

COMBINATION ORAL CONTRACEPTIVE PILL

INTRODUCTION

The oral contraceptive pill (combined OC) was first introduced in 1960. Since then it has undergone many modifications and has been used by millions of women worldwide. In Canada, 18% of women aged 15 to 49 use the combined OC.1 Of Canadian women who use contraception, 32% use the combined OC as their method of birth control.2

The combined OC preparations available in Canada are shown in Table 1. Formulations may be monophasic (each tablet contains a fixed amount of estrogen and progestin); biphasic (each tablet contains a fixed amount of estrogen, while the amount of progestin increases in the second half of the cycle); or triphasic (the amount of estrogen may be fixed or variable, while the amount of progestin increases in 3 equal phases). Biphasic and triphasic formulations were initially developed with the intent of lowering the total steroid content of combined OCs.3

Two types of estrogen are used in combined OCs: ethinyl estradiol and mestranol. Mestranol is a “prodrug” that is converted in vivo to ethinyl estradiol.4 Several different progestins, of varying degrees of progestational potency, are used in combined OCs. The progestins may also have estrogenic, anti-estrogenic, or androgenic activity. The “potencies” attributed to different combined OC preparations are based on pharmacological experimental models. These include the mouse uterine weight assay for estrogenic activity, demonstration of glycerogen vacuoles in human endometrium for progestogenic activity, and the rat ventral prostate assay for androgenic activity.5,6 However, there is no clear clinical or epidemiological evidence that compares the relative potencies of currently available combined OCs. The many variables that affect the potency of combined OCs (including dosage, bioavailability, protein binding, receptor binding affinity, and interindividual variability) make it difficult to extrapolate the results of isolated experiments to provide clinically relevant information in humans.4

Progestins can be classified according to their chemical structure as an estrane (norethindrone, ethynodiol diacetate) or as a gonane (levonorgestrel, desogestrel, norgestimate). In general, the gonane progestins appear to be more potent than the estrane derivatives (smaller doses can be used), but otherwise differences between the estrane and gonane compounds are difficult to characterize.7,8 Progestins have also been classified according to the sequence of their development (first, second, or third generation), but the definitions of first, second, or third generation progestins are not universally accepted. Newer progestins (norgestimate and desogestrel) have been shown to have little or no androgenic activity.7,8 These progestins, when administered in combination with ethinyl estradiol, produce a net estrogen-dominant effect, which may partly explain the effects seen on hepatic proteins (increased levels of sex hormone-binding globulin), lipid metabolism (increased levels of triglycerides and high-density lipoprotein-cholesterol), and on haemostatic variables (increased levels of fibrinogen, plasminogen, and Factor VII).7,8

EFFICACY

The combined OC is a highly effective method of reversible contraception. With perfect use, the combined OC is 99.9% effective in preventing pregnancy.9 However, typical user failure rates range from 3 to 8%.10,11

Poor patient compliance is a major factor in limiting effectiveness. In one study, the proportion of women who reported
missing no pills (53 to 59%) was much higher than the proportion recorded electronically (19 to 33%). According to the electronic devices, 30% of women missed 3 or more pills in the first cycle of combined OC use.12 Another study found that 47% of women miss 1 or more pills and 22% miss 2 or more pills per cycle.13

The effect of body weight on the efficacy of the combined OC is controversial. A retrospective cohort study found that women weighing 70.5 kg or more had a significantly increased risk of combined OC failure compared with women of lower body weight. The relative risk of failure was 2.6 among low-dose combined OC users and 4.5 among very-low-dose combined OC users.14 However, a large cohort study failed to find evidence of any influence of body weight on the risk of accidental pregnancy in combined OC users.15 Further studies are required before recommendations can be made.

MECHANISM OF ACTION

The combined OC’s multiple mechanisms of action may contribute to its high efficacy. Its main mechanism of action is to suppress gonadotropin secretion, thereby inhibiting ovulation.16 Other mechanisms of action include:

- Development of endometrial atrophy, making the endometrium unreceptive to implantation;17
- Production of viscous cervical mucus that impedes sperm transport;18
- Possible effect on secretion and peristalsis within the fallopian tube, which interferes with ovum and sperm transport.16

INDICATIONS

In the absence of contraindications, use of the combined OC may be considered for any woman seeking a reliable, reversible, coitally-independent method of contraception. It is particularly suited for women who wish to take advantage of its non-contraceptive benefits.

The use of condoms is still recommended in combined OC users for protection against sexually transmitted infections (STIs) and human immunodeficiency virus (HIV).

CONTRAINDICATIONS

The World Health Organization (WHO) has developed a list of absolute and relative contraindications to the use of combined OCs, based on the available evidence of risks.9

ABSOLUTE CONTRAINDICATIONS

- < 6 weeks postpartum if breastfeeding
- smoker over the age of 35 (≥ 15 cigarettes per day)
- hypertension (systolic ≥ 160mm Hg or diastolic ≥ 100mm Hg)
• current or past history of venous thromboembolism (VTE)
• ischemic heart disease
• history of cerebrovascular accident
• complicated valvular heart disease (pulmonary hypertension, atrial fibrillation, history of subacute bacterial endocarditis)
• migraine headache with focal neurological symptoms
• breast cancer (current)
• diabetes with retinopathy/nephropathy/neuropathy
• severe cirrhosis
• liver tumour (adenoma or hepatoma)

RELATIVE CONTRAINDICATIONS
• smoker over the age of 35 (< 15 cigarettes per day)
• adequately controlled hypertension
• hypertension (systolic 140–159mm Hg, diastolic 90–99mm Hg)
• migraine headache over the age of 35
• currently symptomatic gallbladder disease
• mild cirrhosis
• history of combined OC-related cholestasis
• users of medications that may interfere with combined OC metabolism

NON-CONTRACEPTIVE BENEFITS
In addition to providing effective contraception, the combined OC has a number of non-contraceptive benefits that may make it an attractive option for many women. These include
• cycle regulation
• decreased menstrual flow\textsuperscript{19,20}
• increased bone mineral density\textsuperscript{21-24}
• decreased dysmenorrhea\textsuperscript{19,25-27}
• decreased peri-menopausal symptoms\textsuperscript{28,29}
• decreased acne\textsuperscript{30-36}
• decreased hirsutism\textsuperscript{37}
• decreased endometrial cancer\textsuperscript{38-42}
• decreased ovarian cancer\textsuperscript{43-48}
• decreased risk of fibroid\textsuperscript{49,50}
• possibly fewer ovarian cysts\textsuperscript{51}
• possibly fewer cases of benign breast disease\textsuperscript{52}
• possibly less colorectal carcinoma\textsuperscript{53-55}
• decreased incidence of salpingitis\textsuperscript{56,57}
• decreased incidence or severity of moliminal symptoms\textsuperscript{58}

SIDE-EFFECTS
Some combined OC users will experience minor side-effects, most commonly during the first 3 cycles.\textsuperscript{59} These side-effects may lead to discontinuation of the combined OC. Reassurance and adequate counselling about expected common side-effects can help to prevent unnecessary discontinuation and enhance compliance.\textsuperscript{60-61} The most common reason patients discontinue combined OC use is abnormal menstrual bleeding, followed by nausea, weight gain, mood changes, breast tenderness, and headache.\textsuperscript{60}

1. IRREGULAR BLEEDING
Unexpected bleeding occurs in 10 to 30% of women in the first month of combined OC use\textsuperscript{62-64}, and is a common reason for discontinuing use of combined OCs.\textsuperscript{60,62,65-67} The actual incidence of breakthrough bleeding or spotting is difficult to know as it is defined in various ways in different studies. It does appear that breakthrough bleeding or spotting in women beginning combined OC use improves with time.\textsuperscript{68-70} The likelihood of irregular bleeding is greater during the first 3 cycles of combined OC use, although rates at 3 months do not differ significantly from rates at 1 month.\textsuperscript{69-70} Randomized trials have compared the rates of irregular bleeding between 2 or 3 products, but no single comprehensive study has compared the rates of irregular bleeding in all of the existing combined OC formulations. Amenorrhea occurs in approximately 2 to 3% of cycles.\textsuperscript{62}

2. BREAST TENDERNESS AND NAUSEA
Breast tenderness and nausea may occur, but generally improve with time.\textsuperscript{71} These symptoms may occur less often in women who use combined OCs containing smaller amounts of estrogen.\textsuperscript{59}

3. WEIGHT GAIN
Although weight gain is often thought to be a side-effect of the combined OC,\textsuperscript{72} placebo-controlled trials have failed to show any association between low-dose combined OCs and weight gain.\textsuperscript{73-76} Studies comparing the combined OC to other contraceptive methods have also failed to show a significant OC-associated weight gain.

4. MOOD CHANGES
Although women may report depression and mood changes while taking the combined OC, placebo-controlled trials have not demonstrated a significantly increased risk of mood changes in combined OC users compared to placebo users.\textsuperscript{73}

RISKS
1. VENOUS THROMBOEMBOLISM
The rates of venous thromboembolism in combined OC users are 3- to 4-fold higher than among non-users.\textsuperscript{77} The absolute risk of VTE in combined OC users is 1 to 1.5 per 10 000 users per year of use. The risk of VTE during the first year of use appears to be higher than that in subsequent years of use.\textsuperscript{78-79} (See chapter 6: Special Considerations for more information.)
2. MYOCARDIAL INFARCTION
In women taking a combined OC containing more than 50 µg of ethinyl estradiol, myocardial infarction rates increase 3-fold.\textsuperscript{80,81} However, a number of recent studies have found no significant increase in the risk of myocardial infarction with preparations containing less than 50 µg of ethinyl estradiol, irrespective of age.\textsuperscript{82-85} (See chapter 6: Special Considerations for more information.)

3. STROKE
A significantly increased risk of stroke is seen in users of combined OCs that contain more than 50 µg of ethinyl estradiol.\textsuperscript{86} Although some studies of low-dose combined OCs report no increase in the risk of stroke,\textsuperscript{87-88} others have reported an increased risk of up to 2-fold.\textsuperscript{89-92} Smoking and hypertension are major risk factors for stroke.\textsuperscript{93} Combined OC users with hypertension are at an increased risk of stroke relative to users without hypertension.\textsuperscript{94} A meta-analysis published in 2000 reported an odds ratio of 1.93 (95% confidence interval [CI], 1.35–2.74) for current combined OC preparations in studies that controlled for smoking and hypertension.\textsuperscript{95} (See chapter 6: Special Considerations for more information.)

4. GALLBLADDER DISEASE
Combined OC use increases the secretion of cholic acid in bile, potentially leading to a higher incidence of gallstone formation.\textsuperscript{96} However, there does not appear to be a significantly increased risk of gallstone formation in combined OC users.\textsuperscript{97,98}

5. BREAST CANCER
Despite numerous studies, the risk of breast cancer in combined OC users is still controversial. A case-control study published in 1986 showed no association between the use of the combined OC and the risk of breast cancer.\textsuperscript{99} The best data available until recently were the results of a large meta-analysis published in 1996.\textsuperscript{100} The results of this study suggested that there was a small but significant increase in risk of breast cancer in women who were currently taking the combined OC (relative risk [RR], 1.24; 95% CI, 1.15–1.33) and in the first 10 years after discontinuing it. There did not appear to be a significant excess risk of having breast cancer diagnosed 10 or more years after stopping the combined OC.\textsuperscript{100} To put this into perspective, the cumulative likelihood of breast cancer up to the age of 35 in Canadian women is approximately 2 per 1000 women.\textsuperscript{101} If these 1000 women were using combined OCs, and if the associated breast cancer risk was 1.5-fold higher, they would experience 3 cases of breast cancer by the age of 35 rather than 2 cases. It is unclear whether the small increase in breast cancer risk associated with combined OC use is related to the OC itself or to delaying the first full-term birth.

In a more recent study of over 9000 women between the ages of 35 and 64, there was no significant association between the use of the combined OC and breast cancer.\textsuperscript{102} Among current combined OC users, the relative risk was 1.0 (95% CI 0.8–1.3), and among former users the relative risk was 0.9 (95% CI 0.8–1.0). The risk did not increase with longer periods of use, with different dosages of estrogen, or with different progesterin components. The risk of breast cancer was not increased in women with a family history of breast cancer who used the combined OC, or in women who started using the combined OC at an earlier age.

It is possible that women who carry the BRCA1 gene or BRCA2 gene mutations may be at a higher risk of breast cancer than other women when using combined OCs.\textsuperscript{103-105}

6. CERVICAL CANCER
Although human papillomavirus (HPV) is known to be linked to cervical cancer, many studies did not take this into account when studying combined OC use and the risk of cervical neoplasia. One study suggests that long-term combined OC use may increase the risk of cervical cancer in women who are HPV positive but not in women who are HPV negative.\textsuperscript{106} A systematic review of 28 studies of women with cervical cancer also found that increasing the duration of combined OC use was associated with an increased risk of cervical cancer.\textsuperscript{107} The data, although limited, suggested that the relative risk of cervical cancer may decrease after use of combined OCs ceases. Infection with HPV, the major risk factor for cervical cancer,\textsuperscript{108} is related to sexual behaviour, and sexual behaviour may differ between combined OC users and non-users. A long-term study published in 2002 concluded that, in a well-screened population of HPV-positive women followed for 10 years, combined OC use did not increase the risk of cervical cancer.\textsuperscript{109} The specific role that combined OCs play in the development of cervical cancer remains uncertain.

MYTHS AND MISCONCEPTIONS
Numerous myths and misconceptions exist concerning the combined OC.

1. The combined OC causes cancer.

\textit{Fact:} The combined OC reduces the risks of ovarian and endometrial cancer. The risk of ovarian cancer is reduced by at least half in women who use combined OCs.\textsuperscript{43-48,110} A meta-analysis of 20 studies of combined OC use indicated that the risk of ovarian cancer decreased with increasing duration of OC use, reducing by 10 to 12% after 1 year of use and by approximately 50% after 5 years of use.\textsuperscript{45} This reduction in risk persists for 10 to 20 years after combined OC use has been discontinued. The reduced risk of ovarian cancer in combined OC users has also been noted in women who have a pathogenic mutation in the BRCA1 or BRCA2 gene, a mutation that increases their lifetime risk of developing ovarian cancer.\textsuperscript{48,111} The combined OC is associated with a
50% overall reduction in the risk of endometrial cancer and the protective effect persists long after the combined OC is discontinued. The combined OC may also have a protective effect against colorectal cancer. There appears to be either no increase or a very slight increase in the risk of breast cancer in current combined OC users.

2. Women on the combined OC should have periodic pill breaks.

Fact: This is unnecessary. Pill breaks place a woman at risk for unintended pregnancy and cycle irregularity.

3. The combined OC affects future fertility.

Fact: Fertility is restored within 1 to 3 months after stopping the combined OC.

4. The combined OC causes birth defects if a woman becomes pregnant while taking it.

Fact: There is no evidence that the combined OC causes birth defects if it is taken inadvertently during pregnancy.

5. The combined OC must be stopped in all women over 35 years old.

Fact: Healthy, non-smoking women may continue to use the combined OC until menopause.

6. The combined OC causes acne.

Fact: Acne improves in women using the combined OC due to a decrease in circulating free androgen. Although all combined OCs will result in an improvement of acne, 2 combined OCs in Canada have received official labelling for the treatment of acne; these 2 OCs contain ethinyl estradiol in combination with either levonorgestrel or norgestimate. The combination pill with cyproterone acetate is indicated for the treatment of severe acne and is also a contraceptive.

INITIATION

1. PATIENT ASSESSMENT

Before prescribing a combined OC, a thorough history should be taken, including potential contraindications, smoking history, and medications. The physical examination should include a blood pressure measurement. A pelvic examination, although an important aspect of well-woman care, is not mandatory before providing combined OCs. The pelvic examination may be postponed until a follow-up visit. Negotiating the pelvic examination may be particularly important with adolescents.

No routine laboratory screening is required. Assessing the cholesterol-lipoprotein profile and carbohydrate metabolism should follow the Guidelines from the Canadian Periodic Health Examination. Routine screening for thrombophilies is not recommended.

2. COUNSELLING

Adequate counselling prior to initiation of combined OCs may help to improve compliance (regular use) and adherence (continuation). Counselling with regard to combined OC use should include the following:

- instructions on how to take the combined OC
- information on potential side-effects
- non-contraceptive benefits of the combined OC
- addressing common myths and misconceptions
- discussing risks and warning signs, including when to seek medical care
- discussing what to do if pills are missed
- emphasizing dual protection (the combined OC with condom use to prevent STIs and HIV infection)
- information about emergency contraception in the event of missed pills

3. PRESCRIPTION

- The choice of a combined OC, for first-time users, should take into account the prescriber's clinical judgment and the preferences of the user. A low-dose preparation (≤35 µg of ethinyl estradiol) is preferred. The preparation of choice for the combined OC user is the one that provides effective contraception, acceptable cycle control, and the least side-effects for that individual.
- Various start dates for the combined OC are used. Conventionally, the combined OC is started during the first 5 days of the menstrual cycle or on the first Sunday after menses begin. If the combined OC is started within the first 5 days of the menstrual cycle, a backup method of contraception is not necessary for prevention of pregnancy, provided that no pills have been missed. Another alternative is the Quick Start method, where a combined OC user takes her first pill in the health-care provider’s office after ruling out pregnancy. A back-up method of contraception should be used for the first week after combined OC initiation if the Quick Start method is used. This method, with its simple starting instructions, improves compliance, particularly in adolescents, and is not associated with an increase in the incidence of breakthrough bleeding or other side-effects.
- Women who use a 21-day preparation should be cautioned never to exceed the 7 day pill-free interval between packs.
- The health-care provider may discuss emergency contraception (EC) as well as providing an EC prescription in advance of need.
- Dual protection with condoms should be re-emphasized.
- A follow-up visit should be scheduled to review the combined OC users’ experience, satisfaction, and compliance, as well as to perform a blood pressure check. If indicated, a pelvic examination can be performed at the follow-up visit.

Combined OC prescribers should take steps to reduce long-term costs, and improve follow-up and oral contraceptive tracking, by eliminating indiscriminate “free sampling.” Initiation
of therapy with a single sample pack, for immediate protection and for demonstration purposes, should be accompanied by a prescription. For patients who are unable to pay for their medications and are not covered by a private insurance plan or government assistance, health-care providers can apply to the National Compassionate Oral Contraceptive Program on their behalf. This program ensures that access to contraception is not denied on the basis of lack of funds. (Go to http://sogc.medical.org/forms/pdfs/factSheetCompassion_e.pdf for more information about the program. Go to http://www.sogc.org/forms/pdfs/compassionform%5Fe.pdf to access the application form.)

CONTINUOUS USE OF COMBINED ORAL CONTRACEPTIVE PILLS

The use of combined oral contraceptive pill on a continuous basis was first studied in 1977, using 50 µg ethinyl estradiol pills.119 When given in a continuous fashion, the combined OC may have a number of advantages including decreased incidence of pelvic pain, headaches, bloating/swelling, and breast tenderness for women who experience these symptoms during the pill-free interval120; improved control over symptoms of endometriosis121 and polycystic ovary syndrome122; and greater convenience due to fewer withdrawal bleeds per year. Disadvantages of giving the combined OC in a continuous fashion include little information on long-term safety (although there are long-term data for comparable total estrogenic fashion include little information on long-term safety of administration involved 1055 women and resulted in pregnancy rates of 2.78% at one year with use of a preparation containing 50 µg ethinyl estradiol with 250 µg levonorgestrel (1 Ovral tablet daily), and 4.54% at one year with use of a preparation containing 30 µg ethinyl estradiol with 150 µg desogestrel (1 Orthoest or 1 Marvelon tablet daily). No significant difference in pregnancy rates was reported between these two products when administered vaginally.132 Failure rates in this study were not compared to those seen with oral administration of combined OCs.

VAGINAL ADMINISTRATION OF COMBINED ORAL CONTRACEPTIVES

Six clinical trials have evaluated the administration of combined OCs given vaginally.130-136 Theoretical advantages in administering the combined OC vaginally include avoiding the “first pass” metabolism by the liver, which may help to decrease side-effects and improve tolerance. The largest study of this method of administration involved 1055 women and resulted in pregnancy rates of 2.78% at one year with use of a preparation containing 50 µg ethinyl estradiol with 250 µg levonorgestrel (1 Ovral tablet daily), and 4.54% at one year with use of a preparation containing 30 µg ethinyl estradiol with 150 µg desogestrel (1 Orthoest or 1 Marvelon tablet daily). No significant difference in pregnancy rates was reported between these two products when administered vaginally.132 Failure rates in this study were not compared to those seen with oral administration of combined OCs.

TROUBLESHOOTING

I. BREAKTHROUGH BLEEDING

The rates of irregular bleeding reported by women in clinical trials of combined OCs vary widely.59,68,137-138 Bleeding rates at 3 months do not appear to differ significantly from those at 1 month; therefore, new users of a combined OC should be encouraged to continue with the expectation that any irregular bleeding will subside, rather than switching to another combined OC. An improvement in bleeding patterns is usually seen over time, so that reassurance and a reminder of the usually transient nature of irregular bleeding is essential. A Pap smear, STI testing, or a pregnancy test may be performed if indicated.

If the bleeding persists after the third cycle of use, or has a new onset, other causes of bleeding must be ruled out. Possible reasons for irregular bleeding while taking the combined OC include irregular pill taking,139 smoking,140 uterine or cervical pathology, malabsorption, pregnancy, use of concomitant medications (e.g. anticonvulsants, rifampin, herbal medicines), and infection.141 Health-care providers should rule out these
potential causes of irregular bleeding. The patient should be asked about the duration of pill use, dosage, timing, missed pills, symptoms of pregnancy, diarrhea or vomiting in the last cycle, dyspareunia, vaginal bleeding after intercourse, smoking, and the use of other medication. New onset of irregular bleeding in a long-term combined OC user may be a marker for chlamydia infection (up to 29% of these women may have a positive chlamydia test), so that these women should be screened for Chlamydia infection.

Several empirical regimens have been used to manage breakthrough bleeding once other causes have been eliminated, although there is no reliable evidence to support them. In the case of persistent or new onset bleeding, a short course of oral estrogen may be helpful, such as 1.25 mg of conjugated estrogen or 2 mg of estradiol-17β daily for 7 days. If no improvement is seen, a therapeutic trial of another combined OC may be indicated. It may be useful to offer a combined OC containing a different type of progestin, such as switching from a preparation that contains a gonane progestin to one that contains an estrane progestin (or vice versa). There is no combined OC preparation that is less likely than others to cause breakthrough bleeding. Consistent pill use, dual protection, and smoking cessation should be emphasized.

2. MISSED PILLS
Missing pills at the beginning or end of the 21-day cycle has the effect of lengthening the hormone-free interval. If the hormone-free interval exceeds 7 days, the risk of ovulation and possible conception is increased. Forgetting tablets in the second or third week of the 21-day cycle is unlikely to increase the risk of ovulation if the hormone-free interval does not exceed 7 days.

3. AMENORRHEA
Amenorrhea occurs in 2 to 3% of combined OC users. Pregnancy should first be ruled out in any OC user who develops amenorrhea. Amenorrhea in women taking combined OCs is not dangerous, and many women readily accept the absence of withdrawal bleeding. If amenorrhea is unacceptable, adding exogenous estrogen (e.g., 0.625–1.25 mg conjugated estrogens or 1–2 mg of 17β estradiol) for 10 days per cycle will often result in resumption of bleeding. Switching to another preparation may be effective. There is usually no indication to switch to a pill containing 50 µg ethinyl estradiol.

4. CHLOasma
Chloasma, a darkening of facial skin pigmentation, may occur during OC use. The hyperpigmentation may never completely disappear. The use of sunscreen may help to prevent further pigmentation.

5. BREAST TENDERNESS (MASTALGIA) AND GALACTORRHEA
Mastalgia often resolves after several cycles of combined OC use. Decreasing caffeine intake may be helpful in reducing mastalgia. Decreasing the estrogen content of the combined OC may also be helpful. The presence of galactorrhea during combined OC use is rare and is an indication for performing a serum prolactin assay.

6. NAUSEA
Nausea is a common side effect during the first cycles of combined OC use, and usually decreases with time. However, nausea or vomiting may occur when a woman takes 2 pills at the same time. Taking the pills a few hours apart may be helpful in this case. Taking the pill with food or at bedtime will often control the nausea. A lower estrogen dose may improve the nausea. If nausea occurs in a long-time pill user, pregnancy must be ruled out.

7. PREGNANCY
If pregnancy occurs in a woman taking a combined OC, she should stop taking the pill immediately. She should be informed that there is no increased risk of birth defects as a result of inadvertent combined OC use during pregnancy.

DRUG INTERACTIONS
Ethinyl estradiol is metabolized at several different sites. First, it is sulphated in the intestinal wall, then it is hydroxylated in the cytochrome P450-3A4 pathway of the liver, after which it is conjugated with glucuronides and passes into the enterohepatic system.

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Instructions Regarding Missed Pills

If you miss 1 pill, take it as soon as you remember. This may mean taking 2 pills in 1 day.

If you miss 2 pills in a row during the first 2 weeks of the pack, take 2 pills on the day you remember and 2 on the following day. Use a backup method of contraception if you have sex in the 7 days after you miss the pills.

If you have had unprotected intercourse after missing a pill, use emergency contraception.

If you miss 2 pills in a row in the third week of the pack, throw out the remainder of the pack and start a new pack on the day you remember. You may not have a period this month. If you had unprotected intercourse after missing a pill, use emergency contraception.

If you miss 3 pills in a row, throw out the remainder of the pack and start a new pack on the day you remember. If you had unprotected intercourse after missing a pill, use emergency contraception. Use a backup method of contraception if you have intercourse in the first 7 days of the new pack. You may not have a period this month.
circulation. These processes may vary between women and may be affected by other medications. Drug interactions may occur via alterations in absorption, serum protein binding, receptor binding or in hepatic metabolism. The clinical significance of many of the interactions is questionable. It has been suggested that less than 5% of drug interactions with combined OCs result in pregnancy. Nevertheless, due to the widespread use of combined OCs, health-care professionals must be aware of concurrent medication use and the potential for drug interactions.

Evidence from a single pharmacokinetic interaction study suggests that a woman taking the anticonvulsant phenytoin or carbamazepine should use a combined OC preparation containing 50 µg ethinyl estradiol, rather than a lower-dose preparation. Monitoring of phenytoin concentrations is important because combined OCs may inhibit their metabolism.

Whether or not antibiotic use has an effect on the efficacy of combined OCs has been a matter of controversy. A significant pharmacokinetic interaction between combined OCs and antibiotics, apart from rifampicin and griseofulvin, has not been proven. It has been suggested that if an interaction does exist, it is likely that it occurs in a small number of predisposed individuals. It is not possible at this time to predict who is at risk for potential interaction.

Table 2 shows significant drug interactions with combined OCs. Some medications may result in contraceptive failure if used concomitantly with combined OCs. Some medications may increase the activity of the combined OC, resulting in increased estrogenic side-effects. Oral contraceptives may also decrease the activity of other medications, thereby increasing their activity. Other drug interactions may occur but are not included in the table because of a lack of scientific documentation or questionable clinical significance.

THE TRANSDERMAL CONTRACEPTIVE PATCH

INTRODUCTION

The contraceptive patch was approved for use in Canada in 2002 and became available for use in January of 2004. The contraceptive patch delivers 150 µg of norelgestromin (the primary active metabolite of norgestimate) and 20 µg of ethinyl estradiol daily to the systemic circulation. These doses cannot be compared to the doses of estrogen and progestin in a combined oral contraceptive. One patch is applied weekly for 3 consecutive weeks, followed by 1 patch-free week. The patch is placed on 1 of 4 sites: the buttocks, upper outer arm, lower abdomen or upper torso, excluding the breast.

EFFICACY

Overall, studies have found that the Pearl Index with perfect use of the contraceptive patch is 0.7 (95% CI, 0.31–1.10), while with typical use the Pearl Index is 0.88 (95% CI, 0.44–1.33). A subgroup of women weighing more than 90 kg may have an increased risk of pregnancy while using the patch. In one study, 4 of the 6 pregnancies that occurred were in women weighing at least 90 kg; in a pooled analysis, 5 of the 15 pregnancies that occurred in patch users were in women weighing more than 90 kg. The contraceptive efficacy of other methods of hormonal contraception, including the combined OC, progestin implants, and the vaginal contraceptive ring, may also be influenced by body weight.

MECHANISM OF ACTION

The mechanism of action is similar to that of the combined OC. The contraceptive patch suppresses follicular development and inhibits ovulation. Other mechanisms of action may include the development of endometrial atrophy making the endometrium unreceptive to implantation and cervical mucus changes that impede sperm transport.

INDICATIONS

In the absence of contraindications, the contraceptive patch may be considered for any woman seeking a reliable, reversible, coitally independent method of contraception. It may be especially

Table 2. Drug Interactions With Oral Contraceptives (OCs)

<table>
<thead>
<tr>
<th>Medications Whose Action May Cause Contraceptive Failure</th>
<th>Medications Which May Increase OC Activity</th>
<th>Medications Whose Clearance Can Be Decreased by OCs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Acetaminophen</td>
<td>Amitriptyline</td>
</tr>
<tr>
<td>Griseofulvin</td>
<td>Erythromycin</td>
<td>Caffeine</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Fluoxetine</td>
<td>Cyclosporine</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Fluconazole</td>
<td>Diazepam</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Fluvoxamine</td>
<td>Imipramine</td>
</tr>
<tr>
<td>Primidone</td>
<td>Grapefruit juice</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Nefazodone</td>
<td>Selegiline</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Vitamin C</td>
<td>Theophylline</td>
</tr>
<tr>
<td>St. John’s Wort</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topiramate</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
suited for women seeking a less compliance-demanding method of contraception.

The use of condoms is still recommended in contraceptive patch users for protection against STIs and HIV.

CONTRAINDICATIONS

Contraindications to use of the contraceptive patch are similar to those for the combined oral contraceptive pill. These include current or past history of venous thromboembolism; cerebrovascular or coronary disease; complicated valvular heart disease; severe hypertension; diabetes with end-organ involvement; headaches with focal neurological symptoms; known or suspected breast cancer; undiagnosed genital bleeding; hepatic adenomas or carcinomas; acute or chronic hepatocellular disease with abnormal liver functions; and known or suspected pregnancy. Although not an absolute contraindication, women with a body weight of greater than or equal to 90 kg may find that the contraceptive patch is less effective than in women with lower body weights.153

NON-CONTRACEPTIVE BENEFITS

Cycle control has been shown to be comparable to that seen with the combined OC.138,152-153 Although non-contraceptive benefits are assumed to be similar to those seen with the combined OC, these potential benefits have not been assessed in studies to date.

SIDE EFFECTS

With the exception of application site reactions, the side-effects experienced by contraceptive patch users are similar to those experienced by combined OC users.

1. IRREGULAR BLEEDING/SPOTTING

Overall, the incidence of breakthrough bleeding and spotting is similar to that seen with combined OC users; although for cycles 1 and 2, patch users have significantly higher rates of spotting (18.3% of patch users compared to 11.4% of combined OC users).138 Subsequent cycles showed no significant difference between patch users and combined OC users. The incidence of breakthrough bleeding or spotting tends to decrease with time.138,152-153 Amenorrhea with the contraceptive patch is rare.152

2. BREAST SYMPTOMS AND HEADACHE

Breast symptoms (including discomfort, engorgement, or pain) and headache are the most common side effects reported with patch use in pooled analysis (22% and 21% of users).156 Breast symptoms are more common with the patch than with the combined OC in the first 2 cycles of patch use; but by cycle 3, there is no significant difference between the 2 groups. Most reported breast symptoms are either mild or moderate (86%) and tend to decrease with continued patch use, down to 0% of patients at 13 months.138 Only 1.9% of patients discontinued patch use due to breast symptoms.156 Headaches led to patch discontinuation in 1.1% of study patients.156

3. LOCAL SKIN REACTION

Up to 20% of patients experience an application site reaction.138,152-156 The frequency of application site reactions did not increase over time.138 Most application site reactions are mild to moderate in severity,156 and only 2% of patch users discontinued it for this reason.138,156

RISKS

The risks are assumed to be the same as those known for the combined OC.

MYTHS AND MISCONCEPTIONS

1. The patch won’t stay on during exercise; in hot, humid weather; while swimming; or while in the shower.
   
   Fact: The patch has excellent adhesive properties under a wide range of conditions and climates (including bathing, sauna and whirlpool use, treadmill activity, or cool-water immersion).157 In clinical trials, approximately 1.9% of patches required replacement due to complete detachment.138,152 Over time, the incidence of patch detachment may decrease as the patch user becomes more familiar with the application technique. Despite the fact that detachment is rare, patch users should be advised to check daily to ensure that their patch is adequately attached.

2. Women are more likely to be compliant with the patch if they are older.
   
   Fact: In a randomized, controlled study comparing patch users to combined OC users, a significantly higher proportion of patch users had perfect compliance when compared to the combined OC users (88.2% versus 77.7%).138 Compliance was improved across all of the age groups in comparison to the combined OC, but especially in the younger women (aged 18–24). Perfect compliance rates in younger women using the patch were 88% versus 68% to 74% perfect compliance rates for the combined OC group.

3. Because of the transdermal delivery system, the patch will have less effect on the lipid profile than the combined oral contraceptive pill.
   
   Fact: An increase in serum total cholesterol and triglyceride levels is seen in users of both the patch and the combined OC.138,156

4. Because the patch is a hormonal method of contraception, women who use the patch will gain weight.
   
   Fact: There does not appear to be an association between the
contraceptive patch and weight gain when investigated and compared to placebo. In a pooled analysis of patch users, 78.5% of patients remained within 5% of their baseline weight while using the contraceptive patch.

INITIATION

A “first-day start,” when the patch is applied on the first day of menses, is recommended. This will be the “Patch Change Day.” If the patch is applied after the first day of menses, a backup method of contraception should be used for 1 week. A new patch is applied weekly for 3 weeks including the week in which the patch is started; week 4 is patch-free. Withdrawal bleeding usually occurs during the patch-free week. It is recommended that the patch always be applied on the same day, e.g. on a Monday.

The patch should be applied to clean, dry, healthy, intact skin. The patch may be applied at 1 of 4 sites: the buttock; the abdomen; the upper outer arm; or the upper torso, but not directly to the breast. These 4 sites are therapeutically equivalent. Patch users should be advised to check daily that their patch is adhering well.

A follow-up appointment should be made to assess the patch users’ satisfaction with the method, to discuss any side-effects, to ensure that it is being used correctly, and to answer questions. If indicated, a pelvic examination can be performed at the follow-up visit.

SWITCHING FROM THE COMBINED OC TO THE CONTRACEPTIVE PATCH

The contraceptive patch should be applied on the first day of withdrawal bleeding. If the patch is started after the first day of withdrawal bleeding, a backup method of contraception should be used for 7 days. If more than 5 days have elapsed since the last hormone-containing pill was taken, a backup method of contraception should be used for the first 7 days of patch use.

Alternatively, the patch can be applied on the day after the last hormonal pill is taken. In this case, there would be no hormone-free interval. Back-up contraception would not be needed in this case and the patient would not experience a menstrual bleed in that month.

SWITCHING FROM DEPOT-MEDROXYPROGESTERONE ACETATE (DMPA) TO THE CONTRACEPTIVE PATCH

The first contraceptive patch should be applied on the day that the next DMPA injection would be due. If given at this time, backup contraception is not required.

TROUBLESHOOTING

1. PATCH PARTIALLY OR COMPLETELY DETACHES

If the patch has either partially or completely detached for less than 24 hours, the woman should attempt to reattach the patch. If this is not successful, a new patch should be applied. The patch change day would remain the same. If the patch has been completely or partially detached for more than 24 hours or the timing is uncertain, a new patch should be applied and a new cycle started. Back-up contraception should be used for 1 week.

2. PATCH APPLICATION, CHANGE, OR REMOVAL IS FORGOTTEN

If the patch user forgets to apply the patch in week 1, the patch user should apply a new patch as soon as she remembers. Backup contraception is recommended for 1 week. The patch user then has a new patch change day; although if she prefers to keep the same patch change day, that is an acceptable option.

If the patch user forgets to change the patch in week 2 or 3, the recommended course of action depends on how late the user is in changing the patch. The patch can maintain target hormonal serum concentrations through 9 full days of use. For this reason, if the patch user is less than 48 hours late in changing her patch, she should change it immediately; she will not require backup contraception. The patch change day does not change. If however, she is more than 48 hours late in changing her patch, a new 4 week cycle should be started immediately by applying a new patch. She will have a new patch change day and will need to use backup contraception for 1 week.

If the patch user forgets to remove the patch in week 4, the old patch should be removed as soon as it is remembered. The next patch is applied on the usual patch change day. Back-up contraception is not required if there is less than a 7 day patch-free interval. The patch-free interval should never exceed 7 days.

3. CHANGING THE PATCH-CHANGE DAY

A new cycle should be started by placing the first patch of the new cycle on the new desired patch change day during the patch-free week. The patch-free interval should not exceed 7 days.

DRUG INTERACTIONS

Pharmacokinetic studies have shown no significant interaction between tetracycline and the contraceptive patch. Other drug interactions have not been specifically studied and, at this time, drug interactions that are reported with the combined OC are assumed also to occur with the contraceptive patch.

THE VAGINAL CONTRACEPTIVE RING

INTRODUCTION

The vaginal contraceptive ring (NuvaRing) was approved by the US Food and Drug Administration (FDA) in 2001 and
became available in the US market in 2003. It has been submitted for approval in Canada. It is a flexible, nearly transparent ring that is 54 mm in outer diameter and 4 mm in cross-sectional diameter. The ring releases a constant rate of 15 µg of ethinyl estradiol and 0.120 mg of the progestin etonogestrel per day. Etonogestrel is the active metabolite of desogestrel. Each ring is used for 1 cycle and then removed. A cycle consists of 3 weeks of continuous ring use followed by a 1 week ring-free interval.

**Efficacy**

In several thousand cycles of use, the Pearl Index — with perfect use of the vaginal ring — is between 0.4 and 0.77, while the overall Pearl Index is between 0.65 and 1.18. Knowing that compliance may affect contraceptive efficacy, compliance rates were calculated in studies. Perfect compliance is seen in 85.6 to 91% of contraceptive ring users.

**Mechanism of Action**

The mechanism of action is similar to that of the combined OC. The vaginal contraceptive ring suppresses follicular development and inhibits ovulation. Other mechanisms of action may include the development of endometrial atrophy making the endometrium unreceptive to implantation and cervical mucus changes that impede sperm transport.

**Indications**

In the absence of contraindications, the vaginal contraceptive ring can be considered for any woman seeking a reliable, reversible, coitally independent method of contraception. It may be particularly suited for women who prefer a method of contraception that does not require daily attention.

The use of condoms is still recommended in vaginal contraceptive ring users for protection against STIs and HIV.

**Contraindications**

Contraindications to use of the vaginal ring are similar to those for the combined OC. These include: pregnancy or suspected pregnancy; current or past venous thromboembolism; cerebrovascular or coronary artery disease; complicated valvular heart disease; severe hypertension; diabetes with end-organ involvement; headaches with focal neurological symptoms; known or suspected carcinoma of the breast, endometrium, or cervix; unexplained vaginal bleeding; or an allergic reaction to any of the components of the rings.

Relative contraindications include uterovaginal prolapse or vaginal stenosis if they prevent retention of the ring.

**Non-contraceptive Benefits**

Although assumed to be similar for those seen with the combined OC, no studies have specifically addressed non-contraceptive benefits of the vaginal contraceptive ring.

**Side-effects**

Side-effects are similar to those seen for the combined OC, although certain side-effects are obviously specific to the vaginal ring.

1. **Irregular Bleeding**

Irregular bleeding occurs in up to 6.4% of cycles and usually consists of spotting. Unlike other contraceptive methods, irregular bleeding does not appear to be significantly higher in the first cycles of ring use. When compared to the combined OC, the vaginal ring has significantly less irregular bleeding, most notably in the first cycle of use. Withdrawal bleeding occurs in the majority of cycles.

2. **Hormonal Side-effects**

Headache (11.8%), nausea (4.5%), and breast tenderness (2.8%) are the most common reported hormonal side-effects occurring in ring users.

3. **Vaginal Symptoms**

Vaginitis is the most commonly reported local side-effect, occurring in 13.7% of users, although only 5.3% of cases were felt to be treatment-related. Treatment-related leukorrhea occurs in approximately 5% of women. Although women or their partners may be aware of the device, only 1 to 2.5% of ring users discontinued the ring due to foreign body sensation, coital problems, or expulsion. Vaginal symptoms of discharge and irritation led to discontinuation in about 1 to 2% of women.

**Risks**

The risks are felt to be the same as for oral contraceptives.

**Initiation**

The ring is used vaginally. The first ring cycle is started between day 1 and day 5 of the menstrual cycle. The ring is inserted and left in place for 3 weeks and then removed for 1 week. Withdrawal bleeding usually occurs during the ring-free interval. The ring-free interval should be no longer than 7 days. To switch from the combined OC to the vaginal ring, the ring should be inserted no later than 7 days after the last combined OC tablet. To switch from a progestin-only pill, the vaginal ring is inserted the day after the last pill is taken.
When switching from an injectable contraceptive method, the ring is inserted on the day when the next injection would be due.

**TROUBLESHOOTING**

If the ring is expelled and has been out of the vagina for less than 3 hours, the user should rinse the ring in lukewarm water and reinsert it. Back-up contraception is not required. If the ring is lost, a new ring should be inserted. If it is out of the vagina for longer than 3 hours, a back-up method of contraception should be used for 7 days.

If the ring remains in the vagina for more than 3 weeks (but less than 4 weeks total), it is still effective in preventing pregnancy. The ring should be removed and a new ring inserted after a 1-week ring-free break. If however, the ring has been left in place for more than 4 weeks, it may no longer provide adequate protection against pregnancy. Consideration should be given to the use of emergency contraception and a backup method of contraception should be used until a new ring has been in place for at least 7 days.

**DRUG INTERACTIONS**

In one study, vaginal spermicide use was not found to have any short-term or long-term effects on the efficacy of the vaginal ring. Vaginally administered miconazole was not found to have a significant effect on serum concentrations of ethinyl estradiol or etonogestrel. For more information about spermicides please refer to chapter 8. Until further research is available, other drug interactions are considered similar to those seen with combined OCs.

**COMBINED INJECTABLE CONTRACEPTION**

A monthly injectable contraceptive composed of 5 mg estradiol cypionate and 25 mg medroxyprogesterone acetate (Lunelle) was approved by the FDA in October 2000 for use in the United States. As of January 2004, it has not been submitted for approval in Canada. It is administered by intramuscular injection, with no more than 33 days between injections. In a study of 782 American women followed over 1 year, there were no pregnancies. Its mechanism of action is primarily by inhibition of ovulation. It has the same indications and contraindications as combined oral contraceptive pills. This method should be considered for women who have difficulty remembering to take daily pills, who want monthly predictable bleeding, or have enteric absorption problems (e.g., inflammatory bowel disease).

When compared with DMPA, the combined monthly injectable has more frequent injections (every 28 ± 5 days), and faster return to ovulation. The first normal ovulatory cycle occurs 63 to 112 days following the last injection after 3 monthly injections of Lunelle. The vaginal bleeding with this method is due to estrogen withdrawal, and usually occurs 3 weeks (day 22) after the injection.

When compared with combined OCs, the combined monthly injectable has less breakthrough bleeding, a greater incidence of amenorrhea (14.6% during at least 1 cycle over 1 year, compared with 3.3% for OC users \( p \leq 0.01 \)), better inhibition of ovarian follicular activity than a 20 µg ethinyl estradiol pill, and a weight gain of about 4 pounds over 1 year.

**SUMMARY STATEMENTS**

1. To date, no single low-dose combined oral contraceptive

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**New Oral Contraceptives To Be Launched**

Cyclessa (Organon)

Cyclessa (desogestrel/ethinyl estradiol) is a triphasic oral contraceptive with 25 micrograms of estrogen (ethinyl estradiol). Cyclessa prevents pregnancy by inhibiting ovulation. Cyclessa is designed to reduce women’s overall exposure to hormones while maintaining contraceptive efficacy. Cyclessa consists of 25 µg of estrogen per day for 21 days. The daily progestin dose is 100 µg of desogestrel for days 1 to 7, 125 µg for days 8 to 14, and 150 µg for days 15 to 21. Cyclessa’s dosing regimen reduces hormone exposure to both estrogen and progestin during the 21-day course. The last 7 days of the cycle contains placebo pills.

Mircette (Organon)

Mircette is a 28-day regimen combined oral contraceptive with a unique dosing schedule: 20 µg ethinyl estradiol and 150 µg desogestrel for 21 days, followed by 2 days of placebo tablets and 5 days of low-dose estrogen tablets containing just 10 µg ethinyl estradiol. Mircette has been available in the U.S. since July 1998 and is currently being reviewed by Health Canada.

Yasmin (Berlex Canada)

Yasmin is a monophasic combined OC with a new progestin. Each tablet contains 3 mg drospirenone (DRSP) and 30 µg ethinylestradiol. Drospirenone belongs to an entirely new class of progestin. It is an analogue of spironolactone. It possesses antimineralocorticoid activity that may help to suppress estrogen related fluid retention. The product has been launched in several major countries including the US. Germany was the first to launch Yasmin in November 2000. Health Canada is currently reviewing Yasmin.
OC) preparation has demonstrated unequivocal clinical superiority. Therefore, user preferences and individual response are the basis for choosing a particular preparation. (Level 1)

2. The use of monophasic combined OC preparations continuously for several cycles, without periodic withdrawal, is a reasonable approach to the management of severe dysmenorrhea, menorrhagia, menstrual migraine, or where there is a desire or need to postpone withdrawal bleeding. (Level 1, Level II-2)

3. Combined OC use reduces the risk of developing cancer of the ovary and cancer of the endometrium, and does not increase the overall risk of developing breast cancer. (Level II-2)

4. Use of low-dose combined OCs increases the risk of venous thromboembolism 3- to 4-fold. Because VTE is rare in women of childbearing age, this increase in risk has minimal clinical significance in women without additional risk factors for VTE. (Level II-2)

5. Potential differences in risk of VTE or myocardial infarction attributable to different preparations of combined OCs do not currently justify differential prescribing. (Level III)

6. A pelvic examination is an important part of well woman care, but it is not a prerequisite for providing hormonal contraception or emergency contraception. (Level III)

RECOMMENDATIONS

1. A range of hormonal contraceptives should be available to ensure that the individual receives the preparation most suited for her needs. (Grade C)

2. Women using oral contraceptives should be counselled that antibiotic use does not appear to affect combined OC efficacy (except for griseofulvin and rifampicin). (Grade B)

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CHAPTER 5: PROGESTIN-ONLY HORMONAL CONTRACEPTION

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INTRODUCTION

Progestin-only contraception may be provided in injectable form, as oral medication, or as an implant. Currently, only the injectable and the oral forms are available in Canada.

INJECTABLE PROGESTIN

Depot medroxyprogesterone acetate (DMPA) has been used as a contraceptive agent since 1967 and is extensively used by millions of women in over 90 countries. It was approved for contraceptive use in Canada in 1997. Approximately 2% of Canadian women use DMPA for birth control.1

EFFICACY

DMPA is a highly effective form of contraception, with a failure rate of less than 0.3% per year.2,6

MECHANISM OF ACTION

DMPA works primarily by inhibiting the secretion of pituitary gonadotropins, thereby suppressing ovulation.7 It increases the viscosity of cervical mucus8 and induces endometrial atrophy.2

INDICATIONS

In the absence of contraindications, DMPA may be considered for any woman seeking a reliable, reversible, coitally independent method of contraception. It does not require daily attention and therefore may be more suitable for women who have difficulty complying with other birth control methods. It may be used by women who require an estrogen-free method of contraception or for those who wish to take advantage of its non-contraceptive benefits. It may be suitable for the following women:

• women with known contraindications or sensitivity to estrogen
• women over the age of 35 who smoke
• women with migraine headaches
• women who are breastfeeding
• women with endometriosis
• women with sickle cell disease
• women taking anti-convulsant medications

The use of condoms is still recommended in DMPA users for protection against sexually transmitted infections (STIs) and human immunodeficiency virus (HIV) infection.

CONTRAINDICATIONS

The World Health Organization (WHO) has developed a list of absolute and relative contraindications to the use of DMPA based on the available evidence of risks.6 Absolute contraindications include pregnancy (known or suspected), unexplained vaginal bleeding, and current diagnosis of breast cancer. Relative contraindications include severe cirrhosis, active viral hepatitis, and benign hepatic adenoma.

NON-CONTRACEPTIVE BENEFITS

DMPA use is a reliable method of contraception, and it also has a number of non-contraceptive benefits. These include

• amenorrhea with subsequent reduction in dysmenorrhea and anemia (The rate of amenorrhea is 55 to 60% at 12 months and 68% at 24 months.)3,9-11
• reduced risk of endometrial cancer12
• reduction in symptoms associated with endometriosis,13,14 premenstrual syndrome, and chronic pelvic pain15
• decreased incidence of seizures
• possible reduced risk of pelvic inflammatory disease
• possible decreased incidence of sickle cell crisis.

SIDE EFFECTS

1. MENSTRUAL CYCLE DISTURBANCE
The most common side effect associated with DMPA use is the disruption of menstrual patterns. Irregular bleeding or unwanted amenorrhea may lead to discontinuation of DMPA. In large studies of DMPA users, unpredictable bleeding was common in the first few months of use but decreased in amount and frequency with time. Abnormally heavy or prolonged bleeding occurred in only 1 to 2% of users. At 12 months, 55 to 60% of DMPA users are amenorrheic, and by 24 months up to 68% are amenorrheic.

2. HORMONAL SIDE EFFECTS
Reported hormonal side effects with use of DMPA include headache, acne, decreased libido, nausea, and breast tenderness. Headache is the most common non-bleeding side effect reported by DMPA users, occurring in approximately 17% of DMPA users. Migraine headaches do not constitute a contraindication to DMPA use.

3. WEIGHT GAIN
In one study, 56% of DMPA users reported an increase in weight (mean gain of 4.1 kg), while 44% either lost weight or maintained their baseline weight (mean loss of 1.7 kg). Other studies have failed to find an effect of DMPA on weight.

4. MOOD EFFECTS
Although mood changes have been reported in DMPA users and may lead to discontinuation of DMPA, prospective studies do not appear to demonstrate an increase in depressive symptoms in DMPA users. This suggests that depression is not a contraindication for DMPA use. Further studies are required to determine if there is a causal link.

RISKS

1. DELAYED RETURN OF FERTILITY
Although DMPA is a reversible contraceptive method, there may be a delay in the resumption of ovulation. DMPA users have an average 9-month delay before restoration of full fertility after the last injection. The rate of conception 10 months after the last DMPA injection is 50%, and approximately 90% by 24 months.

2. REDUCTION IN BONE MINERAL DENSITY (BMD)
Although some cross-sectional studies have demonstrated no adverse effect of DMPA on bone mineral density, the majority of studies report a decrease in BMD in DMPA users. Prospective studies have found a mean loss of BMD at the lumbar spine of between 0.87% and 3.52%. Although a decrease in BMD has been observed, it does not appear to induce osteoporosis. Furthermore, two cross-sectional studies of past DMPA users did not demonstrate a measurable difference in BMD compared with controls, suggesting that there is an improvement in BMD after DMPA is discontinued. A prospective cohort study reported a substantial recovery of BMD once DMPA was discontinued. One randomized, double-blind controlled trial suggested that supplemental oral estrogen may attenuate the negative effects of DMPA on BMD.

Larger, long-term prospective studies in current and past users of DMPA are required to evaluate BMD changes further.

3. VENOUS THROMBOEMBOLISM (VTE), CARDIOVASCULAR DISEASE, STROKE
When used in standard contraceptive doses, DMPA does not appear to increase the risk of VTE, but only limited data are available. DMPA users do not appear to have an increased risk of cardiovascular disease, stroke, or myocardial infarction.

MYTHS AND MISCONCEPTIONS

1. DMPA administered inadvertently during pregnancy is associated with birth defects.
Fact: There is no evidence that fetuses exposed to DMPA in utero are at an increased risk of congenital anomalies.

2. All DMPA users will gain weight.
Fact: Although DMPA users may gain weight, a significant percentage of patients will not gain weight while using DMPA. Dietary counselling is advised.

3. DMPA should not be given to breastfeeding women.
Fact: DMPA has been shown to be an effective method of postpartum contraception that has little or no effect on breast milk production or on infant development.

4. DMPA causes cancer.
Fact: DMPA is associated with a decreased risk of endometrial cancer. There does not appear to be an increased risk of ovarian cancer or breast cancer. Studies suggest either a slight or no increase in the risk of cervical cancer.

INITIATION

It is best to administer DMPA during the first 5 days of menses.
in order to avoid inadvertent injection during pregnancy. If the woman is switching from using a combined oral contraceptive (OC) to DMPA, DMPA should be given within the first 5 days of stopping the combined OC. DMPA is given as a 150 mg intramuscular injection every 12 weeks. The injection may be given in the deltoid or gluteus maximus muscles. If given within the first 5 days of the menstrual cycle, contraceptive effect is achieved within 24 hours of injection. However, DMPA can be given at any time during the menstrual cycle if pregnancy or the possibility of pregnancy can be definitely ruled out. If given after the first 5 days of the menstrual cycle, the woman should be advised to use a backup method of birth control for at least 1 week.

**FOLLOW UP**

Follow-up visits should be scheduled every 12 weeks for repeat injections. These follow-up visits allow for an assessment of bleeding patterns and other potential side effects, an assessment of patient satisfaction, and an opportunity to reinforce the issue of condom use for protection against STIs and HIV infection.

**TROUBLESHOOTING**

1. **MENSTRUAL CYCLE DISTURBANCE**
   
   If irregular bleeding persists after the first 6 months of use, underlying causes of abnormal vaginal bleeding should be ruled out. Once this has been done, management options include:
   
   - increasing the DMPA dose to between 225 and 300 mg IM for 2 to 3 injections.
   - decreasing the interval between doses.
   - supplemental estrogen therapy, such as 0.625 mg of conjugated equine estrogen by mouth for 28 days, or 1 to 2 mg of estradiol-17β given by mouth for 28 days. Alternatively, supplemental estrogen therapy can be given transdermally in the form of a 50 µg or 100 µg estradiol-17β patch for a total of 25 days.
   - administration of non-steroidal anti-inflammatory agents, such as ibuprofen 400 to 800 mg twice daily for a total of 10 days.
   - adding a combined oral contraceptive pill for 1 to 3 months.

2. **LATE INJECTION**
   
   If it has been less than 14 weeks since a woman’s last injection, the next DMPA injection can be given. If it has been 14 or more weeks since her last injection, but she has not had intercourse within the last 10 days and she has a negative serum assay for βHCG, the DMPA injection can be given. A backup method of contraception should be used for 2 weeks. If she has had intercourse within the last 10 days, the DMPA injection can be given if the serum assay for βHCG is negative, although she must continue to use a backup method of birth control and have a repeat serum assay for βHCG performed in 2 weeks (the serum assay for βHCG will not be positive until at least 8 days post-conception). DMPA is not teratogenic if given inadvertently during pregnancy.

**DRUG INTERACTIONS**

Few medications will interact with DMPA. Aminoglutethimide and nevirapine have been shown to decrease the effectiveness of DMPA.

**ORAL PROGESTIN: PROGESTIN-ONLY PILL**

Although not as well known or widely used as combined oral contraceptives, progestin-only pills (POPs) used for contraception are very safe and highly effective when used as directed. POPs are also known as “mini-pills.” In Canada, the POP is supplied in packages of 28 tablets, each containing 0.35 mg of norethindrone (Micronor).

**Efficacy**

With perfect use, the POP has a failure rate of approximately 0.5%. Maximal effectiveness depends on consistent pill-taking. With typical use, the failure rate is between 5 and 10%. The failure rate appears to be lower in motivated women.

**Mechanism of Action**

The chief mechanism of action in preventing pregnancy is through alterations in the cervical mucus. POPs reduce the volume of mucus, increase its viscosity, and alter its molecular structure, resulting in little or no sperm penetration. In addition, sperm motility is impaired, making fertilization unlikely. Ovulation may be suppressed or partially suppressed. Forty percent of women using progestin-only contraceptives continue to ovulate. Endometrial changes, reducing the potential for implantation, may occur. For maximal effectiveness, the POP must be taken at the same time every day.

**Indications**

In the absence of contraindications, the POP may be considered for any woman seeking a reliable, reversible, coitally independent method of contraception. It may be used by women who require an estrogen-free method of contraception. For this reason, it may be suitable for women over age 35 who smoke, women who experience migraine headaches with neurological symptoms, women who have unwanted side effects with use of combined oral contraceptives, or women who are breastfeeding.

The use of condoms is recommended for POP users to
CONTRAINDICATIONS

The World Health Organization has developed a list of absolute and relative contraindications to the use of POPs based on the available evidence of risk.6 Absolute contraindications include pregnancy and current breast cancer. Relative contraindications include active viral hepatitis and liver tumours.

NON-CONTRACEPTIVE BENEFITS

In addition to providing an effective method of contraception, the POP may decrease menstrual flow. Up to 10% of users will develop amenorrhea. Menstrual cramping and premenstrual symptoms may decrease.

SIDE EFFECTS

1. IRREGULAR BLEEDING
Irregular bleeding is the most frequently cited reason for discontinuation of the POP.50 Spotting occurs in approximately 12% of users in the first month, but this usually decreases to less than 3% at 18 months. Forty percent of long-term users continue to have regular cycles while using the POP.50

2. HORMONAL SIDE EFFECTS
Hormonal side effects such as headache, bloating, acne, and breast tenderness occur less commonly.

RISKS

Use of POPs is not associated with any major morbidity. Given in contraceptive doses, the POP does not appear to increase the risk of VTE, stroke, or myocardial infarction.41,42,56

MYTHS AND MISCONCEPTIONS

1. The POP can only be used by women who are breastfeeding. Fact: Although the POP is safe to use in breastfeeding women,57–60 it can be considered for any women seeking a reliable, reversible contraceptive method.

2. The POP is not an effective method of birth control. Fact: When used as directed, the POP is a safe and effective method of birth control with a failure rate of approximately 0.5%.2,6

INITIATION

The POP is usually started on the first day of the menstrual cycle, although it may be started at any time during the menstrual cycle as long as pregnancy can be excluded. A pill containing the active hormone norethindrone is taken every day. There is no pill-free interval. A backup method of birth control should be used for the first 7 days. Contraceptive reliability requires regular pill-taking at the same time each day (within 3 hours). Sperm penetration tests have shown that sperm permeability through cervical mucus increases if the interval between POPs is longer than 24 hours.61

POSTPARTUM

There is a theoretical concern that progestins administered within the first 72 hours after delivery may interfere with the fall in serum progesterone levels that triggers lactogenesis, thereby interfering with breast milk production. However, a prospective study did not detect any adverse effect on breast-feeding when progestin-only contraceptive methods were used within the first 72 hours postpartum.59

FOLLOW UP

A follow-up visit should be scheduled. This allows for an assessment of bleeding patterns, an assessment of patient satisfaction, and an opportunity to reinforce the issue of condom use for protection against STIs and HIV. After this visit, a POP user should continue annual well-woman care as for any sexually active woman.

TROUBLESHOOTING

1. IRREGULAR BLEEDING
Irregular bleeding is a common side effect of the POP. Pregnancy, infection, and genital pathology should be ruled out. Once this has been done, treatment options include the use of a non-steroidal anti-inflammatory agent for up to 10 days, switching to a low-dose combined oral contraceptive pill, or adding a short course of supplemental estrogen. Supplemental estrogen therapy can be given orally as 0.625 mg of conjugated equine estrogen for 28 days or 1 to 2 mg of micronized estradiol-17β given for 28 days, or it may be given transdermally in the form of a 50 µg or 100 µg estradiol-17β patch for a total of 25 days.

The use of anti-progestogenic agents has shown some success in the management of irregular bleeding associated with progestin-only contraceptive methods.62,63 These agents, such as mifepristone, are not currently available in Canada.

2. MISSED PILL
If a pill is missed, it should be taken as soon as possible. The next pill should be taken at the regular time, even if it means that 2 pills will be taken at the same time. If the pill use is delayed by more than 3 hours, a backup method of birth control should be used for the next 48 hours.2 If 2 or more pills in a row have been missed, then the individual must take 2 pills.
per day for 2 days and use a backup method of birth control for 48 hours.

In the event of a missed or late pill, the use of emergency contraception may be considered if appropriate. The healthcare provider may choose to provide an advance prescription for emergency contraception for use in these circumstances.

**DRUG INTERACTIONS**

Drug interactions with POPs are less well-known than are those for combined oral contraceptives. The progestins used in POPs are metabolized by the cytochrome P-450 enzyme system, and any medication that will induce this system (such as certain anticonvulsants) may accelerate the metabolism of the POP and reduce its contraceptive effectiveness.

**PROGESTIN IMPLANTS**

At one time, the 6-rod progestin implant called Norplant was available in Canada. Norplant was a highly effective 5-year method of reversible contraception with a failure rate of 0.1% per year.64 Levonorgestrel was released from the 6 rods, thereby suppressing ovulation, inducing endometrial atrophy, and rendering cervical mucus impermeable to sperm. Norplant was removed from the market in Canada in September 2000 because a lower-than-expected hormonal release rate was noted from several lots and there was a concern that contraceptive efficacy may have been affected.65 In July 2002, health-care professionals were informed that there did not appear to be a higher failure rate from these lots, and women were advised that they did not need to continue to use backup contraception. At the same time, the company that manufactured Norplant stated that it had no plans to reintroduce Norplant to the Canadian or US markets.66 For those women who currently have Norplant in place, studies suggest that it remains effective in women who weigh less than 70 kg for up to 7 years (Pearl Indices less than 2 per 100 women-years).67,68

New progestin-only implants with fewer rods have been developed and may become available in Canada in the future. An implant system with fewer rods will have the advantage of greater ease of insertion and removal. However, thorough training in insertion and removal of these implants is still extremely important to avoid injury to blood vessels, skin, and nerves. The following chart compares the characteristics of 2 of the newer devices with the 6-rod Norplant system:

Implanon, which contains etonogestrel as its active ingredient, differs from Norplant models because it appears to consistently inhibit ovulation until the beginning of the third year of use.69 This appears to translate into higher amenorrhea rates compared with levonorgestrel rod implant systems.70 The failure rate for Implanon is quite low, with no reported pregnancy in a database that followed 70 000 cycles of use.71 Any pregnancies that have been reported with this method were felt to have occurred before it was inserted.73 Pregnancies with Norplant (and Norplant-2) are felt to be lower than female sterilization for the first 5 years after insertion.74,75 Prolonged and irregular vaginal bleeding are major reasons for discontinuation of implant methods in all implant users and hence careful pre-insertion counselling is essential.76

**SUMMARY STATEMENTS**

1. Depot injections of medroxyprogesterone acetate (DMPA) and progestin implants are the most effective hormonal methods of contraception, and are appropriate contraceptive choices for Canadian women. (Level II-1)

2. Use of progestin-only preparations has not been shown to decrease breast milk production. The small amounts of steroid hormones secreted into breast milk do not have an adverse effect on the baby. (Level II-2)

3. The use of progestins given at contraceptive doses does not appear to increase the risk of VTE, myocardial infarction, or stroke. (Level II-2)

4. Progestin-only preparations may be appropriate contraceptive choices for women who have a past history of VTE. Whether the use of progestin-only preparations in women with a proven thrombophilia alters the risk of VTE is not known. (Level III)

5. The use of DMPA in healthy young women is associated with a decrease in bone mineral density that appears to be reversible. There is no evidence that use of DMPA causes osteoporosis. (Level II-1)

**RECOMMENDATIONS**

1. Progestin-only methods should be considered as contraceptive options for postpartum women, regardless of

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Implanon™</th>
<th>Norplant-2™</th>
<th>Norplant®</th>
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<tr>
<td>Number of Rods</td>
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<td>6</td>
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<td>Hormone</td>
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<td>Levonorgestrel</td>
<td>Levonorgestrel</td>
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<td>3.4 cm</td>
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<tr>
<td>Diameter of rod</td>
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<td>2.4 mm</td>
<td>2.4 mm</td>
</tr>
<tr>
<td>Amount of hormone</td>
<td>68 mg</td>
<td>75 mg (total 150 mg)</td>
<td>36 mg (total 216 mg)</td>
</tr>
<tr>
<td>Duration of effectiveness</td>
<td>3 years</td>
<td>3–5 years</td>
<td>5–7 years</td>
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</table>

**Comparison of contraceptive implants**
breastfeeding status, and may be introduced immediately after delivery. (Grade B)

2. Progestin-only methods should be considered as contraceptive options for women with a past history of VTE, or for women who are at a higher risk of myocardial infarction or stroke. In women with a proven thrombophilia, progestin-only preparations should be used with caution. (Grade B)

3. Young women who use DMPA should be counselled about dietary and lifestyle factors that will affect their peak bone mass, such as smoking, exercise, and calcium intake. (Grade A)

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CHAPTER 6: SPECIAL CONSIDERATIONS FOR HORMONAL CONTRACEPTION

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INTRODUCTION

In this chapter cardiovascular disease risk and the use of hormonal contraception is discussed. The possible use or non-use
of hormonal contraceptives in women with pre-existing medical conditions is also addressed.

VENOUS THROMBOEMBOLISM, MYOCARDIAL INFARCTION, AND STROKE IN USERS OF COMBINED AND PROGESTIN-ONLY HORMONAL CONTRACEPTION

VENOUS THROMBOEMBOLISM AND COMBINED HORMONAL CONTRACEPTION

Venous thromboembolism (deep vein thrombosis and pulmonary embolism) has been recognized as a complication of the use of combined oral contraceptives (OCs) since their introduction. Most studies dealing with the risk of thrombosis associated with contraception are observational in design, leading to level II evidence. Observational data are reported as point estimates, which measure the magnitude or strength of the association. Point estimates are expressed in cohort studies as the relative risk (risk of the disease in the exposed group divided by risk of the disease in the unexposed group) and in case-control studies as the odds ratio (odds of exposure in the case group divided by odds of exposure in the control group). A point estimate of 1.0 or close to 1.0 indicates that there is no association between the exposure and the outcome. Results are significant if the confidence interval does not overlap 1.0. The absolute risk is the variable of relevance for clinical decisions. When the absolute risk is not available, an estimate can be obtained by multiplying the baseline incidence in the population of interest by the relative risk or odds ratio associated with the risk factor of interest. The attributable risk is the difference between the baseline incidence and the incidence in patients exposed to the risk factor of interest.

The incidence of venous thromboembolism (VTE) is approximately 10 per 10 000 per year in adults. Among healthy non-pregnant women who do not use combined OCs, the incidence is approximately 0.3 per 10 000 per year at age 20 to 24 and increases to approximately 0.6 per 10 000 per year at age 40 to 44. The risk increases exponentially thereafter. The incidence of VTE during pregnancy and the puerperium is approximately 13 per 10 000 deliveries. The case-fatality rate of VTE is 1 to 2%. Venous thromboembolic rates are 3- to 4-fold higher among users of current combined OC preparations than among non-users. This translates into an absolute risk of 1 to 1.5 per 10 000 women per year of use. The risk of VTE during the first year of use has been shown consistently to be much higher than the risk during subsequent use.

The risk of VTE has been attributed to the estrogen content of combined OCs. This risk has declined as the estrogen content of OCs has declined, although this effect was not significant in 1 study. Reductions in the content of ethinyl estradiol below 50 µg have not been associated with a further decrease in thromboembolic risk. As the risk profile improved, small differences between preparations of combined OCs have emerged. A variety of progestogens are currently used in combined oral contraceptives. They are grouped as second-generation progestogens (principally levonorgestrel) and third-generation progestogens (desogestrel and gestodene). Norgestimate is partly converted to levonorgestrel and has been included variably with one or the other group. In 1995, the risk of VTE was reported to be about 2-fold higher in users of combined OCs containing third-generation progestogens than in users of second-generation progestogens. This unexpected finding led to a prolonged controversy over its validity, because of multiple potential biases including the effect of duration of use. A recent meta-analysis of studies published since 1995 has shown an overall adjusted odds ratio of 1.7 (95% confidence interval [CI], 1.4–2.0) for VTE risk in users of third- versus second-generation oral contraceptives. Seven of twenty-seven potentially relevant studies were included in the final analysis. The authors calculated an excess risk of thromboembolic events of 1.5 per 10 000 per year with use of third-generation oral contraceptives. The findings could not be explained by several potential biases. This represents level II-2 evidence. The increase in risk continues to be viewed with caution, both because its validity remains questionable and because the strength of the association is small, translating into small absolute increases in risk (or attributable risk).

Initial data suggested that the risk of VTE in users of combined oral contraceptives containing cyproterone acetate may be increased compared to users of oral contraceptives containing second-generation progestogens. A major flaw in the design of this study was the lack of adjustment for duration of use. Other studies have not found an increase in risk. In a recent best-evidence synthesis on 6 controlled epidemiological studies, Spitzer found a comparable attributable risk of VTE for conventional OCs and OCs containing cyproterone. Furthermore, preparations containing cyproterone are often prescribed for women with severe acne or hirsutism, with or without polycystic ovary syndrome. These women may have inherent differences in thromboembolic risk.

Underlying biologic predisposition to thrombosis (thrombophilia) compounds the effect of combined OCs on the risk of VTE. This effect is greater with severe thrombophilias (deficiency of physiologic inhibitors of coagulation, such as antithrombin, protein C or protein S; and homozygous or combined thrombophilias) than with milder thrombophilias (heterozygous factor V Leiden, heterozygous prothrombin gene mutation). Heterozygous factor V Leiden increases the risk of VTE 5- to 7-fold, and heterozygous prothrombin gene mutation 2- to 3-fold. These mild thrombophilias are found in 5 to 10% of the Caucasian population. Women with
heterozygous factor V Leiden who do not use combined OCs have an incidence of VTE of 5.7 per 10 000 per year.25 Women with heterozygous factor V Leiden who use combined OCs have a 30-fold increase in VTE risk when compared to non-users. This translates into an absolute risk of 28.5 per 10 000 per year.25

Testing for underlying thrombophilias is generally considered indicated in women with a personal or family history of VTE. Screening in asymptomatic women is not recommended. It has been estimated that more than 20 000 women would need to be screened and counselled to prevent 1 episode of venous thrombosis, and two million women would need to be screened and counselled to prevent 1 death from pulmonary embolism.27 The value of these strategies needs to be tested in prospective studies.

Women with known severe thrombophilias should not use combined OCs. Women with milder thrombophilias should probably also avoid combined OCs, but this is less certain.

A history of VTE puts women at risk of recurrence.28 Because of this, combined OCs are generally considered contraindicated in women with previous VTE, especially if the thromboembolic episode was idiopathic or there is underlying thrombophilia. Use of combined OCs can probably be considered in selected women with previous VTE if the thromboembolic episode was associated with a transient risk factor and there is no underlying thrombophilia. Active VTE is considered an absolute contraindication to use of combined OCs.

Adequate counselling should be ensured when prescribing combined OCs to women with an increased risk of VTE.

Cerebral vein thrombosis is also increased in users of combined OCs compared to non-users, and the risk is compounded by underlying thrombophilias.29 The baseline risk of cerebral venous thrombosis is extremely low (estimated incidence, 0.04 per 10 000 per year).29

**MYOCARDIAL INFARCTION AND COMBINED HORMONAL CONTRACEPTION**

Myocardial infarction (MI) is a rare disorder among young women. The baseline incidence in women with no risk factors who do not use combined OCs is estimated at 0.001 per 10 000 women per year at age 20 to 24.5 The incidence rises steeply from age 35 upward.30 At age 40 to 44, the baseline incidence is 0.2 per 10 000 per year.3 The case-fatality rate is about 30%,5,30 with a similar disability rate.

In users of combined OCs with an ethinyl estradiol content of more than 50 µg, MI rates are increased approximately 3-fold.5,31 Both smoking and age over 35 compound this risk.31-32 Because of the very low baseline incidence of MI in women younger than 35, the compounding effect of combined OC use becomes clinically significant chiefly in women over 35 who smoke.31

Several recent studies have found no significant increase in the risk of MI with use of combined OCs containing less than 50 µg ethinyl estradiol, regardless of age.33-36 Because the number of women over age 35 included in these studies is small, the safety of combined OC use in women over 35 needs to be interpreted with caution.

Smoking is a prominent risk factor for MI; the relative risk of MI in women who smoke is approximately 11.5,31 All women should be counselled to stop smoking, regardless of contraceptive choice. In one study,35 no increase in risk with the use of combined OCs was found in women smoking less than 25 cigarettes per day. A non-significant increase in risk with the use of combined OCs was found in heavy smokers (odds ratio [OR], 2.5; 95% CI, 0.9–7.5). Combined OC use had a compounding effect with heavy smoking, with an odds ratio of 32 (95% CI, 12–81) in heavy smokers when compared to non-smoking non-users. Thus, age and smoking are the major risk factors for MI in women who consider using combined OCs. Because of the potential for combined OCs to compound the effects of age and smoking, it is prudent to avoid their use in women over 35 who smoke heavily.

Some studies suggest that the risk of MI is not increased in users of combined OCs containing third-generation progestogens, and increased about 2-fold in users of second-generation progestogens.37-39 It is also suggested that the case-fatality rate is lower with use of third-generation combined OCs.39 A meta-analysis of recent studies suggests that the risk of MI is in fact lower with use of third- than with second-generation combined OCs, with an odds ratio of 0.62 (95% CI, 0.38–0.99).40 If these findings are valid, use of third-generation combined OCs may carry less risk of death and disability than second-generation OCs because of the higher fatality and disability rate associated with MI than that associated with venous thromboembolic disease.41-42 It is too early, however, to recommend preferential prescribing of second- or third-generation contraceptives based on different cardiovascular profiles. Differential prescribing according to age or underlying clinical risk is also not recommended. Further research is necessary to determine the true comparative global risk profile of these contraceptive preparations.

Combined OC users with hypertension are at increased risk of MI, compared to users without hypertension.31 Use of combined OCs should be avoided in women with uncontrolled hypertension, but they may probably be used safely in women with documented hypertension if the blood pressure is controlled by medication and followed closely. Women with hypertension who use combined OCs have a higher risk of poor control of blood pressure with medication.43

A family history of premature atherosclerotic events may warrant evaluation of the lipid profile before prescribing combined OCs. Hereditary thrombophilia does not influence the risk of MI.37 Screening for thrombophilic abnormalities is therefore not indicated solely because of a family history of MI.
STROKE AND COMBINED HORMONAL CONTRACEPTION

The baseline incidence of ischemic stroke in women who do not use combined OCs is estimated at 0.06 per 10,000 women per year at age 20 to 24. The incidence rises steeply from age 35 upward. At age 40 to 44, the incidence is 0.16 per 10,000 per year. The case-fatality rate of ischemic stroke is about 25%, with a 30% disability rate.

A significantly increased risk of stroke is observed in users of combined OCs with a high estrogen content. With current preparations, the risk has been found not to be increased in some studies. An increase in risk up to 2-fold was found in other studies. A recent meta-analysis reported an odds ratio for stroke of 1.93 (95% CI, 1.35–2.74) in users of current preparations, after controlling for smoking and hypertension.

The risk of stroke with use of third-generation combined OCs appears similar to that with second-generation combined OCs, although some data suggest a lower risk. Smoking is a major risk factor for stroke, with an approximate doubling of the risk overall as well as in women who use combined OCs.

Hypertension is a major risk factor for stroke. Combined OC users with hypertension are at increased risk of stroke, compared with users without hypertension. Use of combined OCs should be avoided in women with uncontrolled hypertension, but they can be probably used safely in women with documented hypertension if the blood pressure is controlled by medication and followed closely. Women with hypertension who use combined OCs have a higher risk of poor control with medication.

MIGRAINE AND COMBINED HORMONAL CONTRACEPTION

Women taking combined OCs may notice an increase or a decrease in the severity of their headaches. Tension headaches are not related to combined OC use. Migraine headache is associated with an approximately 3-fold increase in risk of ischemic stroke. The risk of stroke is considered higher in women who have migraine with aura (relative risk approximately 6 compared with women without migraine), although not all studies report a difference. The risk of stroke is further increased by the presence of hypertension, smoking, and the use of combined OCs. Migraine is not considered a contraindication to the use of combined OCs in the absence of aura or other risk factors. Combined OC use is generally considered contraindicated in patients with migraine aura, although visual scintillations lasting less than 1 hour are considered acceptable by some authors. New-onset headache or worsening headache require discontinuation of combined OCs and re-evaluation of the patient. Headache that occurs repeatedly in the pill-free week may be prevented by continuous use.

A small increase in the risk of hemorrhagic stroke with combined OC use has been found in developing countries but nowhere else.

VENOUS THROMBOEMBOLISM AND PROGESTIN-ONLY HORMONAL CONTRACEPTION

Progestins do not appear to increase the risk of VTE in contraceptive doses, but only limited data are available and 1 study found an increased risk even when adjusting for the indication for use. Progestin-only contraception is presently used as an alternative to combined OC use in women at heightened risk of VTE. The safety of this strategy needs to be tested in prospective studies. No data exist for emergency contraception, but the benefits far outweigh the potential risks.

MYOCARDIAL INFARCTION, STROKE, AND PROGESTIN-ONLY HORMONAL CONTRACEPTION

The use of progestin preparations is not associated with an increase in the risk of MI or stroke, even in therapeutic indications. Women at heightened risk of MI or stroke, including women with atypical migraine, can use progestin-only contraception as well as progestin-only emergency contraception.

HORMONAL CONTRACEPTION IN WOMEN WITH PRE-EXISTING CONDITIONS

It is important to balance the risks of pregnancy with the risks of oral contraceptives in women with pre-existing conditions.

HYPERLIPIDEMIA

The presence of hypertriglyceridemia increases the risk of pancreatitis and is a relative contraindication to the use of combined OCs.

DIABETES MELLITUS

Early combined OC formulations impaired glucose metabolism by increasing peripheral insulin resistance. Currently available products have no appreciable effect on carbohydrate metabolism. There is no evidence that use of combined OCs worsens the course of type 1 or 2 diabetes mellitus in the absence of vascular disease. Effective prevention of pregnancy outweighs the small risk of complicating vascular disease in diabetic women who are otherwise healthy, and whose diabetes is well controlled.

LIVER AND GALLBLADDER DISEASE

Combined OC use increases the secretion of cholic acid in bile. Women using combined OCs have a small increase in the risk of symptomatic gallstones. Combined OCs should not be used in women with active liver disease, or in women with known benign or malignant liver tumours.
INFLAMMATORY BOWEL DISEASE

There may be a modest association between the use of combined OCs and the development of inflammatory bowel disease. Combined OCs have been reported to increase the risk of relapse of inflammatory bowel disease in some studies, but not all. Combined OCs may be absorbed inadequately in the presence of chronic inflammation or active diarrhea.

SYSTEMIC LUPUS ERYTHEMATOSUS

Combined OCs are generally not prescribed to women with systemic lupus erythematosus because estrogen can exacerbate the disease. However, their use may be considered in selected cases, in the absence of active nephritis or antiphospholipid antibodies.

SICKLE CELL DISEASE

Women with sickle cell disease are at increased risk of stroke. However, the risk of pregnancy is high in these women, and effective prevention of pregnancy is essential. Despite a paucity of data, the general consensus is that combined OCs can be used. In one study, women randomized to use of depot-medroxyprogesterone acetate (DMPA) or combined OC, reported a more marked improvement in painful crises with the use of DMPA (70% reduction) than with OC (54.5% reduction). Control women had a 50% reduction of crises.

Yoong found some form of cyclical crises in 58% of women and concluded that DMPA should be considered in severe cases.

EPILEPSY

Combined OCs can be used safely in women with epilepsy. Some drugs reduce the efficacy of combined OCs. In this case, the use of combined OCs containing more than 35 µg of ethinyl estradiol may be warranted.

It is recommended that injections of DMPA be given every 10 weeks rather than every 12 weeks in women who are receiving antiepileptic drugs that induce hepatic microsomial enzymes.

ELECTIVE SURGERY

Whether women should discontinue OC use 4 weeks before elective surgery is controversial. The decision must take into account the risk of an unwanted pregnancy during this period of time. Discontinuation should be considered before surgery associated with a high risk of thrombosis, such as surgery for malignancy or surgery followed by prolonged immobilization. Standard recommendations for antithrombotic prophylaxis should be adhered to. Patients in whom OC are continued should be considered for antithrombotic prophylaxis.

MIGRAINE

Please refer to paragraph migraine and combined hormonal contraception.

SUMMARY STATEMENTS

1. The risk of myocardial infarction and stroke is increased significantly with smoking and may be slightly increased with the use of combined OCs. Because cardiovascular disease increases rapidly in women aged over 35, and because risk factors have a compounding effect, the use of combined OCs in smokers significantly increases the cardiovascular risk over the age of 35. (Level II-2)

2. Whether women should discontinue low-dose combined OC use before elective surgery is controversial. The decision must take into account the risk of unwanted pregnancy and the risk of post-operative thromboembolic events. (Level III)

3. The association between antibiotic use and contraceptive failure is based on isolated case reports only. Pharmacologic and cohort studies do not support an effect of antibiotics on combined OC-induced ovulation suppression or contraceptive failure. (Level II-2)

RECOMMENDATIONS

1. All women who smoke should be counselled to stop. Women over 35 who smoke should be advised not to use combined OCs. (Grade A)

2. Women using combined OCs who are undergoing major surgery or surgery that will be followed by prolonged periods of immobility should receive peri-operative antithrombotic prophylaxis. (Grade A) Consideration may be given to discontinuing low-dose combined OCs 4 weeks prior to elective surgery. A reliable contraceptive method (e.g., progestin-only contraception) should be substituted when combined OCs are withdrawn. (Grade C)

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CHAPTER 7: INTRAUTERINE DEVICES

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INTRODUCTION

Worldwide, over 100 million women have used the intrauterine contraceptive device (IUD). However, in North America less than 1% of women use this highly effective method of contraception. In Canada, 2 copper IUDs (Nova-T and Flexi-T 300) and a levonorgestrel-releasing device (Mirena) are currently available.

Mirena is also referred to as a levonorgestrel-releasing intrauterine system (LNG-IUS).

EFFICACY

Intrauterine devices are highly effective methods of reversible contraception. In a large trial, the failure rate of a copper IUD (Nova-T) was 1.26 per 100 women-years (WY) and the rate of ectopic pregnancy was 0.25 per 100 WY. The failure rate of the levonorgestrel-releasing intrauterine system was 0.09 per 100 WY and the ectopic pregnancy rate was 0.02 per 100 WY.

Although the product monograph for the Nova-T copper IUD suggests that it be replaced every 30 months, clinical trials have shown that it is effective for 5 years. The Flexi-T 300 copper IUD and the LNG-IUS should be replaced every 5 years.
MECHANISM OF ACTION

Intrauterine devices have multiple mechanisms of action. The chief mechanism of action of all IUDs appears to be the prevention of fertilization. If fertilization does occur, IUDs also appear to have post-fertilization effects, including the potential inhibition of implantation.

The copper-bearing IUDs consist of a vertical stem with a silver-cored copper wire wound around it. The presence of a foreign body and of copper in the endometrial cavity causes biochemical and morphological changes in the endometrium. These changes adversely affect sperm transport so that fertilization rarely occurs. The copper ions also have a direct effect on sperm motility, reducing the ability of sperm to penetrate cervical mucus. Ovulation is not affected in users of the copper IUD.

The levonorgestrel-releasing intrauterine system consists of a small polyethylene T-shaped frame with a cylindrical reservoir containing levonorgestrel on its vertical arm. This cylinder slowly releases hormone through a rate-limiting membrane. The LNG-IUS produces a weak foreign body reaction and endometrial changes that include endometrial decidualization and glandular atrophy. Endometrial estrogen and progesterone receptors are suppressed. Cervical mucus may become thickened, creating a barrier to sperm penetration. Ovulation may be inhibited in some women.

INDICATIONS

In the absence of contraindications, the IUD may be considered for any woman seeking a reliable, reversible, coitally independent method of contraception. It is particularly suited for women seeking long-term birth control or a method requiring less compliance. Women who have contraindications or sensitivities to estrogen, or women who are breastfeeding, may be good candidates for use of an IUD.

The copper IUD, in appropriately selected patients, may be used for postcoital contraception in women presenting up to 7 days after an act of unprotected intercourse.

The LNG-IUS has been shown to decrease menstrual flow and cramping, and therefore has been used in women with menorrhagia and dysmenorrhea. It should not be used for postcoital contraception.

CONTRAINDICATIONS

The World Health Organization (WHO) has developed a list of absolute and relative contraindications to use of an IUD.

ABSOLUTE CONTRAINDICATIONS

- pregnancy
- current, recurrent, or recent (within past 3 months) pelvic inflammatory disease (PID) or sexually transmitted infection (STI)
- puerperal sepsis
- immediate post-septic abortion
- severely distorted uterine cavity
- unexplained vaginal bleeding
- cervical or endometrial cancer
- malignant trophoblastic disease
- copper allergy (for copper IUDs)
- breast cancer (for LNG-IUS)

RELATIVE CONTRAINDICATIONS

- risk factor for STIs or human immunodeficiency virus (HIV)
- impaired response to infection
  - in HIV-positive women
  - in women undergoing corticosteroid therapy
- from 48 hours to 4 weeks postpartum
- ovarian cancer
- benign gestational trophoblastic disease

NON-CONTRACEPTIVE BENEFITS

Intrauterine devices are used primarily for contraception, but they also provide a number of non-contraceptive health benefits.

Case-control studies provide some evidence that use of non-medicated or copper IUDs reduces the risk of endometrial cancer. This protective effect is not related to the duration or timing of use, and its mechanism is not well understood.

Menorrhagia responds favourably to use of the LNG-IUS, with reported reductions in menstrual blood loss of 74 to 97% and favourable effects on hemoglobin levels. In 2 studies of women scheduled to undergo hysterectomy for menorrhagia, 64 to 80% of women randomized preoperatively to LNG-IUS insertion subsequently cancelled their hysterectomy, compared with 9 to 14% of women randomized to receive other medical treatments. Dysmenorrhea may also improve in LNG-IUS users.

A randomized controlled study found that use of the LNG-IUS protects against endometrial hyperplasia in women on tamoxifen. Small reports support a beneficial effect in the treatment of fibroid-related menorrhagia.
SIDE EFFECTS

1. BLEEDING
Irregular menstrual bleeding or an increase in the amount of bleeding are the most common side effects of IUDs in the first months after insertion. Menstrual blood loss in users of copper IUDs increases by up to 65% over non-users. Use of non-steroidal anti-inflammatory agents (NSAIDs) or tranexamic acid may help to decrease the amount of menstrual blood loss. The average number of days of spotting or bleeding appears to decrease over time. Users of copper IUDs have an average of 13 days of bleeding or spotting in the first month after insertion, decreasing to an average of 6 days at 12 months after insertion. The cumulative termination rates for bleeding problems after 5 years of use are up to 20% for copper IUDs.

By contrast, users of the LNG-IUS experience a reduction in menstrual blood loss of between 74 and 97%. Women using the LNG-IUS have an average of 16 days of bleeding or spotting at 1 month after insertion, and this decreases to an average of 4 days by 12 months after insertion. The cumulative termination rates for bleeding problems after 5 years of use are up to 14% for the LNG-IUS. Between 16 and 35% of LNG-IUS users will become amenorrheic after one year of use. Since information received in advance will improve user satisfaction, patients should be carefully counselled regarding potential menstrual changes prior to IUD insertion.

2. PAIN OR DYSMENORRHEA
Up to 6% of copper IUD and LNG-IUS users will have discontinued use at 5 years because of pain. Pain may be a physiological response to the presence of the device, but the possibility of infection, malposition of the device (including perforation), and pregnancy should be excluded. The LNG-IUS has been associated with a decrease in menstrual pain.

3. HORMONAL
The LNG-IUS appears to exert some systemic hormonal effects, even though the daily dose of levonorgestrel is extremely low. Hormonal side effects include depression, acne, headache, and breast tenderness. Most studies report a low incidence of such adverse effects, which appear to be maximal at 3 months after insertion and then decrease. Although weight gain has been reported as a side effect of LNG-IUS use, a large trial reported no significant difference in weight gain over 5 years in LNG-IUS users and copper IUD users.

4. FUNCTIONAL OVARIAN CYSTS
Functional ovarian cysts have been reported in up to 30% of LNG-IUS users. Since these cysts usually resolve spontaneously, they should be managed expectantly.

RISKS

1. UTERINE PERFORATION
Uterine perforation is a rare complication of IUD insertion, occurring at a rate of 0.6 to 1.6 per 1000 insertions. All uterine perforations, either partial or complete, occur or are initiated at the time of IUD insertion. Risk factors for perforation include postpartum insertion, an inexperienced operator, and a uterus that is immobile, extremely anteverted or extremely retroverted.

2. INFECTION
Methodological flaws in early observational research exaggerated the risk of PID associated with IUD use. Evidence from large cohort studies, case-control studies, and randomized controlled trials indicates that any risk of genital tract infection after the first month of IUD use is small. There appears to be an inverse relation between the risk of infection and the time since IUD insertion. The Women’s Health Study data showed a relative risk of PID of 3.8 in the first month after insertion, reaching baseline risk after 4 months. Investigations by the World Health Organization found the risk to be highest in the first 20 days following insertion. Although insertion of an IUD contaminates the endometrial cavity with bacteria, the cavity becomes sterile soon afterwards. Exposure to STIs, and not the use of the IUD itself, is responsible for PID occurring after the first month of use.

It remains unclear whether the risk of PID is reduced in users of the LNG-IUS compared to users of the copper IUDs. IUD users should continue to use condoms for protection against STIs.

3. EXPULSION
Expulsion of the IUD is most common in the first year of use (2–10% of users). The 5-year cumulative expulsion rate for the copper IUD is 6.7% and for the LNG-IUS is 5.8%. Risk factors for expulsion include insertion immediately postpartum, nulliparity, and previous IUD expulsion. A woman who has expelled one IUD has a 30% chance of expelling a subsequent device.

4. FAILURE
If a woman becomes pregnant with an IUD in situ, the possibility of ectopic pregnancy must be excluded.

The risk of spontaneous abortion is increased in women who continue a pregnancy with an IUD in place. The UK Family Planning Research Network study found that 75% of pregnancies aborted if a copper IUD was left in situ, but that early removal virtually eliminated the risk of septic abortion. If the IUD was removed, 89% of women had a live birth, compared to 25% of women who left the IUD in place. Although the risk of spontaneous abortion appears to be normalized after IUD removal, the risk of preterm delivery remains higher.
MYTHS AND MISCONCEPTIONS

1. Nulliparous women cannot use IUDs.
   
   **Fact:** Nulliparity is not a contraindication to IUD use. In carefully selected nulliparous women, IUDs may be successfully used.

2. IUDs increase the risk of ectopic pregnancy.
   
   **Fact:** IUDs do not increase the risk of ectopic pregnancy. Because IUDs work primarily by preventing fertilization, IUD users have a lower risk of ectopic pregnancy than women who are not using any form of birth control (0.02–0.25/100 WY versus 0.12–0.5/100 WY). However, in women who conceive with an IUD in place, the diagnosis of ectopic pregnancy should be excluded.

3. IUDs increase the risk of infertility.
   
   **Fact:** IUDs do not increase the risk of infertility. Women who discontinue use of an IUD in order to conceive are able to conceive at the same rate as women who have never used an IUD. Copper IUD use is not associated with an increase in tubal factor infertility in nulliparous women.

4. IUDs increase the long-term risk of PID.
   
   **Fact:** The incidence of PID among IUD users is less than 2 episodes per 1000 years of use, similar to that of the general population. The increase in risk of PID associated with IUD use appears to be related only to the insertion process. After the first month of use, the risk of infection is not significantly higher than in women without IUDs.

5. IUDs are not effective contraceptives.
   
   **Fact:** IUDs are a highly effective method of birth control. In fact, in long-term users of IUDs, the failure rate approaches that of tubal ligation.

   The LNG-IUS appears to be as effective as tubal ligation.

INITIATION

Prior to insertion, informed consent should be obtained and the patient should be aware of the risks, benefits, and alternative methods of contraception. Patients should be counselled regarding the potential side effects associated with the IUD of choice, particularly alterations in the menstrual cycle. Patients should also be reminded that the IUD does not protect against STIs or HIV.

The IUD can be inserted at any time during the menstrual cycle once pregnancy or the possibility of pregnancy can be excluded. Although the advantages of inserting the IUD during or shortly after menses include ruling out pregnancy and the masking of insertion-related bleeding, there is no evidence to support the common practice of inserting the IUD only during menses. In fact, infection and expulsion rates may be higher when inserted during menses. The IUD can be removed and replaced at the same time on any day of the menstrual cycle.

Postpartum women may be candidates for immediate IUD insertion (within 10–15 minutes after delivery of the placenta).

These women are at higher risk of expulsion and uterine perforation. In most circumstances, it is best to wait to insert the IUD until the uterus is completely involuted, usually at 4 to 6 weeks postpartum. Women should wait until 6 weeks post-partum to have the LNG-IUS inserted. An IUD can be safely inserted immediately after a first trimester pregnancy termination.

The cost-effectiveness of screening for gonorrhea and chlamydia infection prior to IUD insertion is unclear. The cervix should be carefully inspected prior to IUD insertion, and, if there is any evidence of mucopurulent discharge or pelvic tenderness, cervical swabs should be performed and IUD insertion delayed until the results are known.

ANTIBIOTIC PROPHYLAXIS

A Cochrane Collaboration review concluded that neither doxycycline nor azithromycin before IUD insertion conferred benefit.

According to the American Health Association’s 1997 guidelines for prevention of bacterial endocarditis (SBE), antibiotic prophylaxis is not necessary prior to IUD insertion if there is no obvious infection. However, in the presence of infection, removal of an IUD requires SBE antibiotic prophylaxis.

FOLLOW UP

A follow-up visit should be scheduled post-insertion. This allows for the exclusion of infection, an assessment of bleeding patterns, an assessment of patient and partner satisfaction, and an opportunity to reinforce the issue of condom use for protection against STIs and HIV. After this visit, an IUD user should continue annual well-woman care as for any sexually active woman.

An IUD user should be instructed to contact her healthcare provider if any of the following occur:

- she cannot feel the IUD’s threads
- she or her partner can feel the lower end of the IUD
- she thinks she is pregnant
- she experiences persistent abdominal pain, fever, or unusual vaginal discharge
- she or her partner feel pain or discomfort during intercourse
- she experiences a sudden change in her menstrual periods
- she wishes to have the device removed or wishes to conceive

TROUBLESHOOTING

1. LOST STRINGS

If an IUD user is unable to palpate the IUD strings, a speculum exam should be performed. If the strings are not seen in the cervical os, the device may have been expelled, may have perforated the uterine wall, or the strings may have been drawn up into the cervical canal. Pregnancy should be excluded. Once pregnancy is excluded, the cervical canal should be explored (with a cotton swab, cytobrush, forceps, or similar instrument).
to see if the strings can be found. If the strings cannot be found, ultrasound is the preferred method to identify the location of the IUD. If the device is seen within the uterus, it can be left in situ. If the device is not identified within the uterus or the pelvis, a plain x-ray of the abdomen should be performed to determine whether the device has perforated the uterine wall. Both the LNG-IUS and the copper IUD are radio-opaque.

2. PREGNANCY WITH AN IUD IN PLACE
Once the diagnosis of an ectopic pregnancy has been excluded, the woman should be asked about her wishes for the pregnancy. If she wishes to terminate the pregnancy, the device should be left in place until the procedure. If she wishes to continue with the pregnancy, the IUD should be removed if possible. If the strings are visible, gentle traction is applied to remove the device. If the strings are not visible, gentle exploration of the cervical canal is performed. If no strings are found, the possibility of perforation must be considered. This is best excluded by pelvic ultrasound. Despite reports of successful hysteroscopic IUD removal during the first trimester, if the device remains in the uterus then usually no attempt is made to remove it. Note should be made of recovery of the IUD at the time of delivery.

3. AMENORRHEA OR DELAYED MENSES
Pregnancy must be excluded. Once pregnancy has been excluded, investigation should be as for a woman without an IUD. Up to 35% of LNG-IUS users may experience amenorrhea. If proper positioning of the LNG-IUS is confirmed, it is unnecessary to perform repeated pregnancy tests. If the IUD user is post-menopausal, the device should be removed.

4. PAIN AND ABNORMAL BLEEDING
Increased menstrual bleeding with or without an increase in menstrual cramping may occur in IUD users. In the event of partial expulsion or perforation, the device should be removed and consideration given to inserting another IUD. In the first few months after insertion, pain and spotting can also occur between menses. Once partial expulsion, perforation, pregnancy, and infection are ruled out, treatment with NSAIDs may be helpful in treating these symptoms. The number of days of bleeding or spotting usually decreases over time. If pain or bleeding persists or worsens, removing the IUD must be considered.

IUD users should be informed about potential changes in bleeding patterns, as well as signs and symptoms of infection prior to IUD insertion.

5. DIFFICULTY REMOVING THE IUD
Grasping the string with a ring forceps and exerting gentle traction can usually accomplish removal of an IUD. If the strings cannot be seen, manoeuvres such as those described above can be used to assist in localizing the strings. If further manoeuvres are needed, a paracervical block may be considered. A uterine sound can be passed into the endometrial cavity to localize the IUD. Cervical dilation may be required. Once localized, the IUD can be subsequently grasped with a small grasping instrument directed towards it. If removal is not easily performed, direct visualization of the IUD with ultrasound or hysteroscopy may be required. Occasionally general anesthetic may be needed to carry out IUD removal.

6. STI IDENTIFIED WITH IUD IN PLACE
Appropriate antibiotic therapy should be initiated for an IUD user (and her sexual contacts) found to have chlamydial or gonococcal cervicitis. If there is a suggestion of PID, the device should be removed after pre-treating the woman with antibiotics. She should be counselled regarding the use of barrier contraceptive methods for STI prevention.

7. ACTINOMYCOSIS ON PAP SMEAR
Actinomyces is considered a commensal vaginal organism but may be associated with frank infection. Up to 20% of cervical smears in long-term copper IUD users show evidence of Actinomycosis, although this finding is only noted in up to 3% of LNG-IUS users. However, when cultures are performed, only 40% of women with Actinomyces-like organisms found on Pap smears are shown to be colonized. Removal of the device in women with Actinomycosis on their Pap smear may not be necessary. In the asymptomatic woman, it is reasonable to leave the IUD in place, follow her with annual Pap smears and pelvic examinations, and warn her of potential symptoms of PID. If the decision is made to treat, antibiotic therapy with penicillin G, tetracycline, or doxycycline may be given. If the woman is symptomatic, the IUD should be removed after antibiotic preloading. If the infection is severe, she should be hospitalized, treated for PID, and investigated for possible abscess.

SUMMARY STATEMENTS
1. In women who are at low risk of acquiring STIs, the use of an intrauterine device may be an excellent contraceptive option. Efficacy rates for the levonorgestrel-releasing intrauterine system approach those of surgical sterilization; it is therefore an excellent alternative to surgical sterilization for women who seek long-term contraception. (Level II-2)
2. The copper IUDs (Nova-T and Flexi-T 300) and the LNG-IUS (Mirena) provide effective contraception for 5 years. (Level I)
3. The risk of genital tract infection after the first month of IUD use is small. There appears to be an inverse relation between risk of infection and time since IUD insertion. Although the relative risk of pelvic inflammatory disease (PID) in the first month after insertion is increased slightly, the absolute risk is still low. Exposure to sexually transmitted infections, and
not the use of the IUD itself, is responsible for PID occurring after the first month of use. (Level II-2)

4. Both types of IUDs provide excellent contraceptive efficacy (Level 1). In addition, the copper IUD may decrease the risk of endometrial cancer (Level II-2); the levonorgestrel-releasing IUS may provide an acceptable alternative to hysterectomy, by decreasing menorrhagia and increasing hemoglobin concentrations. (Level I)

RECOMMENDATIONS

1. Health-care professionals providing family planning services should be familiar with the use of the intrauterine device (IUD). (Grade A)

2. Appropriately trained personnel in adequately equipped facilities should be available in order to ensure that women have access to the IUD if they desire this method of contraception. (Grade A)

REFERENCES


35. Tietze C. Evaluation of intrauterine devices: ninth progress report of the


