No. 143 – Part 2 of 3, March 2004

CANADIAN CONTRACEPTION CONSENSUS

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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 rifampicin). (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: Intrauterine Devices

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)

J Obstet Gynaecol Can 2004;26(3):219–54.

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, antiestrogenic, 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 glycogen 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

Table 1. Composition of Various Combination Hormonal Contraceptives

Type	Preparations	Estrogen (mg)	Progestin (mg)
Combination Monophasic			
Ethinyl estradiol / **desogestrel**	Marvelon	0.030	0.15
	Ortho-Cept	0.030	0.15
Ethinyl estradiol / **ethynodiol diacetate**	Demulen 30	0.030	2
Ethinyl estradiol / **levonorgestrel**	Min-Ovral	0.030	0.15
	Alesse	0.020	0.10
Ethinyl estradiol / **norelgestromin**	Evra (patch)	0.020	0.15
Ethinyl estradiol / **norethindrone**	Brevicon 0.5/35	0.035	0.5
	Ortho 0.5/35	0.035	0.5
	Brevicon 1/35	0.035	1
	Ortho 1/35	0.035	1
	Select 1/35	0.035	1
Ethinyl estradiol / **norethindrone acetate**	MinEstrin 1/20	0.020	1
	LoEstrin 1.5/30	0.030	1.5
Ethinyl estradiol / **norgestimate**	Cyclen	0.035	0.25
Ethinyl estradiol / **norgestrel**	Ovral	0.050	0.5
	Lo-Femenol	0.030	0.3
Mestranol / **norethindrone**	Ortho-Novum 1/50	0.050	1
	Norinyl	0.050	1
Ethinyl estradiol / **cyproterone acetate**	Diane 35*	0.035	2
Biphasic			
Ethinyl estradiol / **norethindrone**	Synphasic	0.035 (12 tabs)	0.5
		0.035 (9 tabs)	1
Triphasic			
Ethinyl estradiol / **norethindrone**	Ortho 7/7/7	0.035 (7 tabs)	0.5
		0.035 (7 tabs)	0.75
		0.035 (7 tabs)	1
Ethinyl estradiol / **norgestimate**	Tri-Cyclen	0.035 (7 tabs)	0.18
		0.035 (7 tabs)	0.215
		0.035 (7 tabs)	0.25
Ethinyl estradiol / **levonorgestrel**	Triquilar	0.030 (6 tabs)	0.05
		0.040 (5 tabs)	0.075
		0.030 (10 tabs)	0.125
	Triphasil	0.030 (6 tabs)	0.05
		0.040 (5 tabs)	0.075
		0.030 (10 tabs)	0.125

*indicated for severe acne, should not be prescribed solely for its contraceptive properties

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[19,20]
- increased bone mineral density[21-24]
- decreased dysmenorrhea[19,25-27]
- decreased peri-menopausal symptoms[28,29]
- decreased acne[30-36]
- decreased hirsutism[37]
- decreased endometrial cancer[38-42]
- decreased ovarian cancer[43-48]
- decreased risk of fibroids[49,50]
- possibly fewer ovarian cysts[51]
- possibly fewer cases of benign breast disease[52]
- possibly less colorectal carcinoma[53-55]
- decreased incidence of salpingitis[56,57]
- decreased incidence or severity of moliminal symptoms[58]

SIDE-EFFECTS

Some combined OC users will experience minor side-effects, most commonly during the first 3 cycles.[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.[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.[60]

1. IRREGULAR BLEEDING

Unexpected bleeding occurs in 10 to 30% of women in the first month of combined OC use[62-64], and is a common reason for discontinuing use of combined OCs.[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.[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.[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.[62]

2. BREAST TENDERNESS AND NAUSEA

Breast tenderness and nausea may occur, but generally improve with time.[71] These symptoms may occur less often in women who use combined OCs containing smaller amounts of estrogen.[59]

3. WEIGHT GAIN

Although weight gain is often thought to be a side-effect of the combined OC,[72] placebo-controlled trials have failed to show any association between low-dose combined OCs and weight gain.[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.[73]

RISKS

1. VENOUS THROMBOEMBOLISM

The rates of venous thromboembolism in combined OC users are 3- to 4-fold higher than among non-users.[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.[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.[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.[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.[86] Although some studies of low-dose combined OCs report no increase in the risk of stroke,[87-88] others have reported an increased risk of up to 2-fold.[89-92] Smoking and hypertension are major risk factors for stroke.[93] Combined OC users with hypertension are at an increased risk of stroke relative to users without hypertension.[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.[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.[96] However, there does not appear to be a significantly increased risk of gallstone formation in combined OC users.[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.[99] The best data available until recently were the results of a large meta-analysis published in 1996.[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.[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.[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.[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 progestin 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.[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.[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.[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,[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.[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.

   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.[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.[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.[48,111] The combined OC is associated with a

50% overall reduction in the risk of endometrial cancer[40] and the protective effect persists long after the combined OC is discontinued.[42] The combined OC may also have a protective effect against colorectal cancer.[53-55] There appears to be either no increase[99,102] or a very slight increase[100] 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.[67,112]
3. The combined OC affects future fertility.
   Fact: Fertility is restored within 1 to 3 months after stopping the combined OC.[67,113]
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.[114]
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.[113]
6. The combined OC causes acne.
   Fact: Acne improves in women using the combined OC[30-36] due to a decrease in circulating free androgen.[115] 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 thrombophilias is not recommended.

2. COUNSELLING

Adequate counselling prior to initiation of combined OCs may help to improve compliance (regular use) and adherence (continuation).[60-61,66] 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.[116-118] A back-up method of contraception should be used for the first week after combined OC initiation if the Quick Start method is used.[118] This method, with its simple starting instructions, improves compliance, particularly in adolescents,[116-118] and is not associated with an increase in the incidence of breakthrough bleeding or other side-effects.[115,117]
- 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 interval[120]; improved control over symptoms of endometriosis[121] and polycystic ovary syndrome[122]; 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 estrogen-progestin doses per month[123]) and a slightly higher cost for medications (an extra 3 pill packages per year for a 91-day cycle). These potential disadvantages must be weighed against the likely reduction in the cost of sanitary supplies, in pain medication, and in time off work or school; more breakthrough bleeding initially[124-125]; and possible delay in the recognition of pregnancy.

In 2 surveys of women, many respondents preferred amenorrhea or less painful and shorter periods to having menstrual bleeding every 4 weeks. In Australia, 46% of (158) female patients and 55% of (20) young female doctors surveyed would choose to bleed at intervals of 3 months or greater if they could choose their own pill regimen.[126] In the Netherlands, adolescent females preferred less painful and shorter menstrual bleeding, and women age 45 to 49 preferred amenorrhea to having menstrual bleeding every 4 weeks.[127]

A retrospective study of 267 women who initiated a continuous OC regimen found that 64% of the women continued with this regimen; 86% reported an improvement in their original problem such as headache and dysmenorrhea and 76% reported a high degree of satisfaction.[120] The women were counselled to take the combined OC until they experienced breakthrough bleeding, or completed 2 pill packages (42 days), 3 pill packages (63 days), or 4 pill packages (84 days). The mean cycle length was 84 days, with most women choosing a hormone-free interval of 4 to 5 days. Breakthrough bleeding and spotting was a common reason for returning to a 21-day combined OC regimen. It is therefore essential to counsel that breakthrough bleeding will decrease over time.[128] The use of a monophasic pill regimen[129] or a 21-day OC regimen prior to extending the cycle[128] has been shown to decrease the incidence of breakthrough bleeding when using the extended combined OC regimens. To reduce the incidence of breakthrough bleeding and improve patient satisfaction, women should have minimal side-effects during their 21 hormone days before extending their regimen.

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 Orthocept 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

1. 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[69]; 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.[113] 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[141]), so that these women should be screened for Chlamydia infection.[62]

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.[62] 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.[62] 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.[113] 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. If chloasma occurs, changing to another pill will not help.[113] 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.[113] Decreasing caffeine intake may be helpful in reducing mastalgia. Decreasing the estrogen content of the combined OC may also be helpful.[113] 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.[71] 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.[113,142] 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.[143]

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 P450-3Δ4 pathway of the liver, after which it is conjugated with glucuronides and passes into the enterohepatic

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.[144] 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.[145,146] 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.[146] 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.[147] Monitoring of phenytoin concentrations is important because combined OCs may inhibit their metabolism.[146]

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,[148] 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.[148] 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, [146,149,150] resulting in increased estrogenic side-effects. Oral contraceptives may also decrease the clearance of other medications, thereby increasing their activity.[146,149,150] 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.[151] 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).[138,152,153] A subgroup of women weighing more than 90 kg may have an increased risk of pregnancy while using the patch.[152,153] In one study, 4 of the 6 pregnancies that occurred were in women weighing at least 90 kg[152]; in a pooled analysis, 5 of the 15 pregnancies that occurred in patch users were in women weighing more than 90 kg.[153] The contraceptive efficacy of other methods of hormonal contraception, including the combined OC[14], progestin implants[154], 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.[155] 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)

Medications Whose Action May Cause Contraceptive Failure	Medications Which May Increase OC Activity	Medications Whose Clearance Can Be Decreased by OCs
Carbamazepine	Acetaminophen	Amitriptyline
Griseofulvin	Erythromycin	Caffeine
Oxcarbazepine	Fluoxetine	Cyclosporine
Phenobarbitol	Fluconazole	Diazepam
Phenytoin	Fluvoxamine	Imipramine
Primidone	Grapefruit juice	Phenytoin
Rifampin	Nefazadone	Selegiline
Ritonavir	Vitamin C	Theophylline
St. John's Wort		
Topiramate		

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; cerebrovasuclar 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.[158] In a pooled analysis of patch users, 78.5% of patients remained within 5% of their baseline weight while using the contraceptive patch.[156]

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.[159] 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. Back-up 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.[160] 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.[151] 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.[161] Etonorgestrel 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.[162,163] while the overall Pearl Index is between 0.65 and 1.18.[162,163] 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.[162,163]

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.[164,165] 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.[166]

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.[162] 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.[167] Withdrawal bleeding occurs in the majority of cycles.[162]

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.[162]

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.[162] Treatment-related leukorrhea occurs in approximately 5% of women.[162] 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.[162]

RISKS

The risks are felt to be the same as for oral contraceptives.[162]

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.[163] 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.[161] 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.[168] Vaginally administered miconazole was not found to have a significant effect on serum concentrations of ethinyl estradiol or etonogestrel.[168] 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 25mg 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.[169] Its mechanism of action is primarily by inhibition of ovulation.[170] 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.[170] The vaginal bleeding with this method is due to estrogen withdrawal, and usually occurs 3 weeks (day 22) after the injection.[171]

When compared with combined OCs, the combined monthly injectable has less breakthrough bleeding[171], a greater incidence of amenorrhea (14.6% during at least 1 cycle over 1 year, compared with 3.3% for OC users [$p \leq 0.01$])[171], better inhibition of ovarian follicular activity than a 20 µg ethinyl estradiol pill,[172] and a weight gain of about 4 pounds over 1 year.[173]

SUMMARY STATEMENTS

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

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 25µg of estrogen per day for 21 days. The daily progestin dose is 100µg of desogestrel for days 1 to 7, 125µg for days 8 to 14, and 150µg 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: 20µg ethinyl estradiol and 150µg desogestrel for 21 days, followed by 2 days of placebo tablets and 5 days of low-dose estrogen tablets containing just 10µg ethinyl estradiol. It therefore has a shortened hormone-free interval of 2 days, instead of the typical 7 days of most other pills. 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 3mg drospirenone (DRSP) and 30µg 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)

REFERENCES

1. Wilkins K, Johansen H, Beaudet MP, Neutel CI. Oral contraceptive use. 2000;11(4):25–37. Statistics Canada. Health Reports.
2. Fisher W, Boroditsky R, Morris B. The 2002 Canadian Contraception Study. J Obstet Gynaecol Can 2003. (in Press)
3. Upton GC. The phasic approach to oral contraception: the triphasic concept and its application. Int J Fertil 1983;28:121–40.
4. Fotherby K. Bioavailablity of orally administered sex steroids used in oral contraceptives and hormone replacement therapy. Contraception 1996;544:59–69.
5. Dickey RP. Managing contraceptive pill patients. 8th ed. Dallas: Emis Medical Publishers;1994.
6. Weems Chihal HL, Peppler RD, Dickey RP. Estrogen potency of oral contraceptive pills. Am J Obstet Gynecol 2003;121:75–83.
7. Kuhl H. Comparative pharmacology of newer progestins. Drugs 1996;51:188–215.
8. Fotherby K, Caldwell AD. New progestins in oral contraception. Contraception 1994;49:1–32.
9. World Health Organization. Improving access to quality care in family planning: medical eligibility criteria for contraceptive use. 2nd ed. Geneva:WHO; 2001.
10. Hatcher RA, Trussell J, Stewart F, Cates W, Stewart GK, Guest F, et al. Contraceptive Technology. 17th ed. New York: Ardent Media Inc; 1998.
11. Fu H, Darroch JE, Haas T, Ranjit N. Contraceptive failure rates: new estimates from the 1995 National Survey of Family Growth. Fam Plann Perspect 1999;31:56–63.
12. Potter L, Oakley D, de Leon-Wong E, Canamar R. Measuring compliance among oral contraceptive users. Fam Plann Perspect 1996;28(4):154–8.
13. Rosenberg MJ, Waugh MS, Burnhill MS. Compliance, counseling and satisfaction with oral contraceptives: a prospective evaluation. Fam Plann Perspect 1998;30(2):89–92.
14. Holt VL, Cushing-Haugen KL, Daling JR. Body weight and risk of oral contraceptive failure. Obstet Gynecol 2002;99(5):820–7.
15. Vessey M. Oral contraceptive failures and body weight: findings in a large cohort study. J Fam Plann Reprod Health Care 2001;27(2):90–1.
16. Diczfalusy E. Probable mode of action of oral contraceptives. Res Steroids 1966;2:389–92.
17. Mitra PK, Roychadhuri J. Effect of oral contraceptives on the ultrastructure of the endometrium. J Gynaecol Endocrinol 1987;3(1-4):13–5.
18. Rossmanith WG, Steffens D, Schramm G. A comparative randomized trial on the impact of two low-dose oral contraceptives on ovarian activity, cervical permeability, and endometrial receptivity. Contraception 1997;56(1):23–30.
19. Larsson G, Milsom I, Lindstedt G, Rybo G. The influence of a low-dose combined oral contraceptive on menstrual blood loss and iron status. Contraception 1992;46(4):327–34.
20. Iyer V, Farquhar C, Jepson R. Oral contraceptive pills for heavy menstrual bleeding (Cochrane Methodology Review). In: The Cochrane Database of Systematic Reviews, Issue 4 2003.
21. Berenson AB, Radecki C, Grady JJ, et al. A prospective, controlled study of the effects of hormonal contraception on bone mineral density. Obstet Gynecol 2001;98(4):576–82.
22. Petitti DB, Piaggio G, Mehta S, Cravioto MC, Meirik O. Steroid hormone contraception and bone mineral density: a cross-sectional study in an international population. The WHO Study of Hormonal Contraception and Bone Health. Obstet Gynecol 2000;95(5):736–44.
23. Gambacciani M, Spinetti A, Taponeco F, Cappagli B, Piaggesi L, Fioretti P. Longitudinal evaluation of perimenopausal vertebral bone loss: effects of a low-dose oral contraceptive preparation on bone mineral density and metabolism. Obstet Gynecol 1994;83(3):392–6.
24. Kritz-Silverstein D, Barrett-Connor E. Bone mineral density in postmenopausal women as determined by prior oral contraceptive use. Am J Public Health 1993;83:100–2.
25. Hendrix SL, Alexander NJ. Primary dysmenorrhea treatment with a desogestrel-containing low-dose oral contraceptive. Contraception 2002;66(6):393–9.
26. Milsom I, Sundell G, Andrersch B. The influence of different combined oral contraceptives on the prevalence and severity of dysmenorrhea. Contraception 1990;42(5):497–506.
27. Sundell G, Milsom I, Andersch B. Factors influencing the prevalence and severity of dysmenorrhoea in young women. Br J Obstet Gynaecol 1990;97:588–94.
28. Casper RF, Dodin S, Reid RL. The effect of 20mcg ethinyl estradiol/1 mg norethindrone acetate (Minestrin), a low-dose oral contraceptive, on vaginal bleeding patterns, hot flashes, and quality of life in symptomatic perimenopausal women. Menopause 1997;4:139–47.
29. Shargril AA. Hormone replacement therapy in perimenopausal women with a triphasic contraceptive compound: a three year prospective study. Int J Fertility 1985;30(15):18–28.
30. Redmond GP, Olson WH, Lippman JS, Kafrissen ME, Jones TM, Jorizzo JL. Norgestimate and ethinyl estradiol in the treatment of acne vulgaris: a randomized, placebo-controlled trial. Obstet Gynecol 1997;89(4): 615–22.
31. Lemay A, Poulin Y. Oral contraceptives as anti-androgenic treatment of acne. J Obstet Gynaecol Can 2002;24(7):559–67.
32. Thiboutot D, Archer DF, Lemay A, Washenik K, Roberts J, Harrison DD. A randomized, controlled trial of a low-dose contraceptive containing 20 microg of ethinyl estradiol and 100 microg of levonorgestrel for acne treatment. Fertil Steril 2001;76(3):461–8.
33. Lucky AW, Henderson TA, Olson WH, Robisch DM, Lebwohl M, Swinyer LJ. Effectiveness of norgestimate and ethinyl estradiol in treating

moderate acne vulgaris. J Am Acad Dermatol 1997;37(5 Pt 1):746–54.
34. Thorneycroft IH, Stanczyk FZ, Bradshaw KD, Ballagh SA, Nichols M, Weber ME. Effect of low-dose oral contraceptives on androgenic markers and acne. Contraception. 1999;60(5):255-62.
35. Mango D, Ricci S, Manna P, et al. Clinical and hormonal effects of ethinyl estradiol combined with gestodene and desogestrel in young women with acne vulgaris. Contraception 1996;53:163–70.
36. Carlborg L. Cyproterone acetate versus levonorgestrel combined with ethinyl estradiol in the treatment of acne: results of a multicenter study. Acta Obstet Gynecol Scand Suppl 1986;134:29–32.
37. Dewis D, Petsos M, Anderson DC. The treatment of hirsutism with a combination of desogestrel and ethinyl estradiol. Clin Endocrin 1985;22:29–36.
38. Centers for Disease Control and Prevention. Combination oral contraceptive use and the risk of endometrial cancer. The Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development. JAMA 1983;257(6):796–800.
39. Collins JA, Schlesselman JJ. Perimenopausal use of reproductive hormones effects on breast and endometrial cancer. Obstet Gynecol Clin North Am 2002;29(3):511–25.
40. Schlesselman JJ. Risk of endometrial cancer in relation to use of combined oral contraceptives: a practitioner's guide to meta-analysis. Hum Reprod 1997;12:1851–63.
41. Schlesselman JJ. Net effect of oral contraceptive use on the risk of cancer in women in the United States. Obstet Gynecol 1995;85(5):793–801.
42. Sherman ME, Sturgeon S, Brinton LA, Potischman N, Kurman RJ, Berman ML, et al. Risk factors and hormone levels in patients with serous and endometrioid uterine carcinomas. Mod Pathol 1997;10:963–8.
43. Bosetti C, Negri E, Trichopoulos D, Franceschi S, Beral V, Tzonou A, et al. Long-term effects of oral contraceptives on ovarian cancer risk. Int J Cancer 2002;102(3):262–5.
44. Gross TP, Schlesselman JJ. The estimated effect of oral contraceptive use on the cumulative risk of epithelial ovarian cancer. Obstet Gynecol 2003;83(3):419–24.
45. Hankinson SE, Colditz GA, Hunter DJ, Spencer TL, Rosner B, Stampfer MJ. A quantitative assessment of oral contraceptive use and ovarian cancer. Obstet Gynecol 1992;80:708–14.
46. Ness RB, Grisso JA, Klapper J, Schlesselman JJ, Silberzweig S, Vergona R, et al. Risk of ovarian cancer in relation to estrogen and progestin dose and use characteristics of oral contraceptives. SHARE Study Group. Steroid Hormones and Reproductions. Am J Epidemiol 2000;152(3):233–41.
47. Walker GR, Schlesselman JJ, Ness RB. Family history of cancer, oral contraceptive use, and ovarian cancer risk. Am J Obstet Gynecol 2003;186(1):8–14.
48. Narod SA, Risch H, Moslehi R, Dorum A, Neuhausen S, Olsson H, et al. Oral contraceptives and the risk of hereditary ovarian cancer. N Engl J Med 1998;339(7):424–8.
49. Ross RK, Pike MC, Vessey MP, Bull D, Yeates D, Casagrande JT. Risk factors for uterine fibroids: reduced risk associated with oral contraceptives. BMJ 1986;293(6543):359–62.
50. Chiaffarino F, Parazzini F, La Vecchia C, Marsico S, Surace M, Ricci E. Use of oral contraceptives and uterine fibroids: results from a case-control study. Br J Obstet Gynaecol 1999;106:857–60.
51. Lanes SF, Birmann B, Walker AM, Singer S. Oral contraceptive type and functional ovarian cysts. Am J Obstet Gynecol 1992;166:956–61.
52. Brinton LA, Vessey MP, Flavel R, Yeates D. Risk factors for benign breast disease. Am J Epidemiol 1981;113:203–14.
53. Martinez ME, Grodstein F, Giovannucci E, Colditz GA, Speizer FE, Hennekens C, et al. A prospective study of reproductive factors, oral contraceptive use, and risk of colorectal cancer. Cancer Epidemiol Biomarkers Prev 1997;6:1–5.
54. Fernandez E, La Vecchia C, Franceschi S, Braga C, Talamini R, Negri E, et al. Oral contraceptive use and risk of colorectal cancer. Epidemiology 1998;9:295–300.
55. Franceschi S, La Vecchia C. Oral contraceptives and colorectal tumors: a review of epidemiologic studies. Contraception 1998;58:335–43.
56. Cates W, Washington AE, Peterson HB. The pill, chlamydia and PID. Fam Plann Perspect 1985;17(4):175–6.
57. Panser La, Phipps WR. Type of oral contraceptive in relation to acute, initial episodes of pelvic inflammatory disease. Contraception 1991;43(1):91–9.
58. Walker A, Bancroft J. Relationship between premenstrual symptoms and oral contraceptive use: a controlled study. Psychosom Med 1990;52: 86-96.
59. Rosenberg MJ, Meyers A, Roy V. Efficacy, cycle control, and side effects of low- and lower-dose oral contraceptives: a randomized trial of 20 µg and 35 µg estrogen preparations. Contraception 1999;60(6):321–9.
60. Rosenberg MJ, Waugh MS. Oral contraceptive discontinuation: a prospective evaluation of frequency and reasons. Am J Obstet Gynecol 1998;179(3):577–82.
61. The ESHRE Capri Workshop Group. Continuation rates for oral contraceptives and hormone replacement therapy. Hum Reprod 2000;15(8):1865–71.
62. Thorneycroft I. Cycle control with oral contraceptives: a review of the literature. Am J Obstet Gynecol 1999;180(2 Pt 2):280–7.
63. Casper RF, Powell AM. Evaluation and therapy of breakthrough bleeding in women using a triphasic oral contraceptive. Fertil Steril 1991;55:292–6.
64. Saleh WA, Burkman RT, Zacur HA, Kimball AW, Kwiterovich P, Bell WK. A randomized trial of three oral contraceptives: comparison of bleeding patterns by contraceptive types and steroid levels. Am J Obstet Gynecol 1993;168(6 Pt 1):1745–7.
65. Ansbacher R. Low-dose oral contraceptives: health consequences of discontinuation. Contraception 2000;62(6):285–8.
66. Clark LR. Will the pill make me sterile? Addressing reproductive health concerns and strategies to improve adherence to hormonal contraceptive regimens in adolescent girls. J Ped Adolesc Gynecol 2001;14(4):153–62.
67. Borgelt-Hansen L. Oral contraceptives: an update on health benefits and risks. J Am Pharm Assoc 2001;41:875–86.
68. Endrikat J, Dusterberg B, Ruebig A, Gerlinger C, Strowitzki T. Comparison of efficacy, cycle control, and tolerability of two low-dose oral contraceptives in a multicenter clinical study. Contraception 1999;60(5):269–74.
69. Halbe HW, de Melo NR, Bahamondes L, Petracco A, Lemgruber M, de Andrade RP, et al. Efficacy and acceptability of two monophasic oral contraceptives containing ethinylestradiol and either desogestrel or gestodene. Eur J Contracept Reprod Health Care 1998;3(3):113–20.
70. Archer DF, Maheux R, Delconte A, O'Brien FB. Efficacy and safety of a low-dose monophasic combination oral contraceptive containing 100 microg levonorgestrel and 20 microg ethinyl estradiol (Alesse). Am J Obstet Gynecol 1999;181:39–44.
71. Zichella L, Sbrignadello C, Tomassini A, Di Lieto A, Montoneri C, Zarbo G, et al. Comparative study on the acceptability of two modern monophasic oral contraceptive preparations: 30 microgram ethinyl estradiol combined with 150 microgram desogestrel or 75 microgram gestodene. Adv Contracept 1999;15(3):191–200.
72. Fisher WA, Boroditsky R, Bridges ML. The 1998 Canadian Contraception Study. Can J Human Sexuality 1999;8(3):161–216.
73. Redmond G, Godwin AJ, Olson W, Lippman JS. Use of placebo controls in an oral contraceptive trial: methodological issues and adverse event incidence. Contraception 1999;60(2):81–5.
74. Coney P, Washenik K, Langley RGB, DiGiovanna JJ, Harrison DD. Weight change and adverse event incidence with a low-dose oral contraceptive: two randomized, placebo-controlled trials. Contraception 2001;63(6):297–302.
75. Gupta S. Weight gain on the combined pill: is it real? Hum Reprod Update 2000;6(5):427–31.
76. Endrikat J, Hite R, Bannemerschult R, Gerlinger C, Schmidt W. Multicenter, comparative study of cycle control, efficacy and tolerability of two low-dose oral contraceptives containing 20 microg ethinylestradiol/100 microg levonorgestrel and 20 microg ethinylestradiol/500 microg norethisterone. Contraception 2001;64(1):3–10.
77. Vandenbroucke JP, Rosing J, Bloemenkamp KW, Middeldorp S,

Helmerhorst FM, Bouma BN, et al. Oral contraceptives and the risk of venous thrombosis. N Engl J Med 2001;344(20):1527–35.
78. Lidegaard O, Edstrom B, Kreiner S. Oral contraceptives and venous thromboembolism: a five-year national case-control study. Contraception 2002;65(3):187–96.
79. Lidegaard O, Edstrom B, Kreiner S. Oral contraceptives and venous thromboembolism: a case-control study. Contraception 1998;57(5):291–301.
80. Farley TM, Collins J, Schlesselman JJ. Hormonal contraception and risk of cardiovascular disease: an international perspective. Contraception 1998;57(3):211–30.
81. WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Acute myocardial infarction and combined oral contraceptives: results of an international multicentre case-control study. Lancet 1997;349(9060):1202–9.
82. Sidney S, Siscovick DS, Petitti DB, Schwartz SM, Quesenberry CP, Psaty BM, et al. Myocardial infarction and use of low-dose oral contraceptives: a pooled analysis of 2 US studies. Circulation 1998;98(11):1058–63.
83. Sidney S, Petitti DB, Quesenberry CP Jr, Klatsky AL, et al. Myocardial infarction in users of low-dose oral contraceptives. Obstet Gynecol 1996;88(6):939–44.
84. Rosenberg L, Palmer JR, Rao RS, Shapiro S. Low-dose oral contraceptive use and the risk of myocardial infarction. Arch Intern Med 2001;161(8):1065–70.
85. Dunn N, Thorogood M, Faragher B, de Caestecker L, MacDonald TM, McCollum C, et al. Oral contraceptives and myocardial infarction: results of the MICA case-control study. BMJ 1999;318(7198):1579–83.
86. Poulter NR. Ischaemic stroke and combined oral contraceptives: results of an international, multicentre, case-control study. WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Lancet 1996;348(9026):498–505.
87. Schwartz SM, Petitti DB, Siscovick DS, Longstreth WT Jr, Sidney S, Raghunathan TE, et al. Stroke and use of low-dose oral contraceptives in young women: a pooled analysis of two US studies. Stroke 1998;29(11):2277–84.
88. Petitti DB, Sidney S, Bernstein A, Wolf S. Stroke in users of low-dose oral contraceptives. N Engl J Med 1996;335(1):8–15.
89. Lidegaard O, Kreiner S. Contraceptives and cerebral thrombosis: a five-year national case-control study. Contraception 2002;65(3):197–205.
90. Lidegaard O. Oral contraception and risk of a cerebral thromboembolic attack: results of a case-control study. BMJ 1993;306(6883):956–63.
91. Heinemann LA, Lewis MA, Spitzer WO, Thorogood M, Guggenmoos-Holzmann I, et al. Thromboembolic stroke in young women: a European case-control study on oral contraceptives. Contraception 1998;57(1):29–37.
92. Kemmeren JM, Tanis BC, van den Bosch MA, Bollen EL, Helmerhorst FM, van der Graaf Y, et al. A. Risk of arterial thrombosis in relation to oral contraceptives (RATIO) study: oral contraceptives and the risk of ischemic stroke. Stroke 2002;33(5):1202–8.
93. Goldstein LB, Adams R, Becker K, Furberg CD, Gorelick PB, Hademenos G, et al. Primary prevention of ischemic stroke: a statement for healthcare professionals from the Stroke Council of the American Heart Association. Stroke 2001;32(1):280–99.
94. Curtis KM, Chrisman CE, Peterson HB. Contraception for women in selected circumstances. Obstet Gynecol 2002;99(6):1100–12.
95. Gillum LA, Mamidipudi SK, Johnston SC. Ischemic stroke risk with oral contraceptives: a meta-analysis. JAMA 2000;284(1):72–8.
96. Bennion LJ, Ginsberg RL, Gernick MB, Bennett PH. Effects of oral contraceptives on the gallbladder bile of normal women. N Engl J Med 1976;294(4):189–92.
97. Benign gallbladder disease: newer data suggest little or no excess risk with oral contraceptive use. Contracept Rep 1997;8(5):9–11.
98. Grodstein F, Colditz GA, Hunter DJ, Manson JE, Willett WC, Stampfer MJ. A prospective study of symptomatic gallstones in women: relation with oral contraceptives and other risk factors. Obstet Gynecol 1994;84(2):207–14.
99. Oral-contraceptive use and the risk of breast cancer. The Cancer and Steroid Hormone Study of the Centers for Disease Control and the National Institute of Child Health and Human Development. N Engl J Med 1986;315(7):405–11.
100. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. Collaborative Group on Hormonal Factors in Breast Cancer. Lancet 1996;347(9017):1713–27.
101. Bryant HE, Brasher PM. Risks and probabilities of breast cancer: short-term versus lifetime probabilities. CMAJ 1994;150(2):211–6.
102. Marchbanks PA., McDonald JA., Wilson HG, Folger SG, Mandel MG, Daling JR, et al. Oral contraceptives and the risk of breast cancer. N Engl J Med 2002;346(26):2025–32.
103. Narod SA, Dube MP, Klijn J, Lubinski J, Lynch HT, Ghadirian P, et al. Oral contraceptives and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. J Natl Cancer Inst 2002;94(23):1773–9.
104. Ursin G, Henderson BE, Haile RW, et al. Does oral contraceptive use increase the risk of breast cancer in women with BRCA1/BRCA2 mutations more than in other women? Cancer Res 1997;57(17):3678–81.
105. Heimdal K, Skovlund E, Moller P. Oral contraceptives and risk of familial breast cancer. Cancer Detect Prev 2002;26(1):23–7.
106. Moreno V, Bosch FX, Munoz N, Meijer CJ, Shah KV, Walboomers JM, et al. International Agency for Research on Cancer. Multicentric Cervical Cancer Study Group. Effect of oral contraceptives on risk of cervical cancer in women with human papillomavirus infection: the IARC multicentric case-control study. Lancet 2002;359(9312):1085–92.
107. Smith JS, Green J, Berrington de Gonzalez A, Appleby P, Peto J, Plummer M, et al. Cervical cancer and use of hormonal contraceptives: a systematic review. Lancet 2003;361(9364):1159–67.
108. Franco EL, Duarte-Franco E, Ferenczy A. Cervical cancer: epidemiology, prevention and the role of human papillomavirus infection. CMAJ 2001;164:1017–25.
109. Castle PE, Wacholder S, Lorincz AT, Scott DR, Sherman ME, Glass AG, et al. A prospective study of high-grade cervical neoplasia risk among human papillomavirus-infected women. J Natl Cancer Inst 2002;94(18):1406–14.
110. Royar J, Becher H, Chang-Claude J. Low-dose oral contraceptives: protective effect on ovarian cancer risk. Int J Cancer 2001;95(6):370–4.
111. Modan B, Hartge P, Hirsh-Yechezkel G, Chetrit A, Lubin F, Beller U, et al. Parity, oral contraceptives, and the risk of ovarian cancer among carriers and noncarriers of a BRCA1 or BRCA2 mutation. N Engl J Med 2001;345(4):235–40.
112. Shulman LP. Oral contraceptives: risks. Obstet Gynecol Clin N Am 2000;27(4):695–704.
113. Hatcher RA, Guillebaud MA. The pill: combined oral contraceptives. In: Hatcher RA, Trussell J, Stewart F, Cates Jr. W, Stewart GK, Guest F, editors. Contraceptive technology. New York: Ardent Media; 1998. p. 405–66.
114. Briggs GG, Freeman RK, Yaffe SJ, editors. Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2001.
115. van der Vange N, Blankenstein MA, Kloosterboer HJ, Haspels AA, Thijssen JH. Effects of seven low-dose combined oral contraceptives on sex hormone binding globulin, corticosteroid binding globulin, total and free testosterone. Contraception 1990;41:345–52.
116. Lara-Torre E, Schroeder B. Adolescent compliance and side effects with Quick Start initiation of oral contraceptive pills. Contraception 2002;66(2):81–5.
117. Westhoff C, Kerns J, Morroni C, Cushman LF, Tiezzi L, Murphy PA. Quick Start: a novel oral contraceptive initiation method. Contraception 2002;66(3):141–5.
118. Westhoff C, Morroni C, Kerns J, Murphy PA. Bleeding patterns after immediate vs. conventional oral contraceptive initiation: a randomized, controlled trial. Fertil Steril 2003;79(2):322–9.
119. Loudon N, Foxwell M, Potts D, Guild A, Short R. Acceptability of an oral contraceptive that reduces the frequency of menstruation: the tri-cycle pill regimen. BMJ 1977;2(6085):487–90.
120. Sulak P, Kuehl T, Ortiz M, Shull B. Acceptance of altering the standard 21-day/7-day oral contraceptive regimen to delay menses and reduce hormonal withdraw symptoms. Am J Obstet Gynecol 2002;186:1142–9.

121. Vercellini P, De Giorgi O, Mosconi P, Stellato G, Vicentini S, Crosignani PG. Cyproterone acetate versus a continuous monophasic oral contraceptive in the treatment of recurrent pelvic pain after conservative surgery for symptomatic endometriosis. Fertil Steril 2002;77(1):52–61.
122. Falsetti L, Galbignani E. Long-term treatment with the combination ethinylestradiol and cyproterone acetate in polycystic ovary syndrome. Contraception 1990;42(6):611–9.
123. Grimes D. The safety of oral contraceptives: epidemiologic insights from the first 30 years. Am J Obstet Gynecol 1992;166(6 Pt 2):1950–4.
124. Miller L, Hughes JP. Continuous combination oral contraceptive pills to eliminate withdrawal bleeding: a randomized trial. Obstet Gynecol 2003;101(4):653–61.
125. Anderson FD, Hait H. A multicenter, randomized study of an extended cycle oral contraceptive. Contraception 2003;68(2):89–96.
126. Rutter W, Knight C, Vizzard J, Mira M, Abraham S. Women's attitudes to withdrawal bleeding and their knowledge and beliefs about the oral contraceptive pill. Med J Aust 1988;149(8):417–9.
127. den Tonkelaar, Oddens B. Preferred frequency and characteristics of menstrual bleeding in relation to reproductive status, oral contraceptive use, and hormone replacement therapy use. Contraception 1999;59(6):357–62.
128. Cachrimanidou AC, Hellberg D, Nilsson S, Waldenstrom U, Olsson SE, Sikstrom B. Long-interval treatment regimen with a desogestrel-containing oral contraceptive. Contraception 1993;48(3):205–16.
129. Hamerlynck J, Vollebregt J, Doomebos C, Muntendam P. Postponement of withdrawal bleeding in women using low-dose combined oral contraceptives. Contraception 1987;35(3):199–205.
130. Ziaei S, Rajaei L, Faghihzadeh S, Lamyian M. Comparative study and evaluation of side effects of low-dose contraceptive pills administered by the oral and vaginal route. Contraception 2002;65(5):329–31.
131. Coutinho EM, Mascarenhas I, de Acosta OM, Flores JG, Gu ZP, Ladipo OA, et al. Comparative study on the efficacy, acceptability, and side effects of a contraceptive pill administered by the oral and the vaginal route: an international multicenter clinical trial. Clin Pharmacol Ther 1993;54(5):540–5.
132. Coutinho EM, de Souza JC, da Silva AR, de Acosta OM, Alvarez F, Brache V, et al. Comparative study on the efficacy and acceptability of two contraceptive pills administered by the vaginal route: an international multicenter clinical trial. Clin Pharmacol Ther 1993;53(1):65–75.
133. Coutinho EM, O'Dwyer E, Barbosa IC, Gu ZP, Shaaban MM, Aboul-Oyoon M, et al. Comparative study on intermittent versus continuous use of a contraceptive pill administered by vaginal route. Contraception 1995;51(6):355–358.
134. Souka AR, el Sokkary H, Hassan M. The effect of vaginal administration of low-dose oral contraceptive tablets on human ovulation. Contraception 1986;33(4):365–71.
135. Coutinho EM, da Silva AR, Carreira C, Rodrigues V, Goncalves MT. Conception control by vaginal administration of pills containing ethinyl estradiol and dl-norgestrel. Fertil Steril 1984;42(3):478–81.
136. Coutinho EM, Silva AR, Carreira C, Barbosa I. Ovulation inhibition following vaginal administration of pills containing norethindrone and mestranol. Contraception 1984;29(2):197–202.
137. Schilling LH, Bolding OT, Chenault CB, Chong AP, Fleury F, Forrest K, et al. Evaluation of the clinical performance of the triphasic oral contraceptives: a multicenter, randomized, comparative trial. Am J Obstet Gynecol 1989;160:1264–8.
138. Audet MC, Moreau M, Koltun WD, Waldbaum AS, Shangold G, Fisher AC, et al. ORTHO EVRA/EVRA 004 Study Group. Evaluation of contraceptive efficacy and cycle control of a transdermal contraceptive patch vs an oral contraceptive: a randomized controlled trial. JAMA 2001;285(18):2347–54.
139. Rosenberg MJ, Waugh MS, Higgens JE. The effect of desogestrel, gestodene, and other factors on spotting and bleeding. Contraception 1996;53:85–90.
140. Rosenberg MJ, Waugh MS. Smoking and cycle control among oral contraceptive users. Am J Obstet Gynecol 1996;174(2):628–32.
141. Krettek JE, Arkin SI, Chaisilwattana P, Monif GR. Chlamydia trachomatis in patients who used oral contraceptives and had intermenstrual spotting. Obstet Gynecol 1993;81(5 Pt 1):728–31.
142. Rosenberg MJ, Meyers A, Roy V. Efficacy, cycle control, and side effects of low- and lower-dose oral contraceptives: a randomized trial of 20 [mu]g and 35 [mu]g estrogen preparations. Contraception 1999;60(6):321–9.
143. Bracken MB. Oral contraception and congenital malformations in offspring: a review and meta-analysis of the prospective studies. Obstet Gynecol 1990;76(3 Pt 2):552–7.
144. D'Arcy PF. Drug interactions with oral contraceptives. Drug Intell Clin Pharm 1986;20:353–62.
145. Fotherby K. Interactions with oral contraceptives. Am J Obstet Gynecol 1990;163:2153–9.
146. Oesterheld JR. Gynecology: oral contraceptives. In: Cozza KL, Armstrong SC, editors. The cytochrome P450 system drug interaction principles for medical practice. Washington DC: American Psychiatric Publishing Inc; 2001. p. 103–14.
147. Crawford P, Chadwick DJ, Martin C, Tjia J, Back DJ, Orme M. The interaction of phenytoin and carbamazepine with combined oral contraceptive steroids. Br J Clin Pharmacol 1990;30:892–6.
148. Dickinson BD, Altman RD, Nielsen H, Sterling ML. Drug interactions between oral contraceptives and antibiotics. Am J Obstet Gynecol 2001;98(5 Pt 1):853–60.
149. Hachad H, Ragueneau-Majlessi I, Levy RH. New antiepileptic drugs: review on drug interactions. Ther Drug Monit 2002;24(1):91–103.
150. Schwarz UI, Buschel B, Kirch W. Unwanted pregnancy on self-medication with St John's wort despite hormonal contraception. Br J Clin Pharmacol 2003;55(1):112–3.
151. Abrams LS, Skee DM, Natarajan J, Wong FA. Pharmacokinetic overview of Ortho Evra/Evra. Fertil Steril 2002;77(2 Suppl 2):S3–S12.
152. Smallwood GH, Meador ML, Lenihan JP, Shangold GA, Fisher AC, Creasy GW; ORTHO EVRA/EVRA 002 Study Group. Efficacy and safety of a transdermal contraceptive system. Obstet Gynecol 2001;98:799–805.
153. Zieman M, Guillebaud J, Weisberg E, Shangold G, Fisher AC, Creasy GW. Contraceptive efficacy and cycle control with Ortho Evra/Evra transdermal system: the analysis of pooled data. Fertil Steril 2002;77 (2 Suppl 2):S13–S18.
154. Gu S, Sivin I, Du M, Zhang L, et al. Effectiveness of Norplant implants through seven years: a large-scale study in China. Contraception 2003;52(2):99–103.
155. Pierson RA, Archer DF, Moreau M, Shangold GA, Fisher AC, Creasy GW. Ortho Evra™/Evra™ versus oral contraceptives: follicular development and ovulation in normal cycles and after an intentional dosing error. Fertil Steril 2003;80(1):34–42.
156. Sibai BM, Odlind V, Neador ML, Shangold G, Fisher AC, Creasy GW. A comparative and pooled analysis of the safety and tolerability of the contraceptive patch. Fertil Steril 2002;77(2 Suppl 2):S19–S26.
157. Zacur HA, Hedon B, Mansour D, Shangold G, Fisher AC. Integrated summary of ortho evra/evra contraceptive patch adhesion in varied climates and conditions. Fertil Steril 2002;77(2 Suppl 2):S32–S35.
158. Gallo MF, Grimes DA, Schulz KF, Helmerhorst FM. Combination contraceptives: effects on weight (Cochrane Review). In: The Cochrane Library, Issue 4 2003. Oxford: Update Software.
159. Abrams LS, Skee DM, Natarajan J, Wong FA, Anderson GD. Pharmacokinetics of a contraceptive patch (Evra/Ortho Evra) containing norelgestromin and ethinyloestradiol at four application sites. Br J Clin Pharmacol 2002;53(2):141–6.
160. Abrams LS, Skee DM, Wong FA, Anderson NJ, Leese PT. Pharmacokinetics of norelgestromin and ethinyl estradiol from two consecutive contraceptive patches. J Clin Pharmacol 2001;41(11):1232–7.
161. Timmer CJ, Mulders TM. Pharmacokinetics of etonogestrel and ethinylestradiol released from a combined contraceptive vaginal ring. Clin Pharmacokinet 2000;39(3):233–42.
162. Roumen FJ, Apter D, Mulders TM, Dieben TO. Efficacy, tolerability and acceptability of a novel contraceptive vaginal ring releasing etonogestrel and ethinyl oestradiol. Hum Reprod 2001;16(3):469–75.
163. Dieben TO, Roumen FJ, Apter D. Efficacy, cycle control, and user acceptability of a novel combined contraceptive vaginal ring. Obstet Gynecol 2002;100(3):585–93.

164. Mulders TM, Dieben TO. Use of the novel combined contraceptive vaginal ring NuvaRing for ovulation inhibition. Fertil Steril 2001;75(5):865–70.
165. Mulders TM, Dieben TO, Bennink HJ. Ovarian function with a novel combined contraceptive vaginal ring. Hum Reprod 2002;17(10):2594–9.
166. Killick S. Complete and robust ovulation inhibition with NuvaRing. Eur J Contracept Reprod Health Care 2002;7:13–8.
167. Bjarnadottir RI, Tuppurainen M, Killick SR. Comparison of cycle control with a combined contraceptive vaginal ring and oral levonorgestrel /ethinyl estradiol. Am J Obstet Gynecol 2002;186(3):389–95.
168. Alexander NJ, Haring T, Mulders TM. A pharmacokinetic interaction study of NuvaRing and a vaginally administered spermicide or antimycotic [abstract 0-63]. Fertil Steril 2002;78(Suppl 1):S24–5.
169. Kaunitz AM, Garceau RJ, Cromie MA. Comparative safety, efficacy, and cycle control of Lunelle monthly contraceptive injection (medroxyprogesterone acetate and estradiol cypionate injectable suspension) and Ortho-Novum 7/7/7 oral contraceptive (norethindrone/ethinyl estradiol triphasic). Contraception 1999;60(4):179–87.
170. Rahimy MH, Ryan KK. Lunelle monthly contraceptive injection (medroxyprogesterone acetate and estradiol cypionate injectable suspension): assessment of return of ovulation after three monthly injections in surgically sterile women. Contraception 1999;60(4):189–200.
171. Garceau RJ, Wajszczuk CJ, Kaunitz AM. Bleeding patterns of women using Lunelle monthly contraceptive injections (medroxyprogesterone acetate and estradiol cypionate injectable suspension) compared with those of women using Ortho-Novum 7/7/7 (norethindrone/ethinyl estradiol triphasic) or other oral contraceptives. Contraception 2002;62(6):289–95.
172. Jain JK, Ota F, Mishell DR. Comparison of ovarian follicular activity during treatment with a monthly injectable contraceptive and a low-dose oral contraceptive. Contraception 2000;61(3):195–8.
173. Kaunitz AM, Garceau RJ, Cromie MA. Comparative safety, efficacy, and cycle control of Lunelle monthly contraceptive injection (medroxyprogesterone acetate and estradiol cypionate injectable suspension) and Ortho-Novum 7/7/7 oral contraceptive (norethindrone/ethinyl estradiol triphasic). Lunelle Study Group. Contraception 1999;60(4):179-87.

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 mucus[8] 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 cancer[12]
- reduction in symptoms associated with endometriosis,[13,14] premenstrual syndrome, and chronic pelvic pain[15]

- decreased incidence of seizures[16]
- possible reduced risk of pelvic inflammatory disease[17,18]
- possible decreased incidence of sickle cell crisis.[19]

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.[9] 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.[3,20] At 12 months, 55 to 60% of DMPA users are amenorrheic, and by 24 months up to 68% are amenorrheic.[3,9-11,20]

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.[3,21] Migraine headaches do not constitute a contraindication to DMPA use.[6]

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).[9] Other studies have failed to find an effect of DMPA on weight.[22-24] Weight gain associated with DMPA use is thought to be due to appetite stimulation[25] and a possible mild anabolic effect. The product monograph suggests the following average weight gains in DMPA users: 2.5 kg in the first year of use, 3.7 kg after the second year of use, and 6.3 kg after the fourth year of use. DMPA users should be given counselling regarding healthy eating and exercise.

4. MOOD EFFECTS

Although mood changes have been reported in DMPA users[3] and may lead to discontinuation of DMPA, prospective studies do not appear to demonstrate an increase in depressive symptoms in DMPA users.[26,27] 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.[7,28,29] The rate of conception 10 months after the last DMPA injection is 50%, and approximately 90% by 24 months.[7]

2. REDUCTION IN BONE MINERAL DENSITY (BMD)

Although some cross-sectional studies have demonstrated no adverse effect of DMPA on bone mineral density,[30,31] the majority of studies report a decrease in BMD in DMPA users.[32-37] Prospective studies have found a mean loss of BMD at the lumbar spine of between 0.87% and 3.52%.[35,36,37] Although a decrease in BMD has been observed, it does not appear to induce osteoporosis. Furthermore, two cross-sectional studies of past DMPA users[38,39] 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[36] 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.[40] 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,[41,42] but only limited data are available. DMPA users do not appear to have an increased risk of cardiovascular disease, stroke, or myocardial infarction.[41]

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.[43,44]
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.[9] 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.[43,45-48]
4. DMPA causes cancer.
   Fact: DMPA is associated with a decreased risk of endometrial cancer.[12] There does not appear to be an increased risk of ovarian cancer[49] or breast cancer.[50-52] Studies suggest either a slight or no increase in the risk of cervical cancer.[52-56]

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.[8,43] 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.[8,44]

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.[45]

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.[46,47]

DRUG INTERACTIONS

Few medications will interact with DMPA. Aminoglutethimide[48] 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%.[2,6] Maximal effectiveness depends on consistent pill-taking. With typical use, the failure rate is between 5 and 10%.[2,49] The failure rate appears to be lower in motivated women.[50]

MECHANISM OF ACTION

The chief mechanism of action in preventing pregnancy is through alterations in the cervical mucus.[51] POPs reduce the volume of mucus, increase its viscosity, and alter its molecular structure, resulting in little or no sperm penetration.[52] In addition, sperm motility is impaired, making fertilization unlikely.[53] Ovulation may be suppressed or partially suppressed. Forty percent of women using progestin-only contraceptives continue to ovulate.[54] Endometrial changes, reducing the potential for implantation, may occur.[55] 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

protect against sexually transmitted infections and infection with the human immunodeficiency virus.

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 health-care 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 anti-convulsants) 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.[71] The failure rate for Implanon is quite low, with no reported pregnancy in a database that followed 70 000 cycles of use.[72] 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.[74]

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

Comparison of contraceptive implants

Characteristics	Implanon®	Norplant-2®	Norplant®
Number of Rods	1	2	6
Hormone	Etonorgestrel	Levonorgestrel	Levonorgestrel
Length of rod	4 cm	4.3 cm	3.4 cm
Diameter of rod	2 mm	2.4 mm	2.4 mm
Amount of hormone	68 mg	75 mg (total 150 mg)	36 mg (total 216 mg)
Duration of effectiveness [69,70]	3 years	3–5 years	5–7 years

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)**

REFERENCES

1. Fisher W, Boroditsky R, Morris B. The 2002 Canadian contraception study. J Obstet Gyneacol Can 2003. In press.
2. Hatcher RA, Trussell J, Stewart F, Cates W, Stewart GK, Guest F, et al. Contraceptive technology. 17th ed. New York: Ardent Media Inc; 1998.
3. Schwallie PC, Assenzo JR. Contraceptive use: efficacy study utilizing medroxyprogesterone acetate administered as an intramuscular injection once every 90 days. Fertil Steril 1973;24:331–9.
4. Said S, Omar K, Koetsawang S, Kiriwat O, Srisatayapan Y, Kazi A, et al. A multicentred phase III comparative clinical trial of depot-medroxyprogesterone acetate given three-monthly at doses of 100 mg or 150 mg: I. contraceptive efficacy and side effects. World Health Organization Task Force on Long-Acting Systemic Agents for Fertility Regulation. Special Programme of Research, Development and Research Training in Human Reproduction. Contraception 1986;34:223–36.
5. The World Health Organization. Multinational comparative clinical evaluation of two long acting injectable contraceptive steroids: norethisterone enanthate and medroxyporogesterone acetate. Final report. Contraception 1983;28(1):1–20.
6. The World Health Organization. Improving access to quality care in family planning: medical eligibility criteria for contraceptive use. 2nd ed. Geneva: WHO; 2001.
7. Schwallie PC, Assenzo JR. The effect of depo-medroxyprogesterone acetate on pituitary and ovarian function, and the return of fertility following its discontinuation: a review. Contraception 1974;10:181–202.
8. Petta CA, Faundes A, Dunson TR, Ramos M, DeLucio M, Faundes D, et al. Timing of onset of contraceptive effectiveness in Depo-Provera users: part I. changes in cervical mucus. Fertil Steril 1998;69:252–7.
9. Polaneczky M, Guarnaccia M. Early experience with the contraceptive use of depot medroxyprogesterone acetate in an inner-city clinic population. Fam Plann Perspect 1996;28:174–8.
10. Betsey EM and Task Force on Long-Acting Systemic Agents for Fertility Regulation. Menstrual bleeding patterns in untreated women and with long-acting methods of contraception. Adv Contracept 1991;7:257–70.
11. Said S, Omar K, Koetsawang S, Kiriwat O, Srisatayapan Y, Kazi A, et al. A multicentered phase III comparative clinical trial of depot-medroxyprogesterone acetate given three-monthly at doses of 100 mg or 150 mg: II. the comparison of bleeding patterns. World Health Organization. Task Force on Long-Acting Systemic Agents for Fertility Regulation Special Programme of Research, Development and Research Training in Human Reproduction. Contraception 1987;35:591–610.
12. Depot-medroxyprogesterone acetate (DMPA) and risk of endometrial cancer. The WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Int J Cancer 1991;49:186–90.
13. Prentice A, Deary AJ, Bland A. Progestagens and anti-progestagens for pain associated with endometriosis. Cochrane Database Syst Rev 2000;2:CD002122.
14. Vercellini P, Cortesi I, Crosignani PG. Progestins for symptomatic endometriosis: a critical analysis of the evidence. Fertil Steril 1997;68:368–93.
15. Stones RW, Mountfield J. Interventions for treating chronic pelvic pain in women (Cochrane Review). In: The Cochrane Library, Issue 4 2003. Oxford: Update Software.
16. Mattson RH, Cramer JA, Caldwell BV, Siconolfi BC. Treatment of seizures with medroxyprogesterone acetate: preliminary report. Neurology 1984;34:1255–8.
17. Gray RH. Reduced risk of pelvic inflammatory disease with injectable contraceptives. Lancet 1985;1(8436):1046.
18. Baeten JM, Nyange PM, Richardson BA, Lavreys L, Chohan B, Martin HL Jr, et al. Hormonal contraception and risk of sexually transmitted disease acquisition: results from a prospective study. Am J Obstet Gynecol 2001;185:380–5.
19. de Abood M, de Castillo Z, Guerrero F, Espino M, Austin KL. Effect of Depo-Provera or Microgynon on the painful crises of sickle cell anemia patients. Contraception 1997;56:313–6.
20. Sangi-Haghpeykar H, Poindexter AN 3rd, Bateman L, Ditmore JR. Experiences of injectable contraceptive users in an urban setting. Obstet Gynecol 1996;88:227–33.
21. Nelson A. Counseling issues and management of side effects for women using depot medroxyprogesterone acetate contraception. J Reprod Med 1996;41(5 Suppl):391–400.
22. Moore LL, Valuck R, McDougall C, Fink W. A comparative study of one-year weight gain among users of medroxyprogesterone acetate, levonorgestrel implants, and oral contraceptives. Contraception 1995;52:215–9.
23. Mainwaring R, Hales HA, Stevenson K, Hatasaka HH, Poulson AM, Jones KP, et al. Metabolic parameter, bleeding, and weight changes in U.S. women using progestin-only contraceptives. Contraception 1995;51:149–53.
24. Taneepanichskul S, Reinprayoon D, Jaisamrarn U. Effects of DMPA on weight and blood pressure in long term acceptors. Contraception 1999;59:301–3.
25. Rees HD, Bonsall RW, Michael RP. Pre-optic and hypothalamic neurons accumulate [3H]medroxyprogesterone acetate in male cynomolgus monkeys. Life Sci 1986;39:1353–9.
26. Westhoff C, Truman C, Kalmuss D, Cushman L, Davidson A, Rulin M, et al. Depressive symptoms and depo-provera. Contraception 1998;57:237–40.
27. Gupta N, O'Brien R, Jacobsen LJ, Davis A, Zuckerman A, Supran S, et al. Mood changes in adolescents using depot-medroxyprogesterone acetate for contraception: a prospective study. J Pediatr Adolesc Gynecol 2001;14:71–6.
28. Pardthaisong T. Return of fertility after use of the injectable contraceptive Depo Provera: up-dated data analysis. J Biosoc Sci 1984;16:23–34.
29. Fotherby K, Howard G. Return of fertility in women discontinuing injectable contraceptives. J Obstet Gynaecol 1986;6(Suppl 2):S110–5.
30. Perrotti M, Bahamondes L, Petta C, Castro S Forearm bone density in long term users of oral combined contraceptives and depot medroxyprogesteron acetate. Fertil Steril 2001;76:469–74.
31. Gbolade B, Ellis S, Murby B, Randall S, Kirkman R. Bone density in long term users of depot medroxyprogesterone acetate. Br J Obstet Gynaecol 1998;105:790–4.
32. Cromer BA, Blair JM, Mahan JD, Zibners L, Naumovski Z.. A prospective comparison of bone density in adolescent girls receiving depo-medroxyprogesterone acetate (Depo-Provera), levonorgestrel (Norplant), or oral contraceptives. J Pediatr 1996;129:671–6.
33. Cundy T, Cornish J, Roberts H, Elder H, Reid IR. Spinal bone density in women using depot medroxyprogesterone contraception. Obstet Gynecol 1998;92:569–73.
34. Scholes D, Lacroix AZ, Ott SM, Ichikawa LE, Barlow WE. Bone mineral density in women using depot medroxyprogesterone acetate for contraception. Obstet Gynecol 1999;93:233–8.
35. Berenson AB, Radecki CM, Grady JJ, Rickert VI, Thomas A. A prospective, controlled study of the effects of hormonal contraception on bone mineral density. Obstet Gynecol 2001;98:576–82.
36. Scholes D, Lacroix AZ, Ichikawa LE, Barlow WE, Ott SM. Injectable

hormone contraception and bone density: results from a prospective study. Epidemiology 2002;13:581–7.
37. Busen NH, Britt RB, Rianon N. Bone mineral density in a cohort of adolescent women using depot medroxyprogesterone acetate for one to two years. J Adolesc Health 2003;32:257–9.
38. Orr-Walker BJ, Evans MC, Ames RW, Clearwater JM, Cundy T, Reid IR. The effect of past use of the injectable contraceptive depot medroxyprogesterone acetate on bone mineral density in normal postmenopausal women. Clin Endocrinol 1998;49:615–8.
39. Petitti DB, Piaggio G, Mehta S, Cravioto MC, Meirik O. Steroid hormone contraception and bone mineral density: a cross-sectional study in an international population. The WHO Study of Hormonal Contraception and Bone Health. Obstet Gynecol 2000;95:736–44.
40. Cundy T, Ames R, Horne A, Clearwater J, Roberts H, Gamble G, et al. A randomized controlled trial of estrogen replacement therapy in long-term users of depot medroxyprogesterone acetate. J Clin Endocrinol Metab 2003;88:78–81.
41. World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Cardiovascular disease and use of oral and injectable progestogen-only contraceptives and combined injectable contraceptives: results of an international, multicenter, case-control study. Contraception 1998;57:315–24.
42. Vasilakis C, Jick H, del Mar Melero-Montes M. Risk of idiopathic venous thromboembolism in users of progestagens alone. Lancet 1999;354 (9190):1610–1.
43. Mishell DR, Jr. Pharmacokinetics of depot medroxyprogesterone acetate contraception. J Reprod Med 1996;41(5 Suppl):381–90.
44. Petta CA, Faundes A, Dunson TR, Ramos M, DeLucio M, Faundes D, et al. Timing of onset of contraceptive effectiveness in Depo-Provera users. II. Effects on ovarian function. Fertil Steril 1998;70:817–20.
45. SOGC Committee Opinion. Injectable medroxyprogesterone acetate for contraception. August. Policy statement no.94. JSOGC 2000; 22(8):616–20.
46. Pardthaisong T, Yenchit C, Gray R. The long-term growth and development of children exposed to Depo-Provera during pregnancy or lactation. Contraception 1992;45:313–24.
47. Borgatta L, Murthy A, Chuang C, Beardsley L, Burnhill MS. Pregnancies diagnosed during Depo-Provera use. Contraception 2002;66:169–72.
48. Hatcher RA, Schnare S. Ask the experts: progestin-only contraceptives. Contracept Technol Update 1993;14:114–5.
49. Sheth A, Jain U, Sharma S, Adatia A, Patankar S, Andolsek L, et al. A randomized, double-blind study of two combined and two progestogen-only oral contraceptives. Contraception 1982;25:243–52.
50. Broome M, Fotherby K. Clinical experience with the progestogen-only pill. Contraception 1990;42:489–95.
51. Perheentupa A, Critchley HO, Illingworth PJ, McNeilly AS. Effect of progestin-only pill on pituitary-ovarian axis activity during lactation. Contraception 2003;67:467–71.
52. Moghissi KS, Syner FN, McBride LC. Contraceptive mechanism of microdose norethindrone. Obstet Gynecol 1973;41:585–94.
53. Kesseru-Koos E. Influence of various hormonal contraceptives on sperm migration in vivo. Fertil Steril 1971;22:584–603.
54. Landgren BM, Diczfalusy E. Hormonal effects of the 300 mcg norethisterone minipill. Contraception 1980;21:87–113.
55. Moghissi KS, Marks C. Effects of microdose progestogens on endogenous gonadotrophic and steroid hormones, cervical mucus properties, vaginal cytology and endometrium. Fertil Steril 1971;22:424–34.
56. Heinemann LA, Assmann A, DoMinh T, Garbe E. Oral progestogen-only contraceptives and cardiovascular risk: results from the Transnational Study on Oral Contraceptives and the Health of Young Women. Eur J Contracept Reprod Health Care 1999;4:67–73.
57. Truitt ST, Frazer AB, Grimes DA, Gallo MF, Schulz KF. Combined hormonal versus nonhormonal versus progestin-only contraception in lactation (Cochrane Review). In: The Cochrane Library, Issue 4 2003. Oxford: Update Software.
58. World Health Organization (WHO) Task Force on Oral Contraceptives. Effects of hormonal contraceptives on breast milk composition and infant growth. Stud Fam Plann 1988;19(6 Pt 1):361–9.
59. Halderman LD, Nelson AL. Impact of early postpartum administration of progestin-only hormonal contraceptives compared with nonhormonal contraceptives on short-term breast-feeding patterns. Am J Obstet Gynecol 2002;186:1250–8.
60. Tankeyoon M, Dusitsin N, Chalapati S, Koetsawang S, Saibiang S, Sas M, et al. Effects of hormonal contraceptives on milk volume and infant growth. WHO Special Programme of Research, Development and Research Training in Human Reproduction Task Force on Oral Contraceptives. Contraception 1984;30:505–22.
61. Guillebaud J. Contraception: your questions answered. New York NY: Pitman; 1985.
62. Cheng L, Zhu H, Wang A, Ren F, Chen J, Glasier A. Once a month administration of mifepristone improves bleeding patterns in women using subdermal contraceptive implants releasing levonorgestrel. Hum Reprod 2000;15:1969–72.
63. Gemzell-Danielsson K, van Heusden AM, Killick SR, Croxatto HB, Bouchard P, Cameron S, et al. Improving cycle control in progestogen-only contraceptive pill users by intermittent treatment with a new antiprogestogen. Hum Reprod 2002;17:2588–93.
64. The World Health Organization. Improving access to quality care in family planning: medical eligibility criteria for contraceptive use. 2nd ed. Geneva: WHO; 2001.
65. Wyeth-Ayerst comments on Norplant® system. Available on-line at <http://www.wyeth.com/news/Pressed_and_Released/pr08_17_2000.asp>. Web site updated August 17, 2000. Accessed January 20, 2004.
66. Wyeth-Ayerst comment: Back-up contraception no longer required for women using norplant system. Available on-line at <http://www.wyeth.com/news/Pressed_and_Released/pr07_26_2002.asp>. Web site updated July 26, 2002. Accessed January 20, 2004.
67. Sivin I, Mishell DR Jr, Diaz S, Biswas A, Alvarez F, Darney P, et al. Prolonged effectiveness of Norplant capsule implants: a seven year study. Contraception 2000;61:187–94.
68. Gu S, Sivin I, Du M, Zhang L, Ying L, Meng F, et al. Effectiveness of Norplant implants through seven years: a large-scale study in China. Contraception 1995;52:99–103.
69. Meckstroth K, Darney P. Implant contraception. Semin Reprod Med 2001;19:339–54.
70. Croxatto HB. Progestin implants for female contraception. Contraception 2002;65:15–9.
71. Affandi B. An integrated analysis of vaginal bleeding patterns in clinical trials of Implanon. Contraception 1998;58:99S–107S.
72. Herjan J, Bennink TC. Introduction: presentation of clinical data on implanon. Contraception 1998;58:75S–7S.
73. Kennedy H, Murnaghan M. Implanon: when is the ideal time to insert? J Fam Plann Reprod Health Care 2001;27:158.
74. Sivin I, Mishell D, Darney P, Wan L, Christ M. Levonorgestrel capsule implants in the United States: a 5 year study. Obstet Gynecol 1998;92:337–44.
75. Sivin I, Alvarez F, Mishell DR Jr, Darney P, Wan L, Brache V, et al. Contraception with two levonorgestrel rod implants: a 5-year study in the United States and Dominican Republic. Contraception 1998;58:275–82.

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.1 Most studies dealing with the risk of thrombosis associated with contraception are observational in design, leading to level II evidence.[1-2] Observational data are reported as point estimates, which measure the magnitude or strength of the association.[3] 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.[3] 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.[3]

The incidence of venous thromboembolism (VTE) is approximately 10 per 10 000 per year in adults.[4] 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.[5] The risk increases exponentially thereafter.[6] The incidence of VTE during pregnancy and the puerperium is approximately 13 per 10 000 deliveries.[7] The case-fatality rate of VTE is 1 to 2%.[5,8]

Venous thromboembolic rates are 3- to 4-fold higher among users of current combined OC preparations than among non-users.[9] 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.[10-11]

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,[12] although this effect was not significant in 1 study.[13] Reductions in the content of ethinyl estradiol below 50 µg have not been associated with a further decrease in thromboembolic risk.[10,14]

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.[15] 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.[16-17] This unexpected finding led to a prolonged controversy over its validity, because of multiple potential biases including the effect of duration of use.[18-19] 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.[20] 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.[21] 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.[14,22] 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.[23] 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.[24]

Underlying biologic predisposition to thrombosis (thrombophilia) compounds the effect of combined OCs on the risk of VTE.[25] 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).[26] 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.[26] 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.[5] 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.[5] The incidence rises steeply from age 35 upward.[5] At age 40 to 44, the incidence is 0.16 per 10 000 per year.[5] The case-fatality rate of ischemic stroke is about 25%,[5] with a 30% disability rate.[41]

A significantly increased risk of stroke is observed in users of combined OCs with a high estrogen content.[44] With current preparations, the risk has been found not to be increased in some studies.[45-46] An increase in risk up to 2-fold was found in other studies.[47-49] 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.[50]

The risk of stroke with use of third-generation combined OCs appears similar to that with second-generation combined OCs,[49,51] although some data suggest a lower risk.[52]

Smoking is a major risk factor for stroke, with an approximate doubling of the risk overall[53] as well as in women who use combined OCs.[44]

Hypertension is a major risk factor for stroke.[53] Combined OC users with hypertension are at increased risk of stroke, compared with users without hypertension.[54] Use of combined OCs should be avoided in women with uncontrolled hypertension, but they can be 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 with medication.[43]

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.[55,56] The risk of stroke is considered higher in women who have migraine with aura (relative risk approximately 6 compared with women without migraine),[57] although not all studies report a difference.[56] The risk of stroke is further increased by the presence of hypertension, smoking, and the use of combined OCs.[56,57] Migraine is not considered a contraindication to the use of combined OCs in the absence of aura or other risk factors.[58] Combined OC use is generally considered contraindicated in patients with migraine aura,[58] although visual scintillations lasting less than 1 hour are considered acceptable by some authors.[59] 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.[60]

VENOUS THROMBOEMBOLISM AND PROGESTIN-ONLY HORMONAL CONTRACEPTION

Progestins do not appear to increase the risk of VTE in contraceptive doses,[61-62] but only limited data are available and 1 study found an increased risk even when adjusting for the indication for use.[63]

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.[47,63] 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.[64]

DIABETES MELLITUS

Early combined OC formulations impaired glucose metabolism by increasing peripheral insulin resistance.[65] Currently available products have no appreciable effect on carbohydrate metabolism.[65] 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.[66-67]

LIVER AND GALLBLADDER DISEASE

Combined OC use increases the secretion of cholic acid in bile.[68] Women using combined OCs have a small increase in the risk of symptomatic gallstones.[69] Combined OCs should not be used in women with active liver disease, or in women with known benign or malignant liver tumours.[70]

INFLAMMATORY BOWEL DISEASE

There may be a modest association between the use of combined OCs and the development of inflammatory bowel disease.[71] Combined OCs have been reported to increase the risk of relapse of inflammatory bowel disease in some studies, but not all.[72-73] Combined OCs may be absorbed inadequately in the presence of chronic inflammation or active diarrhea.[74]

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.[75]

SICKLE CELL DISEASE

Women with sickle cell disease are at increased risk of stroke.[76] 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.[77]

Yoong found some form of cyclical crises in 58% of women and concluded that DMPA should be considered in severe cases.[78]

EPILEPSY

Combined OCs can be used safely in women with epilepsy.[79] Some drugs reduce the efficacy of combined OCs.[80] In this case, the use of combined OCs containing more than 35 µg of ethinyl estradiol may be warranted.[81]

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.[81]

ELECTIVE SURGERY

Whether women should discontinue OC use 4 weeks before elective surgery is controversial.[82] 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)

REFERENCES

1. Jordan WM. Pulmonary embolism. Lancet 1961;2:1146-7.
2. Lidegaard O. Oral contraceptives and venous thromboembolism: an epidemiological review. Eur J Contracept Reprod Health Care 1996;1:13-20.
3. Williams JK. Evidence-based medicine and contraception. Obstet Gynecol Clin North Am 2000;27:683–93.
4. Anderson FA Jr, Wheeler HB, Goldberg RJ, Hosmer DW, Patwardhan NA, Jovanovic B, et al. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. Arch Intern Med 1991;151:933–8.
5. Farley TMM, Collins J. Schlesselman JJ. Hormonal contraception and risk of cardiovascular disease: an international perspective. Contraception 1998;57:211–30.
6. White RH. The epidemiology of venous thromboembolism. Circulation 2003;107:(23 Suppl 1):14–8.
7. Lindqvist P, Dahlback B, Marsal K. Thrombotic risk during pregnancy: a population study. Obstet Gynecol 1999;94:595–9.
8. Douketis JD, Kearon C, Bates S, Duku EK, Ginsberg JS. Risk of fatal pulmonary embolism in patients with treated venous thromboembolism. JAMA 1998;279:458–62.
9. Vandenbroucke JP, Rosing J, Bloemenkamp KWM, Middeldorp S, Helmerhorst FM, Bouma BN, et al. Oral contraceptives and the risk of venous thrombosis. N Engl J Med 2001;344:1527–35.

10. Lidegaard O, Edstrom B, Kreiner S. Oral contraceptives and venous thromboembolis: a case-control study. Contraception 1998;57:291–301.
11. Bloemenkamp KWM, Rosendaal FR, Helmerhorst FM, Vandenbroucke JP. Higher risk of venous thrombosis during early use of oral contraceptives in women with inherited clotting defects. Arch Intern Med 2000;160:49–52.
12. Crosignani PG, La Vecchia C, on behalf of the ESHRE Capri Workshop Group. Concordant and discordant effects on cardiovascular risks exerted by oestrogen and progestogen in women using oral contraception and hormone replacement therapy. Hum Reprod Update 1999;5:681–7.
13. World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Venous thromboembolic disease and combined oral contraceptives: results of international multicentre case-control study. Lancet 1995;346:1575–82.
14. Farmer RDT, Lawrenson RA, Todd JC, Williams TJ, MacRae KD, Tyrer F, et al. A comparison of the risks of venous thromboembolic disease in association with different combined oral contraceptives. Br J Clin Pharmacol 2000;49:580–90.
15. Rosendaal FR, Helmerhorst FM, Vandenbroucke JP. Female hormones and thrombosis. Arterioscler Thromb Vasc Biol 2002;22:201–10.
16. Jick H, Jick SS, Gurewich V, Myers MW, Vasilakis C. Risk of idiopathic cardiovascular death and nonfatal venous thromboembolism in women using oral contraceptives with differing progestagen components. Lancet 1995;346:1589–93.
17. World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Effect of different progestagens in low oestrogen oral contraceptives on venous thromboembolic disease. Lancet 1995;346:1582–8.
18. Lewis MA, Heinemann LAJ, MacRae KD, Bruppacher R, Spitzer WO, with the Transnational Research Group on Oral Contraceptives and the Health of Young Women. The increased risk of venous thromboembolism and the use of third generation progestagens: role of bias in observational research. Contraception 1996;54:5–13.
19. Lewis MA. The transnational study on oral contraceptives and the health of young women: methods, results, new analyses and the healthy user effect. Hum Reprod Update 1999;5:707–20.
20. Kemmeren JM, Algra A, Grobbee DE. Third generation oral contraceptives and risk of venous thrombosis: meta-analysis. BMJ 2001;323:1–9.
21. Vasilakis-Scaramozza C, Jick H. Risk of venous thromboembolism with cyproterone or levonorgestrel contraceptives. Lancet 2001;358:1427–9.
22. Lidegaard O. Absolute and Attributable risk of venous thromboembolism in women on combined cyproterone acetate and ethynilestradiol. J Obstet Gynaecol Can 2003; 25(7): 575-7.
23. Spitzer WO. Cyproterone acetate with Ethinylestradiol as a risk factor for venous thromboembolism: an epidemiological evaluation. J Obstet Gynaecol Can 2003;25 (12): 1011-8.
24. Seaman HE, de Vries CS, Farmer RDT. The risk of venous thromboembolism in women prescribed cyproterone acetate in combination with ethinyl estradiol: a nested cohort analysis and case-control study. Hum Reprod 2003;18:522–6.
25. Vandenbroucke JP, Koster T, Briet E, Reitsma PH, Bertina RM, Rosendaal FR. Increased risk of venous thrombosis in oral-contraceptive users who are carriers of factor V Leiden mutation. Lancet 1994;344:1453–7.
26. Seligsohn U, Lubetsky A. Genetic susceptibility to venous thrombosis. N Engl J Med 2001;344:1222–31.
27. Vandenbroucke JP, van der Meer FJM, Helmerhorst FM, Rosendaal FR. Factor V Leiden: should we screen oral contraceptive users and pregnant women? BMJ 1996;313:1127–30.
28. Prandoni P, Lensing AWA, Cogo A, Cuppini S, Villalta S, Carta M, Cattelan AM, Polistena P, Bernardi E, Prins MH. The long-term clinical course of acute deep venous thrombosis. Ann Intern Med 1996;125(1):1-7.
29. de Bruijn SFTM, Stam J, Koopman MMW, Vandenbroucke JP, for the Cerebral Venous Sinus Thrombosis Study Group. Case-control study of risk of cerebral sinus thrombosis in oral contraceptive users who are carriers of hereditary prothrombotic conditions. BMJ 1998;316:589–92.
30. Dunn NR, Arscott A, Thorogood M, Faragher B, de Caestecker L, MacDonald TM, et al. Regional variation in incidence and case fatality of myocardial infarction among young women in England, Scotland and Wales. J Epidemiol Community Health 2000;54:293–8.
31. WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Acute myocardial infarction and combined oral contraceptives: results of an international multicentre case-control study. Lancet 1997;349:1202–9.
32. Farley TMM, Meirik O, Chang CL, Poulter NR. Combined oral contraceptives, smoking, and cardiovascular risk. J Epidemiol Community Health 1998;52:775–85.
33. Sidney S, Petitti DB, Quesenberry CP Jr, Klatsky AL, Ziel HK, Wolf S. Myocardial infarction in users of low-dose oral contraceptives. Obstet Gynecol 1996;88:939–44.
34. Sidney S, Siscovick DS, Petitti DB, Schwartz SM, Quesenberry CP, Psaty BM, et al. Myocardial infarction and use of low-dose oral contraceptives: a pooled analysis of 2 US studies. Circulation 1998;98:1058–63.
35. Rosenberg L, Palmer JR, Rao RS, Shapiro S. Low-dose oral contraceptive use and the risk of myocardial infarction. Arch Intern Med 2001;161:1065–70.
36. Dunn N, Thorogood M, Faragher B, de Caestecker L, MacDonald TM, McCollum C, et al. Oral contraceptives and myocardial infarction: results of the MICA case-control study. BMJ 1999;318:1579–83.
37. Tanis BC, van den Bosch MAAJ, Kemmeren JM, Cats VM, Helmerhorst FM, Algra A, et al. Oral contraceptives and the risk of myocardial infarction. N Engl J Med 2001;345:1787–93.
38. Lewis MA, Heinemann LAJ, Spitzer WO, MacRae KD, Bruppacher R, for the Transnational Research Group on Oral Contraceptives and the Health of Young Women. The use of oral contraceptives and the occurrence of acute myocardial infarction in young women. Contraception 1997;56:129–40.
39. Dunn NR, Arscott A, Thorogood M. The relationship between use of oral contraceptives and myocardial infarction in young women with fatal outcome, compared to those who survive: results from the MICA case-control study. Contraception 2001;63:65–9.
40. Spitzer WO, Faith JM, MacRae KD. Myocardial infarction and third generation oral contraceptives: aggregation of recent studies. Hum Reprod 2002;17:2307–14.
41. Lidegaard O. Thrombotic diseases in young women and the influence of oral contraceptives. Am J Obstet Gynecol 1998;179:62–7.
42. Lewis MA. Myocardial infarction and stroke in young women: what is the impact of oral contraceptives? Am J Obstet Gynecol 1998;179:S68–77.
43. Lubianca JN, Faccin CS, Fuchs FD. Oral contraceptives: a risk factor for uncontrolled blood pressure among hypertensive women. Contraception 2003;67:19–24.
44. WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Ischaemic stroke and combined oral contraceptives: results of an international, multicentre, case-control study. Lancet 1996;348:498–505.
45. Petitti DB, Sidney S, Bernstein A, Wolf S, Quesenberry C, Ziel HK. Stroke in users of low-dose oral contraceptives. N Engl J Med 1996;335:8–15.
46. Schwartz SM, Siscovick DS, Longstreth WT Jr, Psaty BM, Beverly RK, Raghunathan TE, et al. Use of low-dose oral contraceptives and stroke in young women. Ann Intern Med 1997;127:596–603.
47. Lidegaard O. Oral contraception and risk of a cerebral thromboembolic attack: results of a case-control study. BMJ 1993;306:956–63.
48. Heinemann LAJ, Lewis MA, Spitzer WO, Thorogood M, Guggenmoos-Holzmann I, Bruppacher R, and the Transnational Research Group on Oral Contraceptives and the Health of Young Women. Thromboembolic stroke in young women: a European case-control study on oral contraceptives. Contraception 1998;57:29–37.
49. Kemmeren JM, Tanis BC, van den Bosch MAAJ, Bollen ELEM, Helmerhorst FM, van der Graaf Y, et al. Risk of arterial thrombosis in relation to oral contraceptives (RATIO) study: oral contraceptives and the risk of ischemic stroke. Stroke 2002;33:1202–8.
50. Gillum LA, Mamidipudi SK, Johnston SC. Ischemic stroke risk with oral contraceptives: a meta-analysis. JAMA 2000;284:72–8.
51. Poulter NR, Chang CL, Farley TMM, Marmot MG, Meirik O, and the WHO Collaborative Study of Cardiovascular Disease and Steroid

Hormone Contraception. Effect on stroke of different progestagens in low oestrogen dose oral contraceptives. Lancet 1999;354:301–4.
52. Lidegaard O, Kreiner S. Contraceptives and cerebral thrombosis: a five-year national case-control study. Contraception 2002;65:197–205.
53. Goldstein LB, Adams R, Becker K, Furberg CD, Gorelick PB, Hademenos G, et al. Primary prevention of ischemic stroke: a statement for healthcare professionals from the Stroke Council of the American Heart Association. Circulation 2001;103:163–82.
54. Curtis KM, Chrisman CE, Peterson HB, for the WHO Programme for Mapping Best Practices in Reproductive Health. Contraception for women in selected circumstances. Obstet Gynecol 2002;99:1100–12.
55. Tzourio C, Tehindrazanarivelo A, Iglesias S, Alperovitch A, Chedru F, d'Anglejan-Chatillon J, et al. Case-control study of migraine and risk of ischaemic stroke in young women. BMJ 1995;310:830–3.
56. Chang CL, Donaghy M, Poulter N, and World Health Organisation Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Migraine and stroke in young women: case-control study. BMJ 1999;318:13–8.
57. Donaghy M, Chang CL, Poulter N, on behalf of the European Collaborators of the World Health Organisation Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Duration, frequency, recency, and type of migraine and the risk of ischaemic stroke in women of childbearing age. J Neurol Neurosurg Psychiatry 2002;73:747–50.
58. The International Headache Society Task Force on Combined Oral Contraceptives and Hormone Replacement Therapy: Bousser MG, Conard J, Kittner S, de Lignières B, MacGregor EA, Massiou H, et al. Recommendations on the risk of ischaemic stroke associated with use of combined oral contraceptives and hormone replacement therapy in women with migraine. Cephalalgia 2000;20:155–6.
59. Becker WJ. Migraine and oral contraceptives. Can J Neurol Sci 1997;24:16–21.
60. Farley TMM, Meirik O, Collins J. Cardiovascular disease and combined oral contraceptives: reviewing the evidence and balancing the risks. Hum Reprod Update 1999;5:721–35.
61. Vasilakis C, Jick H, del Mar Melero-Montes M. Risk of idiopathic venous thromboembolism in users of progestagens alone. Lancet 1999;354:1610–1.
62. Heinemann LAJ, Assmann A, DoMinh T, Garbe E, and the Transnational Research Group on Oral Contraceptives and the Health of Young Women. Oral progestogen-only contraceptives and cardiovascular risk: results from the Transnational Study on Oral Contraceptives and the Health of Young Women. Eur J Contracept Reprod Health Care 1999;4:67–73.
63. Poulter ND, Chang CL, Farley TMM, Meirik O. Risk of cardiovascular diseases associated with oral progestagen preparations with therapeutic indications. Lancet 1999;354:1610.
64. Parker WA. Estrogen-induced pancreatitis. Clin Pharm 1983;2(1):75-9.
65. Skouby SO, Molsted-Pedersen L, Kuhl C, Bennet P. Oral contraceptives in diabetic women: metabolic effects of four compounds with different estrogen/progestogen profiles. Fertil Steril 1986;46:858–64.
66. Kjos SL. Contraception in diabetic women. Obstet Gynecol Clin North Am 1996;23:243–58.
67. Garg SK, Chase HP, Marshall G, Hoops SL, Holmes DL, Jackson WE. Oral contraceptives and renal and retinal complications in young women with insulin-dependent diabetes mellitus. JAMA 1994;271(14):1099-1102.
68. Bennion LJ, Ginsberg RL, Garnick MB, Bennett PH. Effects of oral contraceptives on the gallbladder bile of normal women. N Engl J Med 1976;294:189–92.
69. Grodstein F, Colditz GA, Hunter DJ, Manson JE, Willett WC, Stampfer MJ. A prospective study of symptomatic gallstones in women: relation with oral contraceptives and other risk factors. Obstet Gynecol 1994;84:207–14.
70. Connolly TJ, Zuckerman AL. Contraception in the patient with liver disease. Semin Perinatol 1998;22:178–82.
71. Godet PG, May GR, Sutherland LR. Meta-analysis of the role of oral contraceptive agents in inflammatory bowel disease. Gut 1995;37:668–73.
72. Cosnes J, Carbonnel F, Carrat F, Beaugerie L, Gendre JP. Oral contraceptive use and the clinical course of Crohn's disease: a prospective cohort study. Gut 1999;45:218–22.
73. Timmer A, Sutherland LR, Martin F, and The Canadian Mesalamine for Remission of Crohn's Disease Study Group. Oral contraceptive use and smoking are risk factors for relapse in Crohn's disease. Gastroenterology 1998;114:1143–50.
74. Hanker JP. Gastrointestinal disease and oral contraception. Am J Obstet Gynecol 1990;163:2204–7.
75. Mok CC, Lau CS, Wong RW. Use of exogenous estrogens in systemic lupus erythematosus. Semin Arthritis Rheum 2001;30:426–35.
76. Prengler M, Pavlakis SG, Prohovnik I, Adams RJ. Sickle cell disease: the neurological complications. Ann Neurol 2002;51:543-552.
77. de Abood M, de Castillo Z, Guerrero F, Espino M, Austin KL. Effect of Depo-Provera or Microgynon on the painful crises of sickle cell anemia patients. Contraception 1997;56:313–6.
78. Yoong WC, Tuck SM. Menstrual pattern in women with sickle cell anaemia and its association with sickling crises. J Obstet Gynaecol Can 2002;22(4):399-401.
79. Vessey M, Painter R, Yeates D. Oral contraception and epilepsy: findings in a large cohort study. Contraception 2002;66:77–9.
80. Patsalos PN, Froscher W, Pisani F, van Rijn CM. The importance of drug interactions in epilepsy therapy. Epilepsia 2002;43:365–85.
81. Crawford P. Interactions between antiepileptic drugs and hormonal contraception. CNS Drugs 2002;16:263–72.
82. Oakes J, Hahn PM, Lillicrap D, Reid RL. A survey of recommendations by gynecologists in Canada regarding oral contraceptive use in the perioperative period. Am J Obstet Gynecol 2002;187:1539–43.

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.[1]

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.[1,2] 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.[3] If fertilization does occur, IUDs also appear to have post-fertilization effects, including the potential inhibition of implantation.[4]

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.[5-7] 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.[8] Endometrial estrogen and progesterone receptors are suppressed.[9] Cervical mucus may become thickened, creating a barrier to sperm penetration.[10] Ovulation may be inhibited in some women.[11,12]

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.[1] It should not be used for postcoital contraception.

Comparison of IUD and LNG-IUS Devices

Type of Device	Failure rate per 100 woman-years[1] (Pearl Index)	Ectopic rate per 100 woman-years[1]	Duration of action[1]
Copper IUD (Nova-T)	1.26	0.25	5 years
LNG-IUS	0.09	0.02	5 years

CONTRAINDICATIONS

The World Health Organization (WHO) has developed a list of absolute and relative contraindications to use of an IUD.[13]

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.[14] 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%[15-19] and favourable effects on hemoglobin levels.[20] 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.[21,22] Dysmenorrhea may also improve in LNG-IUS users.[16,23]

A randomized controlled study found that use of the LNG-IUS protects against endometrial hyperplasia in women on tamoxifen.[24] Small reports support a beneficial effect in the treatment of fibroid-related menorrhagia.[25,26]

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.[27,28] 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.[1] The cumulative termination rates for bleeding problems after 5 years of use are up to 20% for copper IUDs.[1]

By contrast, users of the LNG-IUS experience a reduction in menstrual blood loss of between 74 and 97%.[15-18] 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.[20] Between 16 and 35% of LNG-IUS users will become amenorrheic after one year of use.[1,20,29] Since information received in advance will improve user satisfaction, patients should be carefully counselled regarding potential menstrual changes prior to IUD insertion.[30]

2. PAIN OR DYSMENORRHEA

Up to 6% of copper IUD and LNG-IUS users will have discontinued use at 5 years because of pain.[1] 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.[16,23]

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.[1] 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.[1]

4. FUNCTIONAL OVARIAN CYSTS

Functional ovarian cysts have been reported in up to 30% of LNG-IUS users.[31] Since these cysts usually resolve spontaneously,[32] they should be managed expectantly.[31]

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.[33,34] 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,[35] case-control studies,[36] and randomized controlled trials[37] 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.[36] Investigations by the World Health Organization found the risk to be highest in the first 20 days following insertion.[37] 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.[1,38,39] 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%.[1] Risk factors for expulsion include insertion immediately postpartum, nulliparity, and previous IUD expulsion.[40] A woman who has expelled one IUD has a 30% chance of expelling a subsequent device.[41]

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.[42] Although the risk of spontaneous abortion appears to be normalized after IUD removal, the risk of preterm delivery remains higher.[43]

MYTHS AND MISCONCEPTIONS

1. Nulliparous women cannot use IUDs.
   Fact: Nulliparity is not a contraindication to IUD use.[44] 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.[45]
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,[37,46] 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.[47]

   The LNG-IUS appears to be as effective as tubal ligation.[48]

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.[46,49] 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.[50] 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.[51]

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.[52] 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,[53,54] 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.[1,20,29] 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.[1] 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 gonoccocal 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

Actinomycosis is considered a commensal vaginal organism[55] 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.[56] 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.[55] 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

1. Andersson K, Odlind V, Rybo G. Levonorgestrel-releasing and copper-releasing (Nova-T) IUDs during five years of use: a randomized comparative trial. Contraception 1994; 49:56–72.
2. No author. The TCu380A, TCu220C, multiload 250 and Nova T IUDS at 3,5 and 7 years of use--results from three randomized multicentre trials. World Health Organization. Special Programme of Research, Development and Research Training in Human Reproduction: Task Force on the Safety and Efficacy of Fertility Regulating Methods. Contraception 1990; 42:141–58.
3. Videlo-Rivero L, Etchepareborda JJ, Kesseru E. Early chorionic activity in women bearing inert IUD, copper IUD, and levonorgestrel releasing IUD. Contraception 1987; 36:217–26.
4. Stanford J, Mikolajczyk R. Mechanisms of action of intrauterine devices: Update and estimation of postfertilization effects. Am J Obstet Gynecol 2002; 187:1699–1708.
5. Sivin I. IUDs are contraceptives, not abortifacients: a comment on research and belief. Stud Fam Plann 1989; 20:355–9.
6. Ortiz ME, Croxatto HB, Bardin CW. Mechanisms of action in intrauterine devices. Obstet Gynecol Surv 1996; 51(12 Suppl):S42–S51.
7. Wilcox AJ, Weinberg CR, Armstrong EG, Canfield RE. Urinary human chorionic gonadotropin among intrauterine device users: detection with a highly specific and sensitive assay. Fertil Steril 1987; 47:265–9.
8. Critchley HO, Wang H, Jones RL, Kelly RW, Drudy TA, Gebbie AE, et al. Morphological and functional features of endometrial decidualization following long-term intrauterine levonorgestrel delivery. Hum Reprod 1998;13:1218-24.
9. Zhu P, Liu X, Luo H, Gu Z, Cheng J, Xu R, et al. The effect of a levonorgestrel-releasing intrauterine device on human endometrial oestrogen and progesterone receptors after one year of use. Hum Reprod 1999;14:970-5.
10. Jonsson B, Landgren B, Eneroth P. Effects of various IUDs on the composition of cervical mucus. Contraception 1991;43:447-58.
11. Nilsson CG, Lahteenmaki PL, Luukkainen T. Ovarian function in amenorrheic and menstruating users of a levonorgestrel-releasing device. Fertil Steril 1984; 41:52–5.
12. Barbosa I, Bakos O, Olsson SE, Odlind V, Johansson ED.. Ovarian function during use of a levonorgestrel-releasing IUD. Contraception 1990; 42:51–66.
13. The World Health Organization. Improving access to quality care in family planning: medical eligibility criteria for contraceptive use. 2ed ed. Geneva: WHO; 2001.
14. Benshushan A, Paltiel O, Rojansky N, Brzezinski A, Laufer N. IUD use and the risk of endometrial cancer. Eur J Obstet Gynecol 2002;105:166–9.
15. Andersson JK, Rybo G. Levonorgestrel-releasing intrauterine device in the treatment of menorrhagia. Br J Obstet Gynaecol 1990;97:690–4.
16. Barrington JW, Bowens-Simpkins P. The levonorgestrel intrauterine system in the management of menorrhagia. Br J Obstet Gynaecol 1997;104:614–6.
17. Irvine GA, Campbell-Brown MB, Lumsden MA, Heikkila A, Walker JJ, Cameron IT. Randomized comparative trial of the levonorgestrel intrauterine system and norethisterone for treatment of idiopathic menorrhagia. Br J Obstet Gynaecol 1998;105:592–8.
18. Istre O, Trolle B. Treatment of menorrhagia with the levonorgestrel intrauterine system versus endometrial resection. Fertil Steril 2001;76:304–9.
19. Lethaby AE, Cooke I, Rees M. Progesterone/progestogen releasing intrauterine systems for heavy menstrual bleeding (Cochrane Methodology Review). In: The Cochrane Library, Issue 4 2003.
20. Ronnerdag M, Odlind V. Health effects of long-term use of the intrauterine levonorgestrel-releasing system: a follow-up study over 12 years of continuous use. Acta Obstet Gynecol Scand 1999;78:716–21.
21. Lahteenmaki P, Haukkamaa M, Puolakka J, Riikonen U, Sainio S, Suvisaari J, et al. Open randomised study of use of levonorgestrel releasing intrauterine system as alternative to hysterectomy. BMJ 1998;316:1122–6.
22. Hurskainen R, Teperi J, Rissanen P, Aalto AM, Grenman S, Kivela A, et al. Quality of life and cost-effectiveness of levonorgestrel-releasing intrauterine system versus hysterectomy for treatment of menorrhagia: a randomised trial. Lancet 2001;357:273–7.
23. Pakarinen P, Toivonen J, Luukkainen T. Therapeutic use of the LNG IUS, and counseling. Semin Reprod Med 2001;19:365–72.
24. Gardner FJ, Konje JC, Abrams KR, Brown LJ, Khanna S, Al-Azzawi F, et al. Endometrial protection from tamoxifen-stimulated changes by a levonorgestrel-releasing intrauterine system: a randomised controlled trial. Lancet 2000;356:1698–9.
25. Fong YF, Singh K. Effect of the levonorgestrel-releasing intrauterine system on uterine myomas in a renal transplant patient. Contraception 1999;60:51–3.
26. Starczewski A, Iwanicki M. Intrauterine therapy with levonorgestrel releasing IUD of women with hypermenorrhea secondary to uterine fibroids. Ginekol Pol 2000;71:1221–5.
27. Milsom I, Andersson K, Jonasson K, Lindstedt G, Rybo G. The influence of the Gyne-T 380S IUD on menstrual blood loss and iron status. Contraception 1995;52:175–9.
28. Larsson G, Milsom I, Jonasson K, Lindstedt G, Rybo G. The long-term effects of copper surface area on menstrual blood loss and iron status in women fitted with an IUD. Contraception 1993;48:471–80.
29. Luukkainen T, Allonen H, Haukkamaa M, Holma P, Pyorala T, Terho J, et al. Effective contraception with levonorgestrel-releasing intrauterine device: 12 month report of a European multinational study. Contraception 1987;36:169–79.
30. Backman T, Huhtala S, Luoto R, Tuominen J, Rauramo I, Koskenvuo M. Advance information improves user satisfaction with the levonorgestrel intrauterine system. Obstet Gynecol 2002;99:608–13.
31. Jarvela I, Tekay A, Jouppila P. The effect of a levonorgestrel-releasing intrauterine system on uterine artery blood flow, hormone concentrations and ovarian cyst formation in fertile women. Hum Reprod 1998;13:3379–83.
32. Pakarinen PI, Suvisaari J, Luukkainen T, Lahteenmaki P. Intracervical and fundal administration of levonorgestrel for contraception: endometrial thickness, patterns of bleeding, and persisting ovarian follicles. Fertil Steril 1997;68:59–64.
33. The World Health Organization. Mechanism of action, safety, and efficacy of intrauterine devices. Technical Report Series, 753.. Geneva: WHO; 1987.
34. Harrison-Woolrych M, Ashton J, Coulter D. Uterine perforation on intrauterine device insertion: is the incidence higher than previously reported? Contraception 2003;67:53–6.
35. Tietze C. Evaluation of intrauterine devices: ninth progress report of the

Cooperative Statistical Program. Stud Fam Plann 1970;55:1–40.
36. Lee NC, Rubin GL, Ory HW, Burkman RT. Type of intrauterine device and the risk of pelvic inflammatory disease. Obstet Gynecol 1983;62:1–6.
37. Farley TM, Rosenberg MJ, Rowe PJ, Chen JH, Meirik O. Intrauterine devices and pelvic inflammatory disease: an international perspective. Lancet 1992;339:785–8.
38. Toivonen J, Luukkainen T, Allonen H. Protective effect of intrauterine release of levonorgestrel on pelvic infections: three years' comparative experience of levonorgestrel and copper-releasing intrauterine devices. Obstet Gynecol 1991;77:261–4.
39. Sivin I, Stern J, Coutinho E, Mattos CE, el Mahgoub S, Diaz S, et al. Prolonged intrauterine contraception: a seven-year randomized study of the levonorgestrel 20 mcg/day (LNg 20) and the copper T380 Ag IUD. Contraception 1991;44:473–80.
40. Bahamondes L, Diaz J, Marchi NM, Petta CA, Cristofoletti ML, Gomez G. Performance of copper intrauterine devices when inserted after an expulsion. Hum Reprod 1995;10:2917–8.
41. Zhang J, Feldblum PJ, Chi IC, Farr MG. Risk factors for copper-T IUD expulsion: an epidemiological analysis. Contraception 1992;46:427–33.
42. United Kingdom Family Planning Research Network. Pregnancy outcome associated with the use of IUDs. Br J Fam Plann 1989;15:7–10.
43. Chaim W, Mazor M. Pregnancy with an intrauterine device in situ and preterm delivery. Arch Gynecol Obstet 1992;252:21–4.
44. Hubacher D, Lara-Ricalde R, Taylor DJ, Guerra-Infante F, Guzman-Rodriguez R. Use of copper intrauterine devices and the risk of tubal infertility among nulligravid women. N Engl J Med. 2001;345 (8): 561-7.
45. Grimes DA. Intrauterine devices and infertility: sifting through the evidence. Lancet. 2001 Jul 7; 358(9275): 6-7.
46. Jovanovic R, Barone CM, Van Natta FC, Congema E. Preventing infection related to insertion of an intrauterine device. J Reprod Med 1988;33:347–52.
47. Peterson HB, Xia Z, Hughes JM, Wilcox LS, Tylor LR, Trussell J. The risk of pregnancy after tubal sterilization: findings from the U.S. Collaborative Review of Sterilization. Am J Obstet Gynecol. 1996 Apr; 174(4): 1161-8.
48. Sturridge F, Guillebaud J. A Risk-Benefit Assessment of the Levonorgestrel-Releasing Intrauterine System. Drug Safety 1996;15(6):430-440.
49. White MK, Ory HW, Rooks JB, Rochat RW. Intrauterine device termination rates and the menstrual cycle day of insertion. Obstet Gynecol 1980;55:220–4.
50. Grimes D, Schulz K, van Vliet H, Stanwood N. Immediate post-partum insertion of intrauterine devices (Cochrane Methodology Review). In: The Cochrane Library 2003;(4).
51. Grimes DA, Schulz KF. Antibiotic prophylaxis for intrauterine contraceptive device insertion (Cochrane Methodology Review). In: The Cochrane Library 2001;(2).
52. Dajani AS, Taubert KA, Wilson W, Bolger AF, Bayer A, Ferrieri P, et al. Prevention of bacterial endocarditis: recommendations by the American Heart Association. JAMA 1997;277:1794–1801.
53. Assaf A, Gohar M, Saad S, el-Nashar A, Abdel Aziz A. Removal of intrauterine devices with missing tails during early pregnancy. Contraception 1992;45:541–6.
54. Hucke J, Campo RL, Kozlowski P, De Bruyne F. Experience with hysteroscopy or ultrasound-controlled removal of an intrauterine spiral with no visible thread in early pregnancy. Geburtshilfe Frauenheilkd 1991;51(1):31–3.
55. Lippes J. Pelvic actinomycosis: a review and preliminary look at prevalence. Am J Obstet Gynecol 1999;180(2 Pt 1):265–9.
56. Merki-Feld GS, Lebeda E, Hogg B, Keller PJ. The incidence of actinomyces-like organisms in Papanicolaou-stained smears of copper- and levonorgestrel-releasing intrauterine devices. Contraception 2000;61:365–8.