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Canadian Contraception Consensus (Part 3 of 4): Chapter 8 – Progestin-Only Contraception

Canadian Contraception Consensus (Part 3 of 4)
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Abstract

Objective: To provide guidelines for health care providers on the use of contraceptive methods to prevent pregnancy and on the promotion of healthy sexuality.

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

Evidence: Published literature was retrieved through searches of Medline and The Cochrane Database from January 1994 to January 2015 using appropriate controlled vocabulary (e.g., contraception, sexuality, sexual health) and key words (e.g., contraception, family planning, hormonal contraception, emergency contraception). Results were restricted to systematic reviews, randomized control trials/controlled clinical trials, and observational studies published in English from January 1994 to January 2015. Searches were updated on a regular basis in incorporated in the guideline to June 2015. Grey (unpublished) literature was identified through searching the websites of health technology assessment and health technology-related agencies, clinical practice guideline collections, clinical trial registries, and national and international medical specialty societies.

Values: The quality of the evidence in this document was rated using the criteria described in the Report of the Canadian Task Force on Preventive Health Care (Table 1).

Table 1. Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care

Quality of evidence assessment*	Classification of recommendations†
I: Evidence obtained from at least 1 properly randomized controlled trial	A. There is good evidence to recommend the clinical preventive action
II-1: Evidence from well-designed controlled trials without randomization	B. There is fair evidence to recommend the clinical preventive action
II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than 1 centre or research group	C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in the category	D. There is fair evidence to recommend against the clinical preventive action
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	E. There is good evidence to recommend against the clinical preventive action
	L. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

*The quality of evidence reported in these guidelines has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.

†Recommendations included in these guidelines have been adapted from the Classification of recommendations criteria described in The Canadian Task Force on Preventive Health Care.

ABBREVIATIONS

BMD	bone mineral density
BMI	body mass index
CDC	Centers for Disease Control and Prevention
CHC	combined hormonal contraception
COC	combined oral contraceptives
Cu-IUD	copper intrauterine device
DMPA	depot medroxyprogesterone acetate
EC	emergency contraception
ENG	etonogestrel
HIV	human immunodeficiency virus
HMB	heavy menstrual bleeding
IM	intra-muscular
IUC	intrauterine contraceptives
LARC	long-acting reversible contraceptive
LEEP	loop electrosurgical excision procedure
LNG	levonorgestrel
LNG-EC	Levonorgestrel emergency contraception
LNG-IUS	levonorgestrel-releasing intrauterine systems
NNRTI	nuceloside/nucleotide reverse transcriptase inhibitors
NSAIDs	non-steroidal anti-inflammatory drugs
PID	pelvic inflammatory disease
POP	progestin-only pills
RCT	randomized controlled trials
SARC	short-acting reversible contraceptive
STI	sexually transmitted infections
UPA-EC	ulipristal acetate emergency contraception
UPI	unprotected intercourse
VTE	venous thromboembolism
WHO	World Health Organization

Chapter 8: Progestin-Only Contraception

Summary Statements

15. Progestin implants have failure rates as low as permanent contraception. (II-2)
16. The use of a progestin implant immediately postpartum and post-abortion is an effective way of decreasing repeat pregnancy in adolescents and repeat abortions. (II-2)
17. The most common side effect of progestin-only contraceptive methods is menstrual cycle disturbances. (II-2) Amenorrhea is very common with depot medroxyprogesterone acetate and progestin implant use. (II-2)
18. The use of progestins given at contraceptive doses does not appear to increase the risk of venous thromboembolism, myocardial infarction, or stroke. (II-2)
19. The efficacy of progestin implants or depot medroxyprogesterone acetate is not decreased in overweight and obese women. (II-2)
20. Early weight gain with depot medroxyprogesterone acetate use is predictive of continued weight gain. (II-2)
21. Depot medroxyprogesterone acetate use is associated with a delay in resumption of ovulation. (II-2)
22. The use of depot medroxyprogesterone acetate (DMPA) is associated with a decrease in bone mineral density. This decrease is most rapid in the first 2 years of use and appears to be largely reversible once DMPA is discontinued. (I) There is no strong evidence that the use of DMPA causes osteoporosis (II-2) or increases the risk of fracture. (II-2)
23. The use of progestin-only preparations has not been shown to decrease breast milk production. (I) The small amounts of steroid hormones secreted in breast milk do not have an adverse effect on infant growth and development. (II-2)
24. Depot medroxyprogesterone acetate use is associated with a decreased risk of endometrial and ovarian cancer. (II-2)

Recommendations

12. Progestin-only methods of contraception should be considered in women with medical conditions where estrogen is contraindicated or less appropriate, such as women who are recently postpartum, breastfeeding, or in smokers over age 35. (III-A)

13. There should be no restriction on the use of depot medroxy-progesterone acetate (DMPA), including duration of use, among women of reproductive age who are otherwise eligible to use the method. The overall risks and benefits of continuing DMPA use should be discussed with DMPA users at regular intervals throughout the course of treatment. (III-A)
14. Counselling regarding menstrual cycle disturbances should be done prior to initiating a progestin-only method of contraception. (I-A)
15. Health care providers should inform patients of the potential effects of depot medroxyprogesterone acetate on bone mineral density and counsel them on "bone health," including calcium and vitamin D supplementation, smoking cessation, weight-bearing exercise, and decreased alcohol and caffeine consumption. (III-A)
16. If prolonged and/or frequent bleeding occurs in users of progestin-only contraceptives, pregnancy, sexually transmitted infection, and genital pathology should be ruled out. (III-B)
17. Ectopic pregnancy should be ruled out if a pregnancy occurs in a woman using a progestin-only method of contraception. (III-A)

Progestin-Only Contraception

1. PROGESTIN IMPLANTS

INTRODUCTION

The single-rod etonogestrel subdermal implant (Implanon/Implanon NXT/Nexplanon) is a long-acting reversible contraceptive that currently is not available in Canada. It is available in over 85 countries, including the United States, where it was approved in 2010; therefore, Canadian health care providers may encounter women using this method of contraception. The single-rod implant contains 68 mg of the progestin etonogestrel and provides contraception for 3 years. Etonogestrel is the active metabolite of desogestrel. Implanon NXT/Nexplanon differs from the original Implanon implant by a new applicator and the addition of 15 mg of barium sulfate in its ethylene vinyl acetate core, which allows the implant to be identified on X-ray or ultrasound if it is difficult to palpate.[1] Training in insertion and removal of this implant is important to prevent injury to blood vessels, skin, and nerves. The 6-rod levonorgestrel implant was removed from the Canadian market in September 2000 and is no longer manufactured. A 2-rod levonorgestrel implant is available in some countries (Table 6).

Table 6. Comparison of contraceptive implants*

Characteristics	Nexplanon	Norplant-2, Jadelle, Sino-implant II	Norplant†
Number of rods	1	2	6
Hormone	Etonogestrel	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	3 years	3-5 years	5-7 years

*No contraceptive implants are available in Canada at this time.

†Norplant is no longer manufactured.

EFFECTIVENESS

The ENG implant is a very effective method of contraception with identical perfect and typical use failure rates of 0.05%.[2] One-year continuation rates for the ENG implant are up to 84%,[2] and 3-year continuation rates range from 30% to 75%.[3] The first-year probability of pregnancy for the LNG 2-rod implant ranges from 0.0% to 0.1%.[4,5] Implant use immediately postpartum or post-abortion has the potential to significantly decrease repeat pregnancies in adolescents[6–8] and repeat abortions.[9–11]

Summary Statements

15. Progestin implants have failure rates as low as permanent contraception. (II-2)
16. The use of a progestin implant immediately postpartum and post-abortion is an effective way of decreasing repeat pregnancy in adolescents and repeat abortions. (II-2)

MECHANISM OF ACTION

The ENG implant works primarily by inhibiting ovulation[12,13] and consistently does so until the beginning of the third year of use.[13] Ovarian activity, including estradiol synthesis, is still present.[12] The ENG implant causes thickening of the cervical mucus and changes in the endometrial lining.[12–14]

INDICATIONS

In the absence of contraindications, progestin implants may be considered for any woman seeking an effective, reversible, coitally independent method of contraception. It may be particularly suited for women who are seeking longer-term contraception or a method that is "forgettable" and less adherence demanding or for women who require an "invisible" method of contraception. Women who have contraindications and/or sensitivities to estrogen, are breastfeeding, or have trouble remembering daily, weekly, or monthly regimens may be good candidates for use of the implant.

CONTRAINDICATIONS

There are very few contraindications to the use of progestin implants.[15,16] The World Health Organization and the Centers for Disease Control and Prevention have developed guidelines that categorize medical conditions into 1 of 4 categories based on their level of risk.[16,17] The following recommendations are made based on the existing literature and the recommendations of the CDC and WHO:

Category 4 for Initiation of ENG

A condition that represents an unacceptable health risk if the contraceptive method is used.

- Current breast cancer

Category 3 for Initiation of ENG

Theoretical or proven health risks generally outweigh the advantages. Women with a category 3 medical condition may benefit from expert consultation before advising against the method.

- Previous history of breast cancer and no disease for 5 years
- Severe (decompensated) cirrhosis
- Hepatocellular adenoma
- Malignant liver tumor
- Unexplained vaginal bleeding prior to investigation

NONCONTRACEPTIVE BENEFITS

Pain associated with endometriosis is reduced with the use of the ENG implant.[18–20] A small, randomized, controlled trial demonstrated decreased pain in women with pelvic congestion syndrome.[21] Amenorrhea occurs in 22% to 29% of ENG implant users.[22,23] In women with baseline dysmenorrhea, 77% report a complete resolution of dysmenorrhea.[22]

SIDE EFFECTS

Changes in Menstrual Bleeding

ENG implants are associated with unpredictable bleeding patterns, which include amenorrhea (22% to 29.5%) and infrequent (34%), frequent (3.9% to 6.7%), and/or prolonged (11.3% to 17.7%) bleeding.[22,23] The average number of bleeding and spotting days is highest in the first 90-day reference period, then drops to an average of 6 days per month at the third 90-day reference period and remains stable thereafter.[23,24] Overall, the mean number of bleeding/spotting days is less than the number reported in normal menstrual cycles, which may explain the increase in hemoglobin level seen in implant users.[25] Only between 4.2% and 11.3% of implant users discontinue because of bleeding irregularities (usually prolonged or frequent bleeding). However, it still is a major cause of discontinuation and thus preinsertion counselling is essential.[5,22,23]

Summary Statement

17. The most common side effect of progestin-only contraceptive methods is menstrual cycle disturbances. (II-2) Amenorrhea is very common with DMPA and progestin implant use. (II-2)

Drug-Related Side Effects

Reported side effects of the ENG implant include headache (8.5% to 15.5%), weight gain (6.4% to 12.0%), acne (11.4% to 15.3%), breast pain (9.1% to 10.2%), emotional lability (2.5% to 5.8%), and abdominal pain (4.3% to 5.2%).[23,26,27] The major reasons for discontinuation are acne and weight gain.[26,27] A weight gain of 1.9 kg over 2 years has been reported in ENG implant users.[28]

Ovarian cysts have been reported in 5.2% of ENG implant users at 3 months and in 26.7% at 12 months. At both 3 months and 12 months, 13.0% of LNG implant users had ovarian cysts. These cysts usually are transient and do not require medical interventions.[29]

RISKS

Insertion or Removal-Related Complications

Complications during insertion are uncommon (1.0%) and can include pain, mild bleeding, hematoma, difficult insertion, and implant retention in the needle of the applicator.[23,30] Some women will report pain at the implant site (2.9% at any visit, 0.5% at last visit). Complications during removal (1.7%) include implant breakage, inability to locate or palpate the implant due to deep insertion, implant fixation by fibrous tissue, and implant adherence to underlying tissue.[23,31]

Venous Thromboembolism

There does not appear to be an increased risk of VTE in ENG implant users.[23] ENG implant use may be associated with a decrease in thrombin formation and does not appear to induce a prothrombotic pattern in the first 6 months of use.[32]

Summary Statement

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

Effect on Bone Mineral Density

Ovulation is inhibited in ENG implant users, but the endogenous estradiol production continues and serum estradiol levels remain above the threshold for maintaining normal bone mass. The evidence is still limited concerning the effect of implants on BMD beyond 3 years. In a prospective study of ENG and LNG implant users, both groups experienced a reduction in BMD at the mid-shaft of the ulna but not the distal radius.[33] At 36 months, similar findings were seen, but the drop in BMD was not as pronounced in the second 18 months of use.[34] The clinical relevance of this is not clear. More importantly, a 2-year study of ENG implant and copper intrauterine device (Cu-IUD) users did not show any significant differences in BMD at the lumbar spine, femoral neck, Ward's triangle, trochanter, and distal radius between groups or at 2 years of use[28] nor did another recent 1-year prospective study comparing ENG implant users to Cu-IUD users.[35]

Risk of Ectopic Pregnancy

Given its high efficacy, the risk of ectopic pregnancy is extremely low. There are, however, case reports of ectopic pregnancy with an ENG implant *in situ*,[36–39] so if pregnancy occurs, an ectopic pregnancy should be ruled out.

MYTHS AND MISCONCEPTIONS

1. Return to Fertility Is Delayed with Use of the ENG Implant

Fact: There is a rapid return to fertility after removal of the ENG implant, with some pregnancies being reported within 2 weeks of removal.[23] Etonogestrel levels are undetectable within 1 week after removal, and ovulation usually resumes within 3 weeks.[12,13]

2. Obese Women Should Not Use the ENG Implant

Fact: Women with a body mass index (BMI) $\geq$ 30 kg/m^2 can use the ENG implant.[15] Of the women choosing the implant in the Contraceptive CHOICE Project, 28% were overweight and 35% were obese. Their 3-year cumulative failure rate was less than 1% and identical to that of intrauterine contraceptive (IUC) users.[40] Whereas 1 pooled analysis of data from 11 clinical trials documented that women with low body weight had fewer bleeding and spotting days than women with a higher body weight,[22] a retrospective study of 304 women presenting for implant removal found that obese women (BMI $\geq$ 30 kg/m^2) were less likely to have their implant removed for bleeding compared with normal weight women (odds ratio [OR] 2.6; 95% confidence interval [CI] 1.2 to 5.7).[41]

Summary Statement

19. The efficacy of progestin implants or depot medroxyprogesterone acetate is not decreased in overweight and obese women. (II-2)

3. Breastfeeding Women Should Not Use the Implant

Fact: The contraceptive implant generally can be used at any time in the postpartum period, and breastfeeding women who are more than 4 weeks postpartum can use the implant without restriction. Observational studies of progestin-only contraceptives have shown no effect on successful initiation or continuation of breastfeeding nor on infant growth and development.[42] Other studies looking at timing of implant insertion have found no differences in lactogenesis, risk of lactation failure, breast milk composition, and infant growth.[43,44]

INITIATION

The ENG implant can be inserted at any time as long as pregnancy may be reasonably excluded. Back-up contraception or abstinence should be used for 7 days after insertion unless the implant is inserted within the first 5 days of menses or immediately postpartum or post-abortion. If a health care provider is not reasonably certain that a woman is not pregnant, the implant still may be inserted and a follow-up pregnancy test done in 2 to 4 weeks because the benefits of inserting the implant likely outweigh the risks, and the implant does not likely have post-fertilization effects.[45]

Among healthy women, usually there is no need to perform any examination or tests before inserting the contraceptive implant, although weight and BMI calculation may be helpful for monitoring implant users' weight over time. Screening for breast cancer or liver disease is not necessary due to the low prevalence of these conditions among reproductive-aged women.[45]

TROUBLESHOOTING

Irregular Bleeding

If unacceptable bleeding patterns occur, such as prolonged and/or frequent bleeding, then pregnancy, sexually transmitted infections (STI), and genital pathology should be ruled out.[46] In the absence of a definitive cause, there is limited evidence supporting effective treatment options. A randomized controlled trial (RCT) of methods to control prolonged bleeding in ENG implant users found mifepristone plus ethinyl estradiol or mifepristone plus doxycycline were significantly more effective in terminating an episode of bleeding than were placebo, doxycycline alone, or doxycycline plus ethinyl estradiol. However, subsequent

bleeding patterns did not improve.[47] Short-term non-steroidal anti-inflammatory (NSAID) use (5 to 7 days), short-term combined oral contraceptive (COC) or estrogen treatment (10 to 20 days), short courses of progestin-only pills (POP) twice a day for 20 days, or use of mefenamic acid 500 mg 3 times a day for 5 days have been suggested as possible treatment options.[45,46,48]

Amenorrhea occurs in some implant users and does not require medical treatment unless the bleeding pattern has changed abruptly to amenorrhea (pregnancy should be ruled out) or the woman finds it unacceptable. If amenorrhea is unacceptable, counselling on contraceptive alternatives is required.

DRUG INTERACTIONS

Women who are taking nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)—such as abacavir, tenofovir, zidovudine, lamivudine, didanosine, emtricitabine, stavudine—or raltegravir can use ENG implants without restriction (category 1). Women using NNRTIs containing either efavirenz or nevirapine or those using protease inhibitors (atazanavir, darunavir, lopinavir/ritonavir, ritonavir) generally can use ENG implants (category 2). Women using newer NNRTIs containing etravirine or rilpivirine can use all hormonal contraceptives without restriction (category 1).[49]

Women who are taking the following medications generally can use ENG implants, but theoretically these medications may reduce its contraceptive effectiveness: anticonvulsants (barbiturates, carbamazepine, oxcarbazepine, phenytoin, primidone, topiramate), rifampicin, bosentan, St. John's wort,[50,51] and ulipristal acetate.[51] Women treated with any of these medications should use a barrier method in addition to the implant or choose another method of contraception.[3] There are reports in the literature of failure of the ENG implant with the NNRTI efavirenz,[52] the anticonvulsant carbamazepine,[53] and phenytoin, phenobarbital, rifampicin, primidone, St. John's wort, primidone, nelfinavir, and ritonavir.[3]

2. INJECTABLE PROGESTIN

DMPA is a highly effective method of contraception. It has been used as a contraceptive agent since 1967 by millions of women worldwide, particularly in less developed regions,[54] and was approved for contraceptive use in Canada in 1997. In Canada, approximately 2% of women who are using contraception use DMPA as their birth control method, the rate being highest in the 20- to 29-year-old age group (3.4%).[55]

DMPA is available in a dose of 150 mg/mL given as an intra-muscular (IM) injection.[56] The subcutaneous formulation of 104 mg/0.65 mL that is available in other countries was approved by Health Canada in 2010 but has never been available in Canada.[57] DMPA is given intramuscularly at 3-month intervals (every 12 to 13 weeks) and thus is considered a LARC by some[58] and a short-acting reversible contraceptive (SARC) by others.[59] The low solubility of the microcrystals allows pharmacologically active drug levels to persist for a long period of time.

EFFECTIVENESS

DMPA is a highly effective form of contraception with a perfect use failure rate of 0.2% and a typical failure rate of 6%.[2] The "imperfect use" consists mostly of not returning for the next injection and high 1-year discontinuation rates (44%).[2] A more recent review of 139 studies between 1990 and 2008 reported a range of 1-year failure rates between 0.06 and 0.62 per 100 women-years.[60] Although some may not consider DMPA a LARC method,[59] its low failure rate is very similar to LARC.[61]

MECHANISM OF ACTION

DMPA works primarily by inhibiting the secretion of pituitary gonadotropins, thereby suppressing ovulation.[62] Women enter a hypoestrogenic state, and their progesterone is low due to anovulation.[63] DMPA also increases the viscosity of cervical mucus (minor mechanism of action)[64] and induces endometrial atrophy.[65]

INDICATIONS

In the absence of contraindications, DMPA may be considered by any woman seeking a reliable, reversible, discrete, coitally independent method of contraception. It may be more suitable for women who have difficulty complying with other birth control methods, women who require an estrogen-free method of contraception, or women who wish to take advantage of its non-contraceptive benefits. It also provides a more private and "undetectable" method for some women who can receive the injection in a clinical setting. It may be suitable for the following[66]:

- 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[67,68]
- Women taking anticonvulsant medications
- Women who require menstrual suppression due to personal preference or for management of menstrual hygiene
- Women with heavy menstrual bleeding, anemia, or dysmenorrhea (after appropriate investigation)[69]

DMPA is also approved for the treatment of endometriosis.[56] The use of condoms is still recommended in DMPA users for protection against STI and HIV infection.

Recommendation

12. Progestin-only methods of contraception should be considered in women with medical conditions where estrogen is contraindicated or less appropriate, such as women who are recently postpartum, breastfeeding, or in smokers over age 35. (III-A)

CONTRAINDICATIONS

There are very few contraindications to the use of DMPA. The WHO and the CDC have developed guidelines that categorize medical conditions into 1 of 4 categories based on their level of risk.[15,70] The following recommendations are made based on the existing literature and the recommendations of the CDC and WHO:

Category 4 for Initiation of DMPA

A condition that represents an unacceptable health risk if the contraceptive method is used.

- Current diagnosis of breast cancer

Category 3 for Initiation of DMPA

Theoretical or proven health risks generally outweigh the advantages. Women with a category 3 medical condition may benefit from expert consultation before advising against the method.

- History of breast cancer and no evidence of current disease for 5 years
- Unexplained vaginal bleeding (before evaluation)
- Severe decompensated cirrhosis
- Benign hepatocellular adenoma or malignant hepatoma

Recommendation

13. There should be no restriction on the use of DMPA, including duration of use, among women of reproductive age who are otherwise eligible to use the method. The overall risks and benefits of continuing DMPA use should be discussed with DMPA users at regular intervals throughout the course of treatment. (III-A)

NONCONTRACEPTIVE BENEFITS

DMPA has a number of noncontraceptive benefits. These include the following:

- High rates of amenorrhea with subsequent reduction in dysmenorrhea and anemia[71–74]
- Reduced risk of endometrial hyperplasia and cancer[75,76]
- Reduction in symptoms associated with endometriosis[67,68,77–79]
- Reduction of premenstrual syndrome and chronic pelvic pain[80]
- Decreased incidence of seizures[81,82]
- Possible reduced risk of pelvic inflammatory disease (PID)[83,84]
- Possible decreased incidence of sickle cell crisis[85–88]
- Decreased risk of myomas[89]

SIDE EFFECTS

Menstrual Cycle Disturbance

The most common side effect associated with DMPA use is the disruption of menstrual patterns. Irregular bleeding or unwanted amenorrhea may lead to discontinuation of DMPA in 8% to 66% of users.[72,73,90–93] 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.[71,94] At 12 months, normal menstrual patterns were experienced by only 11% of users.[95,96] Abnormally heavy or prolonged bleeding occurred in only 1% to 2% of users.[71,94] An inverse association has been found between weight/obesity and excessive bleeding with DMPA use.[97]

Amenorrhea is very common with DMPA use and may be a noncontraceptive benefit for some women.[98,99] A systematic review showed that the weighted prevalence of amenorrhea in DMPA users at successive 90-day periods was 12%, 25%, 37%, and 46%.[95] By 24 months, up to 68% of DMPA users were amenorrheic.[71–74,94,95] Structured counselling, education, and follow-up can improve compliance and reduce patients' concerns about their menstrual changes.[96]

Recommendation

14. Counselling regarding menstrual cycle disturbances should be done before initiating a progestin-only method of contraception. (I-A)

Weight Gain

Weight gain associated with DMPA use is believed to be due to appetite stimulation and a possible mild anabolic effect.[100] Up to 40% of DMPA users will discontinue the method due to weight gain.[101–103] 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.[56] In an early study on weight gain with DMPA use, 56% of users reported an increase in weight (mean gain of 4.1 kg), whereas 44% either lost weight or maintained their baseline weight (mean loss of 1.7 kg).[72] Even though some studies found weight gain with DMPA use,[104,105] others did not.[106–110] A review of all comparative studies found limited evidence of weight gain (mean weight gain of less than 2 kg up to 12 months) but suggested a change in body composition with an increase in body fat percentage and a decrease in lean body mass.[110]

Adolescents who use DMPA appear to gain more weight than non-users and users of other methods.[104,111] There is no indication that weight at baseline influences further weight gain with DMPA use.[104,105,112,113] However, adolescents who experience more than a 5% weight gain after 6 months of DMPA use may be at risk of continued excessive weight gain.[114] A prospective, observational study found no evidence that general measures of diet were predictive of weight gain in DMPA users.[115] A slow elimination rate of DMPA may be linked to greater weight gain in adolescents.[116]

Summary Statement

20. Early weight gain with DMPA use is predictive of continued weight gain. (II-2)

Mood Effects

Although mood changes have been reported in DMPA users[117] and may lead to discontinuation of DMPA,[101] prospective studies do not demonstrate an increase in depressive symptoms in DMPA users,[118–120] even in the postpartum period.[121] A history of depressive disorders is not a contraindication to DMPA use[70]; however, some researchers suggest being cautious when using DMPA in untreated vulnerable populations.[122]

Other Side Effects

Reported side effects with use of DMPA include headache, acne, decreased libido, nausea, breast tenderness, abdominal pain or discomfort, nervousness, dizziness, and asthenia.[56] Headache is the most common non-bleeding side effect reported by DMPA users, occurring in approximately 17% of DMPA users.[71,123] A cross-sectional survey of adolescents in the United States using DMPA showed that acne and headache were reasons for discontinuation in 9% and 26%, respectively, of DMPA users.[101]

RISKS

Delayed Return of Fertility

Although DMPA is a reversible contraceptive method, there may be a delay in the resumption of ovulation.[71,124–128] In a British cohort study of 2841 women followed for 24 months after contraceptive discontinuation, the mean time to pregnancy after discontinuation of short-term ($<$ 2 years) and long-term DMPA use ($\geq$ 2 years) was 8.5 and 18.8 times longer, respectively, than after discontinuation of condom use.[126] The conception rate was 27.4% at 6 months and 51.6% at 12 months. By 24 months, the conception rate is estimated to be 90%.[71]

Summary Statement

21. DMPA use is associated with a delay in resumption of ovulation. (II-2)

Reduction in Bone Mineral Density (BMD)

Reduction of BMD and future risk of fracture have been concerns for women choosing DMPA for contraception. There is increasing evidence that DMPA use results in a transient and reversible decrease of BMD, probably because of the estrogen deficiency accompanying its use.[129–133]

Although some cross-sectional and longitudinal studies have demonstrated no adverse effect of DMPA on BMD,[134,135] the majority of studies have reported a decrease in BMD among DMPA users.[136–145] Compared with non-users, BMD at the hip and spine of DMPA users decreases by 0.5% to 3.5% after 1 year and 5.7% to 7.5% after 2 years of use.[132,139,141,143,144,146] The greatest loss occurs during the first 1 to 2 years of use, and then BMD levels appear to stabilize.[147–149] It is important to note that the BMD loss experienced by both adult and adolescent DMPA users has never been shown to be below 1 standard deviation of normal level (osteoporosis is defined as a BMD reduction of 2.5 standard deviations below normal level), even after 5 years of use.[150] This reduction also is in the same range as BMD reduction observed during pregnancy or breastfeeding (a decrease of 4% to 5%), which recovers from baseline once pregnancy is over or breastfeeding is discontinued.[150,151]

In November 2004 the U.S. Food and Drug Administration issued a "black box warning" and in June 2005 Health Canada issued an advisory[152] advising providers to only use DMPA if other methods were unsuitable or unacceptable, to limit the duration of use to the shortest time possible, and to

restrict the duration of use to a maximum of 2 years. The Food and Drug Administration also mandated a large, 7-year prospective cohort study of women aged 25 to 35 using DMPA versus non-hormonal contraception to assess its impact on BMD.[146,147] This study confirmed the reduction of BMD during DMPA use and showed that BMD returned toward or to baseline values within 2 years after DMPA discontinuation in women of all ages; BMD in past DMPA users became similar to that in non-users.[146,147] The reversible effect of DMPA on BMD was confirmed in multiple other studies in both adults and adolescents[142,143,148,153–156] and in a systematic review of the literature.[157] Despite these reassuring results and recommendations from various scientific organizations or groups,[58,150,152,158,159] the "black box warning" is still present.

Although the reversibility of DMPA's effect on BMD is reassuring, questions remain concerning the impact of DMPA use on the risk of fracture when reversibility is incomplete or when DMPA is used close to menopause. The use of BMD assessment helps to predict fracture risk in postmenopausal women,[160] but its role in premenopausal women is controversial. Two small descriptive studies in women with developmental disabilities[161] and non-Hispanic white female Army recruits[162] showed increased odds of fracture risk with DMPA use (ORs $\leq$ 2.5). Two large-scale, population-based, case-control studies in Denmark[163] and the United Kingdom[164] also showed a modest increase in the risk of fracture in DMPA users, especially in long-term users (ORs $\leq$ 1.5). A more recent, retrospective, cohort study on more than 1.7 million women-years failed to show any significant increase in fracture risk.[165] The evidence assessing the impact of DMPA use on BMD and/or fracture risk in postmenopausal women is still sparse.[147] Due to a lack of RCTs using fractures as a primary endpoint,[157,166] it is difficult to make a strong conclusion about the effect of DMPA use on the risk of fractures.

Other factors may influence BMD levels and rarely are taken into account in available studies on fracture risk and BMD reduction with DMPA use.[129–131,133,167–171] Older chronologic age, race/ethnicity (African-American), high BMI, weight gain, history of pregnancy, calcium intake, and additional estrogen therapy may be associated with increased BMD, whereas heavy caffeine intake and smoking may be associated with decreased BMD in women using DMPA.

Summary Statement

22. The use of depot medroxyprogesterone acetate (DMPA) is associated with a decrease in bone mineral density. This decrease is most rapid in the first 2 years of use and appears to be largely reversible once DMPA is discontinued. (I) There is no strong evidence that the use of DMPA causes osteoporosis (II-2) or increases the risk of fracture. (II-2)

VTE, Cardiovascular Disease, and Stroke

In a large, multinational, case-control study that WHO published in 1998, the risk for all cardiovascular disease associated with injectable progestogen-only contraceptives compared with non-users was not significantly increased (aOR 1.02; 95% CI 0.68 to 1.54).[172] In this study, the risk of VTE was not increased significantly (OR 2.9; 95% CI 0.66 to 7.26), whereas the risk of stroke among women with a history of high blood pressure using all progestogen-only methods (OR for injectable-only methods not available) was increased significantly (OR 15.7; 95% CI 5.45 to 45.0).[172] Another case-control study performed in 1 country reported that the odds of VTE was higher (OR 3.6; 95% CI 1.8 to 7.1) in DMPA users compared with non-users of hormonal contraception.[173] A subsequent meta-analysis also found an increased odds of VTE (OR 2.67; 95% CI 1.29 to 5.53) with progestin-only injectables, but only 2 studies could be used to compute this value.[174] As stated by several researchers, these results must be interpreted with caution due to the possibility of residual confounding and further studies are needed to evaluate the risk of VTE with DMPA use.[175] The 2015 WHO guidelines do not consider VTE as a contraindication to DMPA use.[70]

HIV Risk

Several recent studies have raised concerns of a possible link between DMPA use and the risk of acquiring HIV. In 2011, 2 studies reported that having high levels of progesterone, such as those seen during pregnancy[176] or with use of DMPA,[177] might raise women's risk for acquiring and transmitting HIV infection. Subsequent cohort studies and meta-analyses reported conflicting results, with some investigators noting a 1.4 to 2.2 times increased risk of HIV acquisition with the use of DMPA or non-specified injectable contraceptives, and others reporting no association.[178–182] Biological mechanisms to explain a possible association were proposed, such as decreased immune defense in the vaginal epithelium,[183,184] in the endometrium and cervix,[185] and in the cervicovaginal secretions.[186] In 2014, WHO released the following guidance:

> *Women at high risk of acquiring HIV can use the following hormonal contraceptive methods without restriction: combined oral contraceptive pills, combined injectable contraceptives, combined*

contraceptive patches and rings, progestogen-only pills, progestogen-only injectables, and levonorgestrel and etonogestrel implants. Women at high risk of HIV who are using progestogen-only injectables should be informed that available studies on the association between progestogen-only injectable contraception and HIV acquisition have important methodological limitations hindering interpretation. Some studies suggest that women using progestogen-only injectable contraception may be at increased risk of HIV acquisition; other studies have not found this association.[187]

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.[188,189]

2. All DMPA Users Will Gain Weight

Fact: Although some DMPA users may gain weight,[104,105] a significant percentage of patients will not gain weight while using DMPA.[106–110] Dietary counselling is advised.

3. DMPA Should Not Be Given to Breastfeeding Women

Fact: DMPA can be used safely by most breastfeeding women. Although there is a theoretical concern regarding neonatal exposure to DMPA and its effect on neural development during the first 6 weeks postpartum, there is no compelling evidence to support this. Studies to date have shown that DMPA has little or no effect on breast milk production or on infant development.[42,188–192] However, the fall of progesterone levels postpartum coincides with the upregulation of prolactin receptors, onset of lactose synthesis, and milk production.[193] Hence women at risk of breastfeeding difficulties (e.g., poor lactation history, perinatal complications, maternal BMI > 30 kg/m^2, and neonatal complications including preterm delivery and those in which the mother needs to pump) may be more vulnerable to the effects of progestin-only contraceptives on breast milk supply and should be counselled carefully on their contraceptive options and potential impact on breastfeeding outcomes.[194]

Summary Statement

23. The use of progestin-only preparations has not been shown to decrease breast milk production. (I) The small amounts of steroid hormones secreted in breast milk do not have an adverse effect on infant growth and development. (II-2)

4. DMPA Causes Cancer

Fact: DMPA is associated with a decreased risk of endometrial and ovarian cancer.[75,195,196] There does not appear to be an increased risk of breast cancer with DMPA use.[197–200] Recent studies regarding cervical cancer are reassuring and show that cervical cancer is associated with smoking status rather than DMPA use.[201–204]

Summary Statement

24. DMPA use is associated with a decreased risk of endometrial and ovarian cancer. (II-2)

5. DMPA Increases the Risk of Osteoporosis and Fractures

Fact: DMPA use results in a transient and reversible decrease of BMD that has not been shown to reach the level of osteoporosis.[146,147,205] There is no clear evidence that it increases the risk of fractures before or after menopause.[165]

INITIATION

Prior to initiating DMPA, a blood pressure measurement is advised. Weight and BMI measurements also may be performed to help monitor DMPA users over time but are not required. DMPA is given as a 150 mg intramuscular injection every 12 to 13 weeks. The injection may be given in the deltoid or in the ventrogluteal muscle.[206–208] DMPA may be administered at any time during the menstrual cycle, provided that pregnancy or the possibility of pregnancy can be reasonably ruled out. Waiting for the next menstrual period is not necessary.[209] Giving DMPA within the first 5 days of menses helps avoid inadvertent administration during pregnancy and prevents ovulation during the first month of use. If given within the first 5 days of the menstrual cycle, contraceptive effect is achieved within 24 hours of injection.[62,64,190]

The first DMPA injection also can be given at the time of the first consultation: the "Depo-Now" or "Quick-Start" method. In these instances, pregnancy must be ruled out and levonorgestrel emergency contraception (LNG-EC) should be administered if unprotected vaginal intercourse occurred in the last 5 days. If DMPA is given after the first 5 days of the menstrual cycle, a woman should be advised to use a back-up method of birth control for 7 days. A pregnancy test should be repeated 3 to 4 weeks after the injection to rule out a pregnancy or at least before the next injection. "Depo-Now" has been shown to reduce unintended pregnancies and to increase satisfaction when compared with using a bridging method before administering DMPA at the next menses.[209,210]

If a woman wants to switch from a combined hormonal contraceptive (CHC) (pill, patch, or ring), DMPA should be given within 5 days of stopping her CHC. If a woman wishes to have her IUC removed and switch to DMPA, she should keep the IUC for an additional 7 days after the DMPA has been given to ensure reliable contraception. When possible, it is recommended that the woman receives her first injection during the use of the previous method and that she continues to use her previous method up to 7 days after the injection.

DMPA users should be counselled regarding healthy eating and exercise. Health care providers should inform patients of the potential effects of DMPA on BMD and counsel them on "bone health," including calcium and vitamin D supplementation, smoking cessation, weight-bearing exercise, and decreased alcohol and caffeine consumption. Women should be informed that there could be a delay of up to 1 year in the return of fertility after stopping the use of injectable contraceptives.[71,124–127]

Recommendation

15. Health care providers should inform patients of the potential effects of depot medroxyprogesterone acetate on bone mineral density and counsel them on "bone health," including calcium and vitamin D supplementation, smoking cessation, weight-bearing exercise, and decreased alcohol and caffeine consumption. (III-A)

Follow-up visits should be scheduled every 12 to 13 weeks for repeat injections. In 2008, a study done in Uganda, Zimbabwe, and Thailand showed that the pregnancy risk per 100 women-years for "on time" (0.6; 95% CI 0.33 to 0.92), "2-week grace" (0.0; 95% CI 0.0 to 1.88) and "4-week grace" (0.4; 95% CI 0.01 to 2.29) injections were low and virtually identical.[211] However, more than one third of the women in this study were breastfeeding and thus possibly subfertile; these results may not be generalizable to Canadian women. Due to the possible higher fertility of most Canadian women using DMPA, it remains preferable to recommend repeat injections at intervals of less than 14 weeks.

Follow-up visits allow for an assessment of bleeding patterns and other potential side effects, an assessment of blood pressure and patient satisfaction, and an opportunity to reinforce the issue of condom use for protection against STI and HIV infection. A combination of enhanced counselling, health information, and intensive reminders may help improve patient adherence to and acceptability of the method.[96] Routine BMD testing in DMPA users is not recommended.

TROUBLESHOOTING

1. Menstrual Cycle Disturbance

The nature of irregular bleeding during DMPA use is different from that of menstruation. Under the prolonged effect of progestins, including DMPA, prominent neovascularization occurs, and newly developing blood vessels are weak and fragile.[212,213] Several strategies have been tried to alleviate this problem and have shown: (1) moderate success, such as with concomitant use of COC or estrogen treatment[48, 214]; (2) mixed results such as with NSAIDs[48]; or (3) no success, such as with doxycycline[215] or vitamins E and C.[48] Mifepristone in varying doses and tranexamic acid have been reported to significantly reduce irregular bleeding with DMPA use.[48,216] Reducing the interval between injections and increasing the DMPA dosage to alleviate bleeding have not been well studied,[217] and because these strategies may increase DMPA risk on BMD, generally they are not recommended.

If irregular bleeding persists after the first 3 to 6 months of use, other possible causes of abnormal vaginal bleeding, such as infection, pregnancy, and other pathology, should be ruled out. Once definitive causes have been ruled out, evidence-based therapeutic management options include:

- Oral conjugated equine estrogen 0.625 to 1.25 mg per day or 1 to 2 mg of 17β-estradiol per day for 28 days. Alternatively, supplemental estrogen therapy can be given transdermally in the form of a 50 μg or 100 μg 17β-estradiol patch per day for a total of 25 days. COC also may be used for 1 to 3 months.
- Administration of NSAIDs, such as oral mefenamic acid 500 mg twice daily for 5 days, ibuprofen 800 mg twice daily for 5 days, or celecoxib 200 mg per day for 5 days.
- Administration of tranexamic acid 500 mg twice daily for 5 days.

Recommendation

16. If prolonged and/or frequent bleeding occurs in users of progestin-only contraceptives, pregnancy, sexually transmitted infection, and genital pathology should be ruled out. (III-B)

2. Late Injection

If a woman presents for her DMPA injection 14 weeks or more after her last injection,[218] pregnancy must first be ruled out.

- If she has not had unprotected intercourse within the last 14 days and her urine pregnancy test is negative, she can

receive her DMPA injection. A back-up method of contraception should be used for the next 7 days.

- If she has had unprotected intercourse within the last 14 days *but not* within the last 5 days and her urine pregnancy test is negative, she can be given her DMPA injection. She must use a back-up method of contraception for the next 7 days. A pregnancy test should be done in 3 to 4 weeks.
- If she has had unprotected intercourse within the last 14 days *and* within the last 5 days and her urine pregnancy test is negative, give LNG-EC and her DMPA injection. In this situation, LNG-EC is preferred to ulipristal acetate emergency contraception (UPA-EC) because of a potential drug interaction between UPA and DMPA. She must use a back-up method of contraception for the next 7 days. A pregnancy test should be done in 3 to 4 weeks.

DMPA is not teratogenic if given inadvertently during pregnancy.[188,189]

DRUG INTERACTIONS

Few medications interact with DMPA. Ulipristal acetate should not be used with progestin-containing contraceptives because each of these drugs may decrease the effectiveness of the other.[219] There is no interaction between DMPA and antiretroviral therapy. Women using nucleoside reverse transcriptase inhibitors (NRTIs), NNRTIs, raltegravir, and protease inhibitors, including those boosted with ritonavir, can use DMPA without restriction (category 1).[70,220–222] Aminoglutethimide, used for the treatment of Cushing syndrome and certain cancers, is known to reduce serum levels of DMPA.[223,224]

3. PROGESTIN-ONLY PILL

Progestin–only pills (POPs, the "mini-pill") provide reliable, reversible contraception and have very few contraindications.[15,16,225] Several oral progestins are available in Canada; however, only 1 is approved for use as a contraceptive. The POP is supplied in packages of 28 tablets, each containing 0.35 mg of norethindrone (Micronor or Movisse), with no hormone-free interval. POPs containing dienogest (2 mg daily) are approved in Canada for the treatment of pelvic pain associated with endometriosis but not for contraception. Despite studies that have shown that ovulation is suppressed,[226] a reliable non-hormonal contraceptive method still is advised in women using dienogest 2 mg daily.[227]

EFFECTIVENESS

With perfect use, the POP has a failure rate of 0.3% in the first year of use.[2] Effectiveness depends on consistent pill taking, and hence the typical use failure rate is 9%, the same as for the COC.[2] The failure rate may be lower in motivated women.[228] POPs that may be more efficacious, such as those containing levonorgestrel or desogestrel,[229] currently are not available in Canada.

MECHANISM OF ACTION

The main mechanism of action is alteration of the cervical mucus, which becomes more viscid, less copious, and inhibits sperm penetration.[230–232] *In vitro* studies have demonstrated impaired sperm motility[233,234] and decreased tubal cilia activity,[235] both of which would delay and prevent fertilization. Negative luteinizing hormone (LH) feedback leads to suppression of ovulation in up to 50% of users.[236,237] POPs containing desogestrel may inhibit ovulation more consistently.[238] Although endometrial receptivity is altered with progestin use, it is not considered a mechanism of action because POPs prevent fertilization.

INDICATIONS

In the absence of any contraindications, the POP may be considered for any woman who requires a reliable, reversible, coitally independent method of contraception. Due to class labelling and prescribing practices, POPs tend to be used largely by parous, postpartum, and breastfeeding women[239]; however, most women can use a POP at any point during their reproductive years.[225] POPs are estrogen-free and thus are particularly useful in conditions in which estrogen is contraindicated or less appropriate, such as in recently postpartum, breastfeeding, or perimenopausal women; women with migraines with aura; smokers over age 35[15]; or in women with systemic lupus erythematosus.[240] POPs do not protect against STIs; consistent and correct use of male condoms is advised to reduce the risk of STIs and HIV.

CONTRAINDICATIONS

There are very few contraindications to the use of POPs.[15,16,225] Only 0.6% to 1.6% of women have contraindications to POPs,[225] and for this reason, there is an argument for making it available over-the-counter without a prescription.[225,241] WHO and the CDC have developed guidelines that categorize medical conditions into 1 of 4 categories based on their level of risk.[16,17,49] The following recommendations are based on the existing literature and the WHO and CDC guidelines:

Category 4 for Initiation of POPs

A condition that represents an unacceptable health risk if the contraceptive method is used

- Current breast cancer

Category 3 for Initiation of POPs

A condition for which the theoretical or proven risks usually outweigh the advantages of using the method. Women with a category 3 medical condition may benefit from expert consultation before advising against the method.

- History of breast cancer and no disease for 5 years
- Severe (decompensated) cirrhosis
- Hepatocellular adenoma
- Malignant liver tumor
- Malabsorptive bariatric surgery procedures
- Certain anticonvulsants (phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine)
- Rifampicin/rifabutin

NONCONTRACEPTIVE BENEFITS

POPs containing norethindrone are not extensively studied for noncontraceptive benefits, but oral progestins may improve menstrual blood loss, dysmenorrhea, and pelvic pain in some women.[232,242] POPs may decrease endometriosis-related pain[243,244] and premenstrual tension.[237] The POP may reduce the frequency and severity of migraine headaches,[245–247] although the evidence is based largely on desogestrel-only contraception. Women with sickle cell disease may experience fewer symptoms and less frequent and severe painful crises when using progestin-only contraceptive methods.[85] POPs also may prevent bone loss in postpartum users.[248]

POPs containing dienogest (2 mg daily) are approved in Canada for the treatment of pelvic pain associated with endometriosis but not for contraception.

SIDE EFFECTS

Menstrual Cycle Disturbances

The most common side effect among POP users is menstrual cycle disturbances, which is one of the main reasons for POP discontinuation.[228,237] Up to 44% of POP users will continue to have normal cycles[228,249] whereas 14% to 30% will have shorter cycles.[249,250] Compared with COC users, POP users will have more spotting/bleeding days but fewer spotting-only days. Many have no spotting at all.[251] Up to 20% of POP users are amenorrheic or have infrequent periods.[249,250] The relationship between type of bleeding and ovulation is unclear.[237]

Hormonal Side Effects

Hormone-related side effects such as headache, breast tenderness, nausea, and mood disturbances may occur, but their incidence is not well reported.[237] Androgenic side effects such as acne and hirsutism have been reported.[250,252] POPs do not appear to cause weight gain.[110]

RISKS

Ectopic Pregnancy

The POP decreases the overall risk of ectopic pregnancy; however, in the event of a POP failure, the proportion of pregnancies that are ectopic may be as high as 10%.[237] This possibly is due to impaired ciliary function.[235] Ectopic pregnancy must be ruled out if a pregnancy is the result of a POP failure.

Recommendation

17. Ectopic pregnancy should be ruled out if a pregnancy occurs in a woman using a progestin-only method of contraception. (III-A)

Other Risks

A meta-analysis found that POPs do not increase the risk of myocardial infarction.[253] Although persistent ovarian follicles are common among POP users, a history of ovarian cysts is not a contraindication to POP use nor is it a reason to discontinue POPs.[237]

MYTHS AND MISCONCEPTIONS

1. The POP Is Not an Effective Method of Contraception

Fact: Used consistently and correctly, the failure rate is 0.3%.[2] With typical use, the failure rate is 9%, which is similar to that of the COC pill.[254] Women must be reminded to take the POP consistently at the same time every day.

2. The POP Should Only Be Used by Breastfeeding Women

Fact: The POP is safe to use during breastfeeding and does not have an adverse effect on breastfeeding performance or infant growth or development.[42] Although commonly considered as a "breastfeeding pill," the POP may be suitable for any woman who requires a reversible method of contraception regardless of breastfeeding status.

3. Women with a History of VTE Should Avoid the POP

Fact: The POP does not increase the risk of VTE.[172,255–257] In most studies, it is not associated with changes in any of the major coagulation factors.[258] One study found that POPs containing desogestrel and LNG were associated with a potentially favourable effect on hemostasis.[259] Several population-based, cohort studies and case-control studies and 1 meta-analysis have failed to show a significant increased VTE risk with POP use.[172,175,255–257,260] Hence the POP may be a suitable contraceptive option for women who are otherwise at an increased risk of VTE.[15,260, 261]

INITIATION

The POP can be started at any time during the menstrual cycle as long as pregnancy can be reasonably excluded. It can be started immediately postpartum and post-abortion.[45] It is not necessary to wait until the next menses. If a health care provider is uncertain whether the woman may be pregnant, the POP still may be started and a follow-up pregnancy test done in 2 to 4 weeks because the benefits of starting the POP likely outweigh the risks.

A pill containing the active progestin hormone is taken every day. *There is no pill-free interval.* If the POP is started within the first 5 days from the onset of menses, no back-up contraception is required. If POPs are started more than 5 days after menses has started, abstinence or a back-up method of contraception is required for the next 48 hours (48 hours is required for POP use to achieve the contraceptive effects on cervical mucus).[237] 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.[237,262]

Among healthy women, usually there is no need to perform any examination or tests before initiating POPs. Screening for breast cancer or liver disease is not necessary due to the low prevalence of these conditions among reproductive-aged women.[45]

If a woman is switching from a different contraceptive method to the POP, she should consider continuing her current method for 48 hours after starting the POP. If a woman switches from IUC to the POP, it is advisable that she starts the POP within 5 days of her last menses preceding IUC removal. If this is not possible, then the IUC should be left in place for at least 48 hours after the POP is initiated (but preferably until the next menses).

A follow-up visit is recommended to assess satisfaction, adherence, side effects, concerns, and any changes in health status, including medications, which would change the appropriateness of POPs. Some groups may benefit from more frequent follow-up than others.

TROUBLESHOOTING

1. Unscheduled Bleeding

Irregular bleeding is a common side effect of POPs, and women should be reassured that it does not mean the POP is not effective as long as it has been taken consistently. Pregnancy, infection, and genital pathology should be ruled out. Once this has been done, there is limited evidence supporting effective treatment options. Extrapolating from the management of unscheduled bleeding for other progestin-only contraceptives, possible options for treatment include exogenous estrogen (conjugated equine estrogen or 17β-estradiol), NSAIDs, and tranexamic acid.[48]

2. Missed Pill

If a POP is missed by more than 3 hours, further management depends on whether the woman has had UPI in the past 5 days. If she has not, she should take 1 pill as soon as possible and then continue taking 1 pill daily at the same time each day. Back-up contraception should be used for 48 hours. If UPI has occurred, emergency contraception (EC) is recommended.[218] In the case of LNG-EC, she should start the POP the next day and use back-up contraception for another 48 hours. In the case of UPA-EC, she should restart the POP 5 days after taking EC and use back-up contraception for another 14 days. Women who frequently miss POPs may be more suitable for less adherence-demanding contraceptive methods.

3. Vomiting or Severe Diarrhea in POP Users

Vomiting or diarrhea theoretically might decrease POP effectiveness, but there is limited evidence to address this. POP users should take another pill as soon as possible if vomiting occurs within 3 hours of ingestion and continue taking pills daily at the same time each day. Back-up contraception or abstinence should be used until 48 hours after the vomiting and diarrhea have stopped. If UPI occurred, consider EC.

DRUG INTERACTIONS

Drug interactions with POPs are less well known than are those for COC. Progestins are metabolized through the cytochrome P450 pathway, and drugs that induce this pathway may lead to increased drug clearance and reduce contraceptive effectiveness. POP effectiveness may be reduced by concurrent use of certain anticonvulsants

(barbiturates, carbamazepine, oxcarbazepine, phenytoin, primidone, topiramate), protease inhibitors (darunavir/ritonavir, fosamprenavir/ritonavir, lopinavir/ritonavir, nelfinavir), bosentan, St. John's wort, rifampin/rifabutin antibiotics, and selective progesterone receptor modulators.[15,49,263,264] Interestingly, studies of women using protease inhibitors and a POP in fact demonstrated reduced norethindrone clearance, increased area under the curve (AUC),[265] and no changes in cervical mucus scores compared with controls.[266]

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