

Injectable Medroxyprogesterone Acetate for Contraception

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Depot medroxyprogesterone acetate (DMPA), available as Depo-Provera[®], has entered into wide use in Canada. A review of the medical literature reveals a paucity of evidence to guide our clinical decisions. The following committee opinion summarizes the available evidence.

MENSTRUAL IRREGULARITY

Menstrual changes occur in all women who use DMPA. Amenorrhea has been reported in up to 30 percent of women after six months of use and rates increase to more than 50 percent after one year and 68 percent after two years of use.^{1,2} In a study of adolescents,³ nearly two-thirds were amenorrheic after six months.

Irregular or frequent bleeding and spotting are more common than prolonged episodes of bleeding during the first 90 days of use (25% versus 1.5%), and decreasing to less than 15 percent after one year of use.^{1,2} Rarely, heavy bleeding may occur.^{1,2} One researcher⁴ investigated menstrual irregularity in women using DMPA by performing endometrial biopsies at three, six, nine, and 12 months of use, and found remnants of proliferative endometri-

um were associated with the irregular menstrual bleeding.

Because menstrual irregularity is an important reason for the discontinuation of DMPA as a contraceptive,³ preinjection counselling is required regarding management of irregular bleeding, and further counselling is essential when abnormal bleeding occurs.

Before any therapy to resolve bleeding or spotting is initiated, other reasons for abnormal vaginal bleeding must be ruled out. Careful medical history is required and sexually transmitted disease (STD) screening should be considered. Fibroids, polyps, and malignancy should be excluded. Thorough investigations are warranted when menstrual irregularity is persistent or appears after several months of amenorrhea. Several therapies have been advocated to control irregular bleeding in the absence of other pathology (see Table I), but none have consistently demonstrated superiority.^{5,6}

The patient who has bleeding only towards the end of the three months will likely benefit from decreasing the interval between injections. Otherwise, all of these options may be of benefit.

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TABLE 1

CLINICAL TIPS TO CONTROL BLEEDING

Bleeding within the first six (6) months: patience and reassurance
 If persistent bleeding after 6 months choose one of the following options:

- NSAID: Ibuprofen 400-800 mg BID for 10 days, repeat if necessary
- Increase dosage of DMPA to 225-300 mg for 2-3 serial injections every three months, then decrease dosage
- Decrease interval between injections to 8-10 weeks
- Oral estrogen equivalent to conjugated estrogens 0.625-1.25 mg daily for 25 days, repeating one to three times if necessary
- Estrogen patches equivalent to 17 β -estradiol 50-100 mg, 25 days, repeating one to three times if necessary

LONG-TERM RISKS ON BONE DENSITY

In 1991, Cundy *et al.*⁷ published a report examining bone mineral density (BMD) in 30 women who were currently using DMPA for a minimum of five years. Finding the BMD to be significantly lower than in matched pre-menopausal controls (though higher than in post-menopausal controls), the group hypothesized that the cause was related to estrogen deficiency induced by DMPA. The study, although frequently quoted, is criticized for its small numbers of subjects and failure to control confounding factors.

In 1993, the same group suggested⁸ bone loss was reversible in two years or more after stopping DMPA, although the recovery in BMD in the femoral neck was less striking than that in the lumbar spine. Once again restoration of relative estrogen deficiency was hypothesized.

In 1998, Cundy reported another cross-sectional study⁹ in which BMD was measured in 200 current users of DMPA (2-26 years of use) compared against 350 control subjects. DMPA was found to be associated with a significant reduction in bone density. Women who had used DMPA for more years and those who had started DMPA before peak bone mass was attained were at higher risk. Questions were raised again concerning control of confounding factors and selection of controls.

Four cross-sectional studies reported a significant decrease in BMD among DMPA users.¹⁰⁻¹³ Four others¹⁴⁻¹⁷ failed to demonstrate any change in BMD compared to women using other contraceptive methods (such as intrauterine device). These studies report conflicting evidence regarding association with age, length of amenorrhea, and duration of use. Three prospective controlled studies¹⁸⁻²⁰ done in adult and adolescent populations measured bone mineral density prior to and after DMPA use. These three studies were characterized by very small sample sizes. They showed that BMD either remained

stable or decreased in DMPA users, while it increased significantly in Norplant users, OC users, and non-hormonal users.

Considering the scientific weakness of these studies (small samples, weak designs, lack of control for confounding factors, selection bias), it is clear that prospective randomized controlled trials are needed to ascertain the effect of long term use of DMPA on BMD. Two such trials are currently underway in the United States. There is currently no scientific evidence that would support routine measurement of bone mineral density or use of estrogen and add-back therapy.²¹

Despite the lack of conclusive evidence, we must caution the individual patient that might suffer osteoporosis. Counseling and investigation should be performed on an individual basis and directed toward women presenting with more than two risk factors, such as eating disorders, smoking, small stature, past long lactation periods, use of steroids, family history of osteoporosis, high alcohol and caffeine intake, and low physical activity level.

WEIGHT GAIN

Women tend to associate weight gain with their hormonal contraceptive method.²² While few case-control studies conducted in developed countries have evaluated weight changes associated with the use of DMPA, a preliminary study²³ has not confirmed reports that DMPA causes weight gain.

Yet concern about weight gain, whether real or perceived, is important to most women in their selection and continuation of a particular contraceptive method.²² In adolescence, fear of gaining weight while using DMPA is a barrier to continuance: up to 50 percent discontinue this method because of weight gain or increased appetite.²⁴ Harel *et al.*²⁴ described an increase in body mass index in DMPA users of 0.40 kg/m at three months, and an even greater increase in body mass index of 0.99 kg/m if the second injection is given earlier; but adolescents who were on oral contraceptives before the initiation of DMPA had increases in body mass index similar to the standard DMPA dosing group.

It is felt that it is not the method necessarily that leads to weight gain, but rather an increased intake of food secondary to

TABLE II

HELPING PATIENTS MANAGE WEIGHT GAIN WITH DMPA

- Advise patient that a weight gain of as much as four to five pounds per year is not uncommon with DMPA
- Inform patient that a healthy balanced diet may help prevent weight gain
- Refer to a dietitian if appropriate
- Encourage patient to participate in a consistent exercise regimen

appetite stimulation.²⁵ While it is conceivable that the hormonal compounds used in hormonal contraception could be metabolized to an androgen and therefore be anabolic, there is no existing evidence that this indeed is the case. Lifestyle reasons are often contributory or causative. Many younger women continue to gain weight and have not really reached their peak body mass.

DEPRESSION AND FATIGUE

These side effects seem to occur relatively infrequently, but are very difficult to study in women using hormonal contraception. Subjective reporting of these symptoms can be markedly increased just by the form (direct or indirect) and frequency of questioning.²⁶ Depression and fatigue may be markedly affected by confounding life situations that result in the use of contraceptives, rather than by the contraceptive itself. Many other variables should also be considered, including gravidity, parity, postpartum status, recent onset of sexual activity, and other inter- and intrapersonal issues. Cromer *et al.*²⁷ reported a 35 percent prevalence of depression and fatigue prior to initiating hormonal contraceptives in adolescents: both symptoms increased in DMPA and oral contraceptive users. Disadvantages of using a long acting hormonal contraceptive are the inability to quickly withdraw this medication and the perception that these symptoms will be long lasting.

TABLE III
HELPING PATIENTS MANAGE DEPRESSION AND FATIGUE
<ul style="list-style-type: none"> • Baseline assessment prior to initiating hormonal contraception • Examine other issues that may have an effect • Ongoing counselling and support

DECREASED LIBIDO

Libido is influenced by numerous factors, including the couple's relationship. Women who ovulate regularly often have cyclic changes in libido and sexual response. Decreased libido has been associated with the use of several types of contraception. DMPA can reduce ovarian production of estrogen and testosterone, and combined oral contraceptive pills increase sex hormone binding globulin, which leads to a decrease in circulating free estrogens and androgens.

It is most important, however, to perform a baseline assess-

TABLE IV
HELPING PATIENTS MANAGE DECREASED LIBIDO
<ul style="list-style-type: none"> • Baseline sexual history • Prepare patient for unpredictable bleeding and/or amenorrhea • Frequent follow-up and counselling

ment and obtain a concise sexual history during initial patient counselling. Some women may admit sexual dysfunction as well as a decrease in libido. Directed questions may set the tone for further counselling if necessary. It is important to stress that the use of DMPA may not improve the woman's sexual satisfaction other than to provide secure contraception. Amenorrhea and unpredictable bleeding while on DMPA may affect sexual response adversely.

HEADACHES

Headache has been reported to occur in 15 to 25 percent of DMPA users. Although there are no good prospective comparative studies of various contraceptive preparations, the overall incidence of headache in oral contraceptive clinical trials is approximately 15 percent. DMPA has not been found to have a significant increase in the occurrence of headache.¹⁸ DMPA is not contraindicated in migraine sufferers.¹⁸

DELAY IN RETURN OF FERTILITY

A delay in return of fertility occurs with DMPA as compared to the users of other methods. DMPA users have been found to have about a nine month delay to restoration of full fertility after the last injection.²⁸ DMPA does not cause infertility. DMPA should not be used in those women who desire pregnancy within the next year or two. In most adolescents this may not be a concern, but assumptions should be avoided. Counselling should address this issue.

TABLE V
HELPING PATIENTS MANAGE DELAY IN RETURN OF FERTILITY
<ul style="list-style-type: none"> • Explain the significance of a nine month delay to restore full fertility after the last DMPA injection • Avoid using DMPA in those women who want to become pregnant in the next year or two unless they clearly understand the significance of this delay • Advise discontinuing DMPA six to nine months prior to attempting conception

DMPA USE IN BREAST FEEDING

DMPA may be used while breast-feeding. When initiated three days postpartum or at six weeks postpartum, DMPA has not been shown to decrease duration of lactation or infant weight gain.^{29,30}

The question of possible consequences of the transfer of steroid to the breast-fed infant has yet to be resolved.³¹ The amount of steroid transmitted in the milk and absorbed by the infant is known to be small, but all studies to date have reported reassuring results.^{32,33} There is no data to suggest that there

is an increased risk of thromboembolic disease if DMPA is used immediately postpartum in lactating women with respect to infant and maternal outcomes.

PROTECTION AGAINST STD

DMPA is not known to provide protection against sexually transmitted diseases (STD), although it may help prevent pelvic inflammatory disease³⁴ by thickening cervical mucus and preventing the penetration of STD organisms and spermatozoa into the upper reproductive tract.

Adolescents particularly are at increased risk of STD (including HIV) because of their tendency to have multiple partners (serial monogamy) and their failure to practice safer sex consistently.^{35,36} Similarly, older women in unstable relationships are also at risk. Questions about condom use and safer sexual practices must be a part of routine sexual history taken prior to the use of any contraceptive, and reinforced at follow-up visits.

TABLE VI

HELPING PATIENTS PROTECT AGAINST STD WITH DMPA

- Baseline sexual history
- Inform patients that DMPA does not protect against STDs and HIV
- Promote safer sexual practices and legitimize noncoital pleasuring

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