SOGC
POLICY STATEMENT

This has been developed by the Reproductive Endocrinology & Infertility Committee, and approved by the council of the Society of Obstetricians and Gynaecologists of Canada.

DEPO-PROVERA IN CONTRACEPTION

Of the available methods for reversible contraception, long-acting injections of progestins provide women with the most effective protection against pregnancy. This has been recognised for some time, but the Health Protection Branch in Canada has not approved the use of the only example of a long-acting progestin injection, depot medroxyprogesterone acetate (DMPA, Depo-Provera), as a contraceptive. For many years, the Food and Drug Administration (FDA) in the United States refused to approve the use of DMPA for use as a contraceptive, ostensibly because of an increase in the incidence of breast tumours in female beagles given very large doses of DMPA during trials in the late 1970’s. The unsuitability of female dogs as test agents for progestins is now recognised, in that all progestins appear to cause breast tumours in these animals. Continuing epidemiological reassurance has resulted in the FDA granting approval for the use of DMPA as a contraceptive in the United States in October 1992.

The use of injectable contraceptives has been controversial for the past two decades, largely because of the lobbying of drug regulatory bodies in industrialised countries (but especially in North America) by political critics. Such critics charged that the use of injectable progestins for contraception, in addition to being unsafe, provided an opportunity for the imposition of fertility control on poorly counselled women, especially in developing countries. The latter charge remains unfounded, but the former - that of safety - has been resoundingly answered by three decades of epidemiological data which provide reassurance that there are no significant long-term risks and several potential health benefits from the use of DMPA.

There are currently approximately nine million women using DMPA for contraception throughout the world, and the drug is approved for contraceptive use in more than 60 countries, but not in Canada. It is the position of the Society of Obstetricians and Gynaecologists of Canada that DMPA should be approved for use as a contraceptive, given that for some women the use of injectable progestin is an appropriate first choice for contraception.
MODE OF ACTION

Long-acting progestins such as DMPA produce contraception primarily by inhibition of ovulation (1). The preparation Depo-Provera 150 contains 150mg of medroxyprogesterone acetate (MPA) in a slow-release vehicle, and is given by deep intramuscular injection at three-month intervals. Peak plasma concentrations of MPA are reached within two weeks of injection, and decrease gradually to undetectable levels by 120 to 200 days after injection (2). Ovulation is reliably inhibited for three months after injection. Additional contraceptive effects include the maintenance of an atrophic endometrium and cervical mucus which does not facilitate sperm transport.

INDICATIONS

Long-action injections of progestins provide the most reliable reversible contraception of all available methods (1,3). If prevention of pregnancy is of paramount importance, especially where pregnancy would result in major maternal or fetal risk, the use of DMPA may be an optimal choice for reversible contraception.

Other situations where the use of DMPA would be appropriate if contraception were desired include:

- intolerance of or contraindication to estrogen
- postpartum and lactating mothers
- smokers, especially over age 35
- women taking medication which would interfere with the effectiveness of oral contraceptives, e.g. phenytoin
- women in whom amenorrhea provides additional advantages, e.g. significant dysmenorrhea, menorrhagia, endometriosis
- repeated failure of other contraceptive methods

CONTRAINDICATIONS

The contraindications to use of DMPA listed in the US package insert for Depo-Provera Contraceptive injection (the information approved by the FDA) are the following:

1. Known or suspected pregnancy or as a diagnostic test for pregnancy
2. Undiagnosed vaginal bleeding
3. Known or suspected malignancy of the breast
4. Active thrombophlebitis, or current or past history of thromboembolic disorders, or cerebral vascular disease
5. Liver dysfunction or disease
6. Known sensitivity to MPA or any of the other components of the injection

These contraindications are broadly similar to the contraindications to use of MPA and DMPA that are listed in the Canadian Compendium of Pharmaceuticals and Specialties (CPS), which is the most commonly-used prescribing reference guide for Canadian physicians. It should be noted, however, that the only current indications for use of DMPA in Canada are in the
treatment of endometriosis and as palliative or adjunctive treatment in some cases of endometrial, renal cell and breast carcinoma. Use of DMPA for contraception should be considered separately.

The reference in the CPS (and in the US package insert) to thrombovascular disorders as a contraindication to the use of DMPA is retained because of the risk of these disorders in users of oral contraceptives. Although it is not unequivocally proven, it is generally accepted that the thrombovascular risk of oral contraceptives relates to the effect of the estrogen component on coagulation factors, and is unrelated to the progestin component. There is no evidence to support an increased risk of thrombosis in users of MPA, and a history of thrombophlebitis or thromboembolic disorder is not now considered a contraindication to the use of DMPA.

ADVERSE EFFECTS

Menstrual changes

Disturbance of the menstrual cycle is the major side-effect of DMPA use, and it is almost universal in users (4). In general, the bleeding pattern is quite unpredictable, although with prolonged use, amenorrhea becomes more common and both the length and frequency of episodes of bleeding is reduced. Approximately 50 percent of women using DMPA for one year will be amenorrheic (2). From the patient’s perspective, amenorrhea is probably the most tolerable of the observed menstrual disturbances, although any of the cycle disturbances may cause discontent. Women who are contemplating the use of DMPA and who are uncomfortable with menstrual disturbances should probably be counselled to consider another form of contraception.

The development of amenorrhea requires no further intervention, but the development of irregular bleeding may require further management if it is persistent or excessive. It should be emphasised that heavy bleeding is rare. Obvious causes of irregular vaginal bleeding other than the use of DMPA (such as cervicitis or cervical polyps) should be considered and excluded before considering further management.

The management of irregular bleeding in women on DMPA is largely unsatisfactory. In women in whom there is no contraindication, the administration of cyclical estrogen (e.g. conjugated estrogens 1.25 to 2.5mg or ethynil estradiol 50ug daily for 10 to 14 days per month) may be successful in eliminating bleeding, but there is frequent recurrence of abnormal bleeding after therapy. Another management option which has been used is to shorten the interval between injections of DMPA to eight to ten weeks. Curettage is rarely indicated or successful. It must be emphasised that there are no results from properly conducted studies to indicate benefit from any of these options. Persistence of significant menstrual disturbances requires, at the very least, continuing reassurance of the woman; if she remains dissatisfied with the menstrual pattern, it is appropriate to discuss the discontinuation of DMPA use and the substitution of another contraceptive method.

Weight gain

An increase of up to three Kg in weight is common with long-term use of DMPA. Weight gain appears to be less in obese women, and 20 to 40 percent of women on DMPA actually lose weight (5). If weight gain occurs, it is unlikely in most cases to lead to discontinuation of therapy.
Mood change

As in users of oral contraceptives, women on DMPA therapy have reported varying degrees of mood change. The mechanism for such mood change is unknown, although progestin-induced changes in serotonin metabolism have been proposed as a contributing factor (6). The most commonly reported mood change is depression. Because of the subjective nature of such a complaint, it is important to evaluate mood change carefully before ascribing cause and effect.

Other subjective side effects

Headache is reported relatively commonly in users of DMPA, although it is usually mild and responds to simple analgesics. Frequencies reported range from five to 15 percent of users. A similar proportion of women may complain of abdominal bloating and sometimes breast discomfort (3). Numerous other side effects have been reported, including lethargy, dizziness, loss of libido, acne, backache, diarrhea and galactorrhea, but with varying frequency. It is doubtful whether any of them can be plausibly related to the use of DMPA.

Changes in bone density

A study of 30 women on DMPA therapy for a minimum of five years suggested that the use of DMPA was associated with a reduction in bone density compared with age-matched controls (7). The mean reduction in bone density was four percent and was reversed when DMPA was discontinued. Other risk-factors for bone loss, including smoking, exercise and family history, were not accounted for in this small series, but it does indicate a need for further examination of this association. The reduction in bone density in DMPA users may be due to suppression of estrogen activity.

Delayed return of fertility

After the discontinuation of DMPA therapy, there is variability in the return of ovulation, apparently as a result of the variable persistence of MPA in the circulation. It is important to emphasise that there is no permanent effect on fertility with the use of DMPA. A single dose of 150mg DMPA delays ovulation for a mean 4.5 months, and six months after the last injection approximately 50 percent of former users will have re-established regular menstruation. Of those women who discontinue DMPA in order to conceive, nearly 70 percent will have done so by 12 months after discontinuation and more than 90 percent after 24 months (8). Cumulative conception rates are approximately the same as those following barrier method, IUD or oral contraceptive use after 24 months.

If desired, it is possible to induce ovulation in women with delayed return of ovulation by use of exogenous gonadotropins or GnRH. However, this is generally not deemed advisable in view of the persistence of MPA in the circulation, even though there is no evidence of teratogenicity with use of DMPA (8,15).

Metabolic effects

Liver function is largely unaffected by the administration of DMPA. Reports have not conclusively shown any effect on lipid metabolism, although there may be a minor decrease in
concentration of HDL cholesterol (9). The significance of this remains uncertain.

Glucose tolerance may be affected by DMPA, with an exaggerated insulin response to the oral or intravenous glucose tolerance test. This appears to be due to a rise in both biologically active insulin and pro-insulin (3). It may be sufficient to worsen impaired glucose tolerance in established diabetes or to precipitate clinical diabetes in women with chemical diabetes. The decision to use DMPA in such circumstances should be made after careful consideration.

THEORETICAL CONCERNS

Possible carcinogenicity

Breast cancer

Animal models have not provided consistently useful data regarding the risk of breast cancer with use of DMPA. The studies which used beagles as a model were felt to be misleading, since it was belatedly recognised that large doses of all progestins, including progesterone, cause breast tumours in female dogs.

The WHO Collaborative Study of Neoplasia and Steroid Contraceptives was established in 1979 and conducted studies of the risk associated with DMPA use in women in Kenya, Mexico and Thailand. The study involved 869 cases of breast cancer with 11,890 controls (10). The overall relative risk for ever-users of DMPA was 1.21, which was not statistically significant (95% confidence interval 0.96-1.52). Women who were under 35 and whose first exposure to DMPA was within the previous four years had an increased relative risk of 2.19 (95% confidence interval 1.23-3.89). This was the highest relative risk calculated in the study. However, the risk did not increase with increasing duration of use and was not seen in women who had first started to use DMPA more than five years previously. These findings suggested that a subpopulation of women may have an increased risk of developing breast cancer subsequent to the use of DMPA. Women who appear to have recognised risk factors for the development of breast cancer and who contemplate use of DMPA should be counselled appropriately.

High doses of DMPA are used in the treatment of hormonally-dependent breast cancer, but the effects of DMPA at contraceptive doses in women with previously treated or suspected hormonally-dependent breast cancer are not known.

Endometrial cancer

Studies in monkeys using standard human doses of DMPA and 10 times standard doses have not shown any evidence of endometrial cancer, but two cases of possible endometrial cancer were found in monkeys given 50 times the human dose (3). The WHO has concluded that the monkey is not a suitable model for DMPA research.

Human studies have not shown any increased risk of endometrial cancer in users of DMPA. The WHO Collaborative Study in fact showed a significantly reduced relative risk of endometrial cancer of 0.21 (95% confidence interval 0.06-0.79), supporting the accepted assumption that progestins are protective against endometrial cancer (11).
Cervical cancer

There is no evidence from human studies to suggest either an increased or a decreased risk of cancer of the cervix in users of DMPA. The overall relative risk calculated in the WHO Collaborative Study was 1.11 (95% confidence interval 0.96-1.29), and there was no increase in the risk with increased duration of use (12). As with the use of oral contraceptives, the regular performance of Pap smears is mandatory for women using DMPA.

Other forms of cancer

No increased risk of developing ovarian or liver tumours has been identified in users of DMPA. The relative risk for epithelial ovarian cancer in the WHO Collaborative Study was 1.07 (95% confidence interval 0.6-1.8) (13).

DEVELOPMENTAL EXPOSURE

In utero

In general, exposure of a developing fetus to the effects of DMPA administered to the mother will be unlikely because of the high contraceptive efficacy of the injection. However, exposure in utero is possible if DMPA is given inadvertently to a woman whose pregnancy is unrecognised. For this reason, it is advisable that the first injection of DMPA is given during menses. The current data do not indicate any significant teratogenic effect of DMPA in humans, although animal data suggest a potential for masculinization of female fetuses (3).

Lactation

DMPA administered to lactating mothers results in the secretion of small amounts of MPA in milk. There appear to be no effects of this on the developing infant, and follow-up of infants exposed to MPA in breast milk show normal physical and mental development (14). Such infants have now been followed for a median 14 to 16 years.

ADMINISTRATION

DMPA may be the best contraceptive choice for women who have received appropriate counselling about potential risks and benefits. As with the use of oral contraceptives, a full physical assessment must be made before DMPA administration begins, and annual assessments of blood pressure, breasts, abdomen, pelvic organs, cervical cytology, and general wellbeing should follow. The standard dose for contraception is 150mg every 90 days, given as a deep intramuscular injection. As described, it is best if the first injection is given during menses, to avoid inadvertent administration during early pregnancy. It should not be given earlier than six weeks post partum, but may be given immediately post abortion.
REFERENCES

2. Depo-Provera Contraceptive Injection US Package Insert (FDA-approved)


Reprints and copies can be ordered by writing to Dr. André Lalonde, SOGC's Executive Vice President, at the following address: 1785 Alta Vista Drive, Suite 102, Ottawa, Ontario, K1G 3Y6.