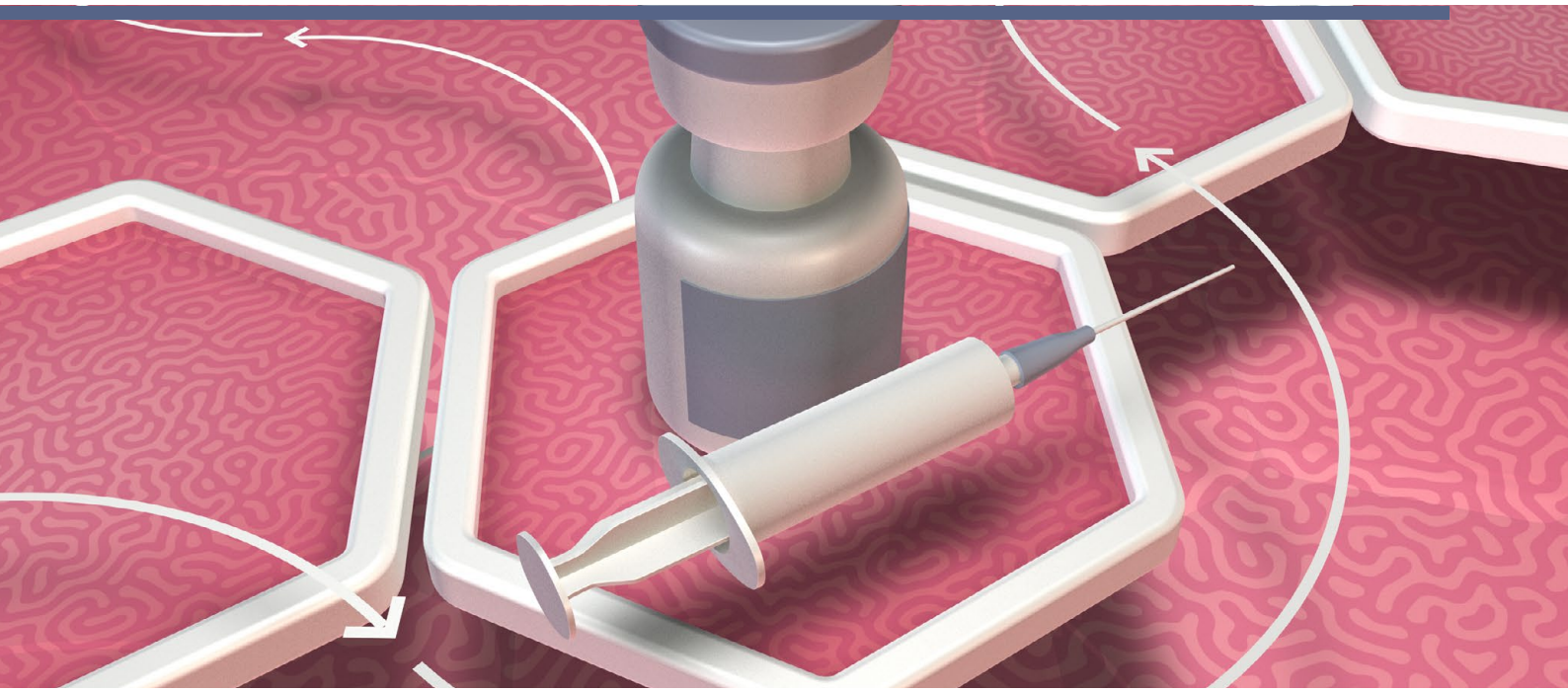

Depot medroxyprogesterone acetate (DMPA) injections: an intermediate option

Depot medroxyprogesterone acetate injections are a form of hormonal contraception administered every 13 weeks for optimal effect. This is an evidence-based change from the previously recommended 12-week dosing interval. Despite being associated with variable changes in bleeding patterns and a delayed return to fertility when stopped, it is a preferred method of contraception for many people as it does not rely on daily adherence or require an insertion procedure.

KEY PRACTICE POINTS:

- DMPA injections are a highly effective form of contraception; the estimated rate of pregnancy during the first year of use is 0.2% with recommended use
- DMPA injections are a suitable option in many cases when oestrogen-containing contraceptives are contraindicated
- The decision to initiate use should involve a comprehensive discussion regarding the potential risks and adverse effects; in particular, the patient should be aware that irregular bleeding patterns are common during the first year of use and that return to fertility can be delayed after stopping injections
- New Zealand guidelines recommend a dosing interval of 13 weeks; this is an evidence-based change from the previously recommended 12-week dosing interval
- Approximately half of those receiving DMPA injections report amenorrhoea after 12 months of use, which may be beneficial in those who have experienced menorrhagia or dysmenorrhoea during their menstrual cycle
- Although evidence of adverse clinical outcomes is lacking, DMPA injections are associated with a reduction in bone mineral density, therefore alternative methods of contraception should be considered first in those aged under 18 years or of any age with risk factors for osteoporosis
- The risks and benefits should be re-evaluated at least once every two years in every person using this form o

This is a revision of a previously published article. What's new for this update:

- Includes recommendations from New Zealand Aotearoa's guidance on contraception, Ministry of Health (Dec, 2020), available from: **https://www.health.govt.nz/system/files/documents/publications/final_aotearoa_contraception_guidance.pdf**
- The recommended dosing interval for DMPA is now 13 weeks. This is an evidence-based recommendation from the New Zealand contraception guidance. Injections can be administered up to seven days late (i.e. a dosing interval of 14 weeks) without need for additional contraception.

Depot medroxyprogesterone acetate (DMPA) injections are an effective form of hormonal contraception

DMPA (Depo-Provera) is a fully funded form of progestogen-only contraception administered via intramuscular injection.[1] Its primary effect is to reduce the chance of ovulation by limiting follicle stimulating hormone and luteinizing hormone secretion.[1] In addition, DMPA injections can alter cervical mucus to prevent sperm penetration, as well as thin the endometrial lining to make it unsuitable for implantation.[1]

DMPA injections may be preferred by people who:[2, 3]

- Have difficulty adhering to daily oral contraceptive regimens, e.g. working irregular shifts, forgetful with daily medicine use
- Prefer a contraceptive with prolonged action but have concerns over the more invasive insertion procedures associated with levonorgestrel implants and intrauterine contraceptives
- Have a contraindication or caution for oestrogen use, e.g. migraine with aura

DMPA injections may also be a useful treatment for heavy menstrual bleeding or dysmenorrhoea, although its effects on bleeding are unpredictable (see: "Altered bleeding patterns are common").[1]

Highly effective contraception when administered on time

When administered at the recommended interval, DMPA has a failure rate of approximately 0.2% in the first year of use, i.e. two pregnancies per 1,000 people treated.[1] New Zealand guidelines recommend a dosing interval of 13 weeks (outside of the product's approved use).[1] This is a change in practice from the previously recommended interval of 12 weeks, and is based on evidence of effectiveness at preventing pregnancy up to 15 weeks following treatment.[1]

With typical use of DMPA, which includes inconsistent, late or incorrect use, the failure rate has been estimated at 6%, which is higher than for long-acting reversible contraceptives (LARCs), e.g. levonorgestrel implants.[1] For this reason, along with the fact that effectiveness is user-dependent (i.e. reliant on adherence to the recommended injection interval), organisations including the Royal Australian and New Zealand College of Obstetricians and Gynaecologists, no longer consider DMPA injections to be a form of LARC.[4]

Injections are generally well-tolerated

DMPA injections are usually well-tolerated, but adverse effects can include acne, nausea, headaches and hot flushes, the occurrence of which will typically decrease over time.[5] Menstrual irregularities and weight gain can also occur, which may be unacceptable for some people (see: "Balancing the benefits and risks of DMPA injections").[1]

Symptoms to monitor. Patients should be advised to report any new-onset chest pain, deep unilateral leg pain or shortness of breath, and investigated for the possibility of a thromboembolic event (see: "Cardiovascular risk factors may be a reason not to use DMPA injections").[5] Mood changes are also sometimes reported.[2] It is recommended that patients with a history of clinical depression are closely monitored during treatment, and the injections stopped if a significant relapse occurs.[5] There is a very small risk of anaphylaxis following DMPA administration.[1, 2]

Suitable if given concurrently with hepatic enzyme-inducing medicines. A notable advantage of DMPA over other forms of hormonal contraception is that its effectiveness is not influenced by the use of hepatic enzyme-inducing medicines, e.g. antiepileptic medicines, so they can be used at the same time.[1]

When should DMPA injections be avoided?

DMPA injections are contraindicated* in people with:[3, 6, 7]

- Current breast cancer; use of hormonal contraceptives in people with a history of breast cancer is generally not recommended unless other methods are not available or acceptable, as the theoretical or proven risks usually outweigh the benefits. Any consideration should ideally be discussed with an oncologist.
- Undiagnosed vaginal bleeding
- Thrombophlebitis or thromboembolic disorders, or in those with a history of these conditions
- Poorly controlled hypertension; systolic blood pressure ≥ 160 mmHg or diastolic ≥ 100 mmHg
- Severe hepatic dysfunction, e.g. people with decompensated cirrhosis or malignant hepatic tumours

DMPA injections should be used with caution* in people with:[6, 7]

- History of ischaemic heart disease, stroke or transient ischaemic attack
- Multiple cardiovascular risk factors, e.g. increasing age, hypertension, obesity, dyslipidaemia, diabetes, smoking
- Increased risk of bone mineral density loss (see: "Be aware of potential changes in bone mineral density")

* For a full list of contraindications and cautions, refer to the New Zealand Formulary: **nzf.org.nz/nzf_10051** and the United Kingdom Medical Eligibility Criteria: **www.fsrh.org/standards-and-guidance/uk-medical-eligibility-criteria-for-contraceptive-use-ukmec/**

Administering DMPA injections

- The upper outer quadrant of the buttock (i.e. dorsogluteal site) is the preferred IM injection site; the ventrogluteal site is an alternative, to reduce sciatic nerve injury. If excessive adipose tissue is present the deltoid muscle site is another alternative that can be used.[1, 2]
- The first injection should be given within the first five days of starting of a menstrual cycle or within the first five days post-partum; however, the risk of heavy or prolonged bleeding is increased when injections are administered shortly after giving birth.[2, 5]
  - If breastfeeding, it is generally recommended to delay the first injection until six weeks post-partum (see: "DMPA injections can be used while breastfeeding")[1, 2, 6]
- No additional contraception is needed when injections are started within the first five days of the menstrual cycle; if initiated later in the menstrual cycle, additional contraception should be used for seven days following the first injection with a follow-up pregnancy test recommended four weeks later[2]
- Although repeat injections should be given every 13 weeks, they can be administered between 10 and 14 weeks if necessary (Table 1)[1]

Table 1: Guidance for repeat DMPA injections administered outside the recommended 13 week interval.[1]

Time since last injection	Recommendation
10 – 13 weeks	Consider administering injection early if bleeding occurs; exclude other causes if bleeding is very heavy
13 – 14 weeks	Administer injection; no additional contraception is required
>14 weeks	Perform a pregnancy test and offer emergency contraception; administer injection if pregnancy is excluded and recommend additional contraception for seven days

For further information on performing intramuscular injections, see: **www.bpac.org.nz/BPJ/2015/December/correspondence.aspx#3**

Balancing the benefits and risks of DMPA injections

Before beginning treatment, it is important to discuss the potential benefits and risks of DMPA injections and to emphasise that its effectiveness is dependent on adherence.

Altered bleeding patterns are common

DMPA injections are likely to cause changes in bleeding pattern such as amenorrhoea, irregular bleeding or spotting, or prolonged bleeding.[1] As the duration of use increases, amenorrhoea becomes more likely (Table 2).[3] Altered bleeding patterns are the most frequent reason for stopping DMPA use in the first year; if information is provided about this and people are reassured that irregular bleeding patterns are normal, and are likely to settle, it may help with longer term adherence. If bleeding is persistent or problematic, after excluding other causes (e.g. cervical pathology), it can be managed using pharmacological intervention (see: "Managing persistent or problematic bleeding").[1] In patients with heavy menstrual bleeding that persists despite pharmacological intervention, an alternative method of contraception may be more suitable, e.g. a levonorgestrel intrauterine system.

Changes in bleeding may be beneficial for some, but are unpredictable

In some people, reduced bleeding or amenorrhoea may be desirable, such as those with menorrhagia or dysmenorrhoea, or those who experience anaemia as a result of heavy bleeding.[1, 3] However, as the bleeding patterns associated with DMPA are unpredictable, this may be an unreliable management strategy. In people with endometriosis, DMPA injections (using a different dosing regimen*) can be useful for reducing bleeding symptoms and pelvic pain.[8]

* The recommended dose for endometriosis is 50 mg weekly or 100 mg every two weeks for at least six months. New Zealand guidance recommends initiating at a lower dose (i.e. 150 mg, three-monthly).[8] Consider increasing the dose if bleeding is troublesome or symptoms are uncontrolled. N.B. Depo-Provera is available in 150 mg/mL vials.

For further information on the pharmacological management of endometriosis, see: **https://bpac.org.nz/2021/endometriosis.aspx**

Table 2: Prevalence of altered bleeding patterns in people administered DMPA injections.

Altered bleeding pattern	After three months	After 12 months
Amenorrhoea[2]	10%	47%
Irregular bleeding[9]	15%	9%
Prolonged bleeding[10]	29%	10%

There is often a delay in the return to fertility with DMPA injections

A significant factor influencing the decision to use DMPA injections is its association with a delay in the return to fertility once treatment is stopped; this delay is variable, but patients should be informed that it may be up to one year.[1] One follow-up study reported an average of six months (range two to eleven months) for return of ovulation.[2, 11] There is no evidence that DMPA injections cause a permanent loss of fertility. Following the final injection, it is estimated that 65% of those who wish to become pregnant do so within 12 months, 83% do so within 15 months and 93% do so within 18 months (median time ten months).[5] As such, those wanting to become pregnant in the near future or shortly after stopping contraceptives should consider an alternative method of contraception until they are ready to conceive. If DMPA injections are stopped, another contraceptive should be initiated at the time the next injection would have been due.[2]

DMPA injections can be used while breastfeeding

DMPA injections are considered safe to use while breastfeeding.[1, 6] The manufacturer recommends delaying administration until six weeks post-partum if breastfeeding, due to theoretical concerns over an infant's ability to metabolise DMPA.[5] However, there is no evidence of adverse effects on infant growth, health or development or on breastfeeding performance, therefore the UKMEC* considers the benefit of use of DMPA in the first six weeks post-partum to outweigh the risks.[6] New Zealand guidelines recommend delaying DMPA administration until day 21 post-partum if breastfeeding.[1]

* United Kingdom Medical Eligibility Criteria: **https://www.fsrh.org/standards-and-guidance/uk-medical-eligibility-criteria-for-contraceptive-use-ukmec/**

DMPA injections are associated with a small amount of weight gain

Current evidence suggests that DMPA injections are the only form of contraception associated with weight gain.[12] In clinical studies, an average increase in weight of one to two kilograms over one year of use has been reported.[3, 12] Weight gain appears to increase with longer durations of treatment and is most strongly associated with use in people aged under 18 years with an initial body mass index ≥ 30 kg/m^2.[1] Switching to an alternative method of contraception may be advised in those who gain more than 5% of their initial body weight within six months as continued weight gain is likely.[1]

Other potential health concerns are not well defined

Be aware of potential changes in bone mineral density

DMPA injections are associated with a small reduction in bone mineral density due to its hypo-oestrogenic effect.[2, 3] This form of contraception is therefore not a first-line choice in people aged under 18 years as there are concerns that it may influence peak bone mineral density.[1, 2] It is recommended that the benefits and risks of treatment should be reassessed every two years, and if risk factors for osteoporosis are identified, e.g. rheumatoid arthritis, inflammatory bowel disease, age over 50 years or perimenopausal, an alternative method of contraception should be recommended.[1, 3]

Further investigation is required to understand the consequences of these changes

It is not known whether the changes in bone mineral density with DMPA use results in an increased fracture risk or whether longer durations of treatment cause greater losses.[2] Some studies suggest that the rate of bone mineral density loss is more significant during the first two years of treatment and slows with continued use, however, this finding has not been consistently replicated. In general, any losses are reversed once treatment is stopped.[2]

The association with cancer risk requires further investigation

Breast cancer. Evidence on the risk of breast cancer in people who have taken DMPA injections is limited.[2] Studies have indicated there may a weak association – similar to findings with combined oral contraceptives – but absolute increases in risk are generally low and appear to diminish once treatment is discontinued, e.g. there is no increased risk more than five years after treatment ceases.[1, 2]

Cervical cancer. Studies have found a slightly increased risk of cervical cancer in people using DMPA injections for five years

or more, however, it is not clear if the association is causal or whether confounding factors are involved.[1, 2] As with breast cancer, the risk reduces after stopping treatment.

Other conditions. DMPA injections are not associated with an increased risk of endometrial or ovarian cancers and evidence suggests they may actually have a protective effect.[1] In addition, studies indicate a potentially reduced risk of colon cancer, acute episodes of pelvic inflammatory disease and ectopic pregnancy when using this form of contraception, however, further investigation is required to confirm these benefits.

Cardiovascular risk factors may be a reason not to use DMPA injections

The effect of taking DMPA injections on cardiovascular disease risk remains under scrutiny. A small increase in the risk of venous thromboembolism (VTE) has been noted in clinical trials of progestogen-only contraceptives, however, a causal relationship has not been confirmed specifically for DMPA injections.[1, 2] In addition, it should be considered that the risk of VTE is considerably lower than that associated with pregnancy or use of combined oral contraceptives. There is also insufficient evidence to conclude whether myocardial infarction and stroke are associated with DMPA.[1] In general, clinical decisions should be made based on the severity and number of risk factors, in addition to the likelihood of follow-up. For example, DMPA injections should usually not be used if the person has multiple risk factors for arterial cardiovascular disease, e.g. hypertension and diabetes.[3]

Acknowledgement: This article is a revision of an original article published by bpac^{nz} in 2019. The original article was reviewed by **Dr Beth Messenger**, National Medical Advisor, Family Planning New Zealand.

Article supported by PHARMAC

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Managing persistent or problematic bleeding while using DMPA

First-line options (recommended in clinical guidelines):

- A combined oral contraceptive for up to three months (with or without placebo pills), e.g. 30 – 35 micrograms ethinylestradiol with levonorgestrel or norethisterone;[13] one month is usually sufficient to manage abnormal bleeding
- Oral mefenamic acid 500 mg (partly funded), two to three times daily, for up to five days; OR oral tranexamic acid 1 g (fully funded), three to four times daily, for up to four days, can be used to reduce an episode of heavy bleeding[13]

Second-line options (low-level, anecdotal or conflicting evidence):

- Oral medroxyprogesterone acetate* 10 mg (fully funded), once daily, for 21 days[7]
- Oral norethisterone 5 mg (fully funded), two to three times daily, for 21 days[7]

* Family Planning New Zealand recommends oral medroxyprogesterone acetate as the preferred second-line option. This is because there is concern that at high doses norethisterone is converted into oestrogenic compounds, which is not suitable for patients with a contraindication to oestrogen treatment.

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This article is available online at:
www.bpac.org.nz/2021/contraception/depot.aspx