Progestogen-only Injectable Contraceptives

The Department of Health promotes the use of long-acting, reversible contraceptives as a method of reproductive control. Their use following emergency contraception is a Quality and Outcomes Framework (QOF) target, although it is no longer a target for women prescribed oral or patch contraception.[1]

A progestogen-only injectable contraceptive (POIC) is a long-acting, reversible contraceptive. A synthetic progesterone, or progestogen, is slowly released into the systemic circulation following intramuscular (IM) or subcutaneous (SC) injection.

There are three forms of depot injection currently available on the UK market:

- **Depo-Provera®** is depot medroxyprogesterone acetate (DMPA) aqueous suspension 150 mg in 1 ml formulated for deep IM injection.[2] This is most commonly used.
- **Sayana Press®** is DMPA 104 mg in 0.65 ml formulated for SC injection first licensed in the UK in 2011.[3] It is bio-equivalent to Depo-Provera®. It may be preferable to Depo-Provera® in women on anticoagulants or with a bleeding disorder. In women who are very obese it may be preferable if there are concerns about being able to administer an IM injection effectively. Self-administration has been studied and found to be feasible and acceptable and it was licensed for this in 2015.[4]
- **Noristerat®** is norethisterone enantate (enanthate) 200 mg in 1 ml in an oily liquid.[5] This is only licensed for short-term use - eg, for women whose partners have undergone vasectomy, until the vasectomy is effective, and after rubella immunisation.

Mechanism of action

- Its main mechanism of action is to suppress ovulation.
- It also makes the endometrium unsuitable for implantation if fertilisation occurs.
- It also increases the viscosity of cervical mucus, making the mucus less easily penetrable to sperm.

Epidemiology

In the National Statistics Opinions Survey of UK households, 3% of women aged 16-49 years said they used the injection as their method of contraception.[6] The percentage is higher (9-11%) amongst women attending community clinics and, having dipped between 2005 and 2011, its usage has returned to previous rates.[7] The majority of these women are young - 18-19 years old.

Depot contraceptives are available only for women in the UK, but trials of monthly testosterone injections for men have been undertaken in China.[6]

Failure rate

Provided that women return every 12 weeks (8 weeks for Noristerat®) for their injection, there is a very low failure rate in studies - around 2 per 1,000 women per year.

However, data from the USA suggest the real-life failure rate is about 6 per 100 women per year; it is more effective than oral contraception, although it is not as effective as the intrauterine devices or contraceptive implant.[8]

Neither obesity nor the use of liver enzyme-inducing medication affects the failure rate of DMPA. The efficacy of Noristerat® is lowered by enzyme-inducing drugs. Broad-spectrum antibiotics do not affect the efficacy of either injectable. Ulipristal acetate (UPA) has the potential to reduce the effectiveness of progestogen-only injectables so additional precautions are advised for 14 days after taking UPA.[10]

Patient selection

**NB:** migraine (with or without aura), diabetes, obesity and breastfeeding are NOT contra-indications to use of DMPA.[11]:

- DMPA is suitable for those who want a reliable but reversible form of contraception that does not require daily vigilance like oral contraceptives, or action at the time of intercourse, like barrier contraceptives. It should only be used in adolescents (aged 12-18) after other methods have been considered unsuitable or unacceptable.[10].
- It is a useful alternative for women who need a reliable form of contraception but who have contra-indications to oestrogen therapy in the combined oral contraceptive (COC) pill. It may be more appealing to women than the contraceptive implant or intrauterine devices, as no intervention is required to remove it. Long-acting reversible contraceptives (LARCs) are recommended by the National Institute for Health and Care Excellence (NICE) on the grounds of their low failure rates and better cost-effectiveness than short-acting methods (eg, COC pill, barrier methods).[11].
- Noristerat® is for short-term use only (maximum of two injections), as mentioned above.
Advantages\textsuperscript{[11]}

- DMPA does not increase the risk of ovarian or endometrial carcinoma and may offer some protection.
- Contraceptive injections give protection against ectopic pregnancy and functional ovarian cysts, because ovulation is inhibited.
- NICE recommends DMPA as a management option for heavy menstrual bleeding\textsuperscript{[12]}. It also improves symptoms of dysmenorrhea and endometriosis\textsuperscript{[13]}.
- No long-acting progestogen injection affects blood pressure.
- Limited evidence suggests that the severity of the pain of sickle cell crises may be less in women on DMPA\textsuperscript{[14]}. It is a safe option although there is a lack of evidence regarding the risks of venous thrombosis in women with sickle cell disease.
- In women with epilepsy, frequency of seizures may be reduced while using DMPA.
- Acne vulgaris, depression and headaches are not associated with the injection.

Contra-indications

See individual drug monographs and UK Medical Eligibility Criteria (UKMEC) for complete list\textsuperscript{[2, 3, 5, 15]}.

- Current breast cancer (within the previous five years).
- Gestational trophoblastic neoplasia with abnormal human chorionic gonadotrophin (hCG) level.
- Current severe impairment of liver function or history of liver adenoma or steroid-induced cholestatic jaundice.
- History of severe arterial disease or very high risk factors - risk of thrombosis and arterial disease may be increased.
- Acute porphyria, even if there is no history of active disease.
- Pregnancy - this should be excluded before injection (a history of recent normal menstruation is adequate).
- Noristerat\textregistered may not be used during breastfeeding of neonates with severe or persistent jaundice.
- Unexplained vaginal bleeding.

Contraceptive injections are not appropriate for those who may wish a return to fertility in the near future\textsuperscript{[10]}:

- Median delay to conception has been reported as 5.5 months plus the estimated duration of the effect of the last injection of Depo-Provera\textregistered. This is compared to 3 months for oral contraceptives and 4.5 months after discontinuing the intrauterine contraceptive device (IUCD)\textsuperscript{[11]}.
- Long-term, there is no difference in failure to conceive.

Risks and side-effects

Progestogen-only contraception, whether in the form of progestogen-only pills (POPs), depot injections or slow-release implants, has an extremely good safety profile\textsuperscript{[11]}.

Irregular bleeding

Altered bleeding patterns are common in women using DMPA\textsuperscript{[10]}:

- The likelihood of amenorrhea increases with duration of use: 41% and 47% of women are amenorrhoeic at 1 year for the 100 mg and 150 mg doses respectively. Spotting and heavy bleeding are also found. Counselling before administration is likely to improve tolerance for this.
- If irregular bleeding occurs, particularly if new, consider STI screening for chlamydia and examine the woman's cervix.
- If irregular bleeding persists for more than 3 months, consider whether further investigations are necessary. See the separate Breakthrough Bleeding with Combined Hormonal Contraception article.
- If bleeding is a problem, the COC pill (if not contra-indicated) or mefenamic acid may be offered for three months\textsuperscript{[16]}.

Bone mineral density (BMD)

There is conflicting evidence that DMPA causes a reduction in BMD\textsuperscript{[10]}:

- Any loss is small and recovered as soon as the injections are stopped\textsuperscript{[11]}.
- The clinical significance of changes in BMD is unclear and a Cochrane review concluded that there was insufficient evidence to determine if there is an increased fracture risk\textsuperscript{[17]}.
- A UK-based study reported that although users of DMPA did experience more fractures than non-users, they had a higher fracture rate prior to starting DMPA use and the rate did not increase after starting DMPA\textsuperscript{[18]}. The fractures were most frequently non-axial and miscellaneous (facial, skull, finger, toe and multiple trauma) rather than hip, pelvis or spine. The authors suggest that this may be due to clinicians tending to recommend DMPA to women who may be more likely to experience trauma\textsuperscript{[19]}.
- The Medicines and Healthcare products Regulatory Agency (MHRA) advises that women aged under 18 years may use DMPA as first-line, only after considering the suitability of other methods and that for all women, the benefit:risk profile should be re-evaluated every 2 years if they wish to continue using it.
- Women with significant risk factors for osteoporosis (family history, smoking, corticosteroids, excessive alcohol, anorexia nervosa, coeliac disease) should consider other methods of contraception.
- For women over the age of 40 the advantages of using DMPA generally outweigh the disadvantages.
- There is no difference in loss of BMD between the two forms of DMPA\textsuperscript{[20]}.
Cardiovascular disease (CVD)
Unfavourable changes in serum cholesterol (particularly low-density lipoprotein (LDL) cholesterol) levels have been demonstrated, but they appear to return to baseline values by 24 months of continued DMPA use[21]. An increased risk of myocardial infarction or stroke has not been shown[10].

In the current World Health Organization (WHO) and UK medical eligibility criteria recommendations, DMPA and norethisterone are category '3' for women with multiple risk factors for arterial CVD, current venous thromboembolism (VTE), ischaemic heart disease or history of stroke[15]. This means that the risks of using POICs usually outweigh the benefits.

Breast cancer
There may be a weak association between breast cancer and DMPA but the studies are small and subject to bias and confounding. This may be because of patient selection, as risk factors for breast cancer are a contra-indication to oestrogen-containing methods of contraception. If there is an increased risk it disappears after 5 years of stopping DMPA[10].

Cervical cancer
There is a weak association between cervical cancer and use of DMPA for more then 5 years which disappears after stopping. It is not known if this is causal or due to confounding factors such as smoking and not using condoms[10].

Weight gain
Weight gain of up to 3 kg in one year may occur. Younger women under 18 who already have a BMI ≥30 kg/m2 and those women who put on more than 5% of their initial weight in the first 6 months, would appear to be at greatest risk of ongoing weight gain[10].

HIV acquisition[22]
A meta-analysis of data on the use of DMPA and HIV acquisition suggests a moderate increased risk. However, other studies have not found this association. The WHO and the Faculty of Sexual and Reproductive Healthcare (FSRH) advise that women at high risk of HIV who are using DMPA should be advised of the unclear nature of the evidence and they stress the need for women at risk of HIV to use condoms.

Congenital malformation
The NICE guidelines state that women should be advised that there is no evidence of harm to the pregnancy or the fetus[11]. The Summary of Product Characteristics (SPC) is more cautious[2]; pregnancy whilst using DMPA is rare.

Administration

Pre-injection counselling[11]
- Always take a full medical history - family, menstrual, contraceptive and sexual.
- Always give full counselling about the injection's prolonged action, delayed return to full fertility and possible side-effects (eg, menstrual irregularities, loss of bone mineral density, etc) backed up with a patient information leaflet. Once an injection is given, clearly it cannot be removed and its effects will last for 3 months.
- Promotion of safer sex and assessment of risk of STIs should form part of the consultation. Screening for STIs should be advised if appropriate.

Route of injection
- Depo-Provera® is given by deep IM injection into the gluteal muscles (preferred, especially if obese), deltoid muscles or the lateral thigh.
- Sayana Press® is given by SC injection into the anterior thigh or abdomen.
- Women can be taught how to self administer Sayana Press®.
- Noristerat® is administered extremely slowly and always deep into the gluteal muscles. A maximum of 2 injections is advised.

Timing of DMPA[10, 11]
- Injections should be started on or before day 5 of the menstrual cycle.
- It can be started later than day 5 but the clinician must be reasonably certain that the woman is not pregnant. Barrier contraceptives should then be used for the next 7 days and a pregnancy test ≥3 weeks after the last episode of unprotected sexual intercourse may be necessary.
- It can be given at any time within 4 weeks postpartum if the patient is not breastfeeding. If the patient is breastfeeding, FSRH advises it should ideally be delayed until day 21 postpartum, although this is outside of the product licence which advises waiting for 6 weeks.
- After first- or second-trimester abortion it can be given immediately. If delayed, additional precautions are required for 7 days.
- The SPCs of IM DMPA (Depo-Provera®) and SC DMPA (Sayana Press®) advise dosing intervals of 12 and 13 weeks respectively but the SPC for Sayana Press® additionally advises that it can be given 1 week late.
- The FSRH recommends a dosing interval of 13 weeks for both IM and SC DMPA although this is outside the terms of the product licence for IM DMPA.
- Of note, the WHO advises that the DMPA can be given up to 16 weeks after the last injection without reducing its effectiveness.
Further reading & references

1. Changes to QOF 2014/15; NHS Employers
2. Summary of Product Characteristics (SPC) - Depo-Provera® 150 mg/ml injection; Pharmacia Limited, electronic Medicines Compendium, April 2015
3. Summary of Product Characteristics (SPC) - Sayana Press® 104 mg/0.65 ml suspension for injection; Pharmacia Limited, electronic Medicines Compendium, Sep 2014
4. Subcutaneous Depot Medroxyprogesterone Acetate (Sayana Press®); Faculty of Sexual & Reproductive Healthcare (June 2013)
5. Summary of Product Characteristics (SPC) - Noristerat® 200 mg solution for intramuscular injection; Bayer Schering, electronic Medicines Compendium, January 2015
6. Contraception and Sexual Health 2009/09; Office for National Statistics
10. Progestogen-only Injectable Contraception Clinical Guidance; Faculty of Sexual and Reproductive Healthcare (December 2014)
11. Long-acting reversible contraception; NICE Clinical Guideline (September 2014)
12. Heavy menstrual bleeding; NICE Clinical Guideline (January 2007)
15. UK Medical Eligibility Criteria for Contraceptive Use; Faculty of Sexual and Reproductive Healthcare (2009 - Revised May 2010)
16. Management of Unscheduled Bleeding in Women Using Hormonal Contraception; Faculty of Sexual and Reproductive Healthcare (2009)
22. Depot medroxyprogesterone acetate CEU Statement; Faculty of Sexual and Reproductive Healthcare, Jan 2015

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