FACULTY OF SEXUAL & REPRODUCTIVE HEALTHCARE

ROYAL COLLEGE OF OBSTETRICIANS & GYNAECOLOGISTS

Faculty of Sexual & Reproductive Healthcare Clinical Guidance

Progestogen-only Injectable Contraception

Clinical Effectiveness Unit

December 2014 (Amended July 2023)

Document reference number	02/FSRH/Injectable/2014
Title	Progestogen-only Injectable Contraception
Author/publisher	Faculty of Sexual & Reproductive Healthcare (FSRH)
Publication date	December 2014 *(Amended July 2023)*
Description/descriptors	Injectable contraception, progestogen-only contraception, long-acting reversible contraception, LARC, method-specific guidance
Cross references	*United Kingdom Medical Eligibility Criteria (UKMEC)* FSRH New Product Review: Subcutaneous Depot Medroxyprogesterone Acetate
Superseded documents	FSRH CEU Guidance Progestogen-only Injectable Contraception 2008
Update/amendment level	Full amendment including changes to recommendations and practice
Review date	December 2019

DETAILS OF CHANGES TO ORIGINAL GUIDANCE DOCUMENT

Since this set of guidelines was first published, the following changes have been made
March 2015 - Amendments made to the document are to CPD questions 3 and 5.
February 2019 - Box 1 and Tables 2-4 updated to reflect updates to other FSRH guidance.
April 2019 - Section 7, 8, 10.1 and 11.2 has been updated to reflect updates to other FSRH guidance
June 2020 - Section 7 has been updated to include advice that (in case of anaphylactic reaction) another competent adult should be present when Sayana Press is self-administered. Note that the risk of anaphylaxis is extremely low.
July 2023 - Section 5.2.2 Breast cancer updated to reflect newly published evidence.

GRADING OF RECOMMENDATIONS

A Evidence based on randomised controlled trials

B Evidence based on other robust experimental or observational studies

C Evidence is limited but the advice relies on expert opinion and has the endorsement of respected authorities

✓ Good Practice Point where no evidence exists but where best practice is based on the clinical experience of the guideline group

NICE accredited
www.nice.org.uk/accreditation

NICE has accredited the process used by the Faculty of Sexual & Reproductive Healthcare to produce its Progestogen-only Injectable Contraception guidance. Accreditation is valid for 5 years from May 2011. More information on accreditation can be viewed at www.nice.org.uk/accreditation.
For full details on our accreditation visit:
www.nice.org.uk/accreditation.

Published by the Faculty of Sexual & Reproductive Healthcare
Registered in England No. 2804213 and Registered Charity No. 1019969

First published in 2014 (Amended July 2023)

CONTENTS

ABBREVIATIONS USED

BMD	bone mineral density
BMI	body mass index
CEU	Clinical Effectiveness Unit
CHC	combined hormonal contraception/contraceptive
CI	confidence interval
CIN	cervical intraepithelial neoplasia
COC	combined oral contraception/contraceptive
Cu-IUD	copper intrauterine device
DMPA	depot medroxyprogesterone acetate
EC	emergency contraception
FSRH	Faculty of Sexual & Reproductive Healthcare
HIV	human immunodeficiency virus
HPV	human papillomavirus
IM	intramuscular
IUD	intrauterine device
LARC	long-acting reversible contraception/contraceptive
LNG	levonorgestrel
LNG-IUS	levonorgestrel intrauterine system
MHRA	Medicines and Healthcare Products Regulatory Agency
MI	myocardial infarction
NET-EN	norethisterone enantate
NICE	National Institute for Health and Care Excellence
OR	odds ratio
RCT	randomised controlled trial
RR	relative risk
SC	subcutaneous
SPC	Summary of Product Characteristics
STI	sexually transmitted infection
UKMEC	*UK Medical Eligibility Criteria for Contraceptive Use*
UPA	ulipristal acetate
UPSI	unprotected sexual intercourse
VTE	venous thromboembolism
WHO	World Health Organization
WHOMEC	*World Health Organization Medical Eligibility Criteria for Contraceptive Use*

SUMMARY OF KEY RECOMMENDATIONS

A When administered at the recommended dosing interval the failure rate of progestogen-only injectable contraception is approximately 0.2% in the first year of use. With typical use the failure rate is approximately 6%.

✓ Health professionals should be familiar with the most up-to-date UK Medical Eligibility Criteria for progestogen-only injectable contraception.

B Amenorrhoea or reduced bleeding is common in progestogen-only injectable users and may benefit women with menstrual problems.

A Depot medroxyprogesterone acetate (DMPA) use may reduce pain associated with endometriosis.

✓ Women should be advised about changes in bleeding patterns.

B Use of DMPA is not associated with an increased risk of ovarian or endometrial cancer and may offer some protection.

B DMPA is a contraceptive option for women with sickle cell disease and may reduce the severity of sickle crisis pain.

B Progestogen-only injectable use is associated with a small loss of bone mineral density, which is usually recovered after discontinuation.

C In women aged under 18 years progestogen-only injectable contraception can be used after consideration of alternative methods.

✓ Women using DMPA who wish to continue use should be reviewed every 2 years to assess individual situations, and to discuss the benefits and potential risks.

C Women are generally advised to switch to another method at age 50 years. If a woman does not wish to stop using DMPA, consideration may be given to continuation, providing the benefits and risks have been assessed and the woman informed of the potential risks.

B The available evidence suggests a possible association between current or recent use of hormonal contraception (including progestogen-only injectables) and a small increase in risk of breast cancer; absolute risk remains very small.

B A causal association between DMPA and venous thrombosis has not been demonstrated in the small number of studies that have investigated this relationship.

B From the limited evidence available it is not possible to confirm or exclude an association between progestogen-only injectable use and myocardial infarction or stroke.

B There is a weak association between cervical cancer and use of DMPA for 5 years or longer. Any increased risk appears to reduce with time after stopping and could be due to confounding factors.

✓ Health professionals should ensure that women requesting DMPA are up-to-date with cervical cytology screening and, if relevant, have completed the human papillomavirus (HPV) vaccination programme.

✓ Women should be informed about the link between HPV and cervical cancer, and advised about strategies that reduce the risk such as condom use, smoking cessation, regular cervical screening and, where appropriate, vaccination against HPV.

B Use of DMPA appears to be associated with weight gain, particularly in women under 18 years of age with a body mass index (BMI) ≥30 kg/m^2.

C Women who gain more than 5% of their baseline body weight in the first 6 months of DMPA use are likely to experience continued weight gain.

B Injection site reactions appear to be more common with use of subcutaneous (SC) DMPA than with use of intramuscular (IM) DMPA.

C Whilst there is little evidence available to demonstrate causation, a number of possible side effects such as acne, decreased libido, mood swings, headache, hot flushes and vaginitis have been reported with use of DMPA.

C The gluteal muscle in the buttock is the preferred site for IM DMPA administration but it can be administered into the deltoid muscle of the upper arm. In women with deep adipose tissue in the gluteal area, standard-length needles may not reach the muscle layer and SC DMPA or deltoid administration of IM DMPA should be considered.

C SC DMPA should be injected into the abdomen or anterior thigh.

✓ Women should be advised to return every 13 weeks for a repeat injection of IM or SC DMPA (outside the product licence for IM DMPA).

B An injection of DMPA can be administered up to 7 days late (up to 14 weeks after the last injection) without the need for additional contraceptive precautions (outside the product licence for IM DMPA).

C If necessary, an early repeat injection of DMPA can be administered from 10 weeks and from 6 weeks for norethisterone enantate (NET-EN) (outside product licence).

B The efficacy of DMPA contraception is not reduced with concurrent use of enzyme-inducing drugs.

B No increased risk of pregnancy has been demonstrated in progestogen-only injectable users with higher body weight, although data are limited in women with a BMI ≥40 kg/m^2.

✓ Women who discontinue their progestogen-only injectable and who do not wish to conceive should be advised to start another contraceptive method before or at the time of their next scheduled injection even if amenorrhoeic.

C Women should be informed that there can be a delay of up to 1 year in the return of fertility after discontinuation of IM or SC DMPA.

B The consistent and correct use of condoms (male or female) can reduce the risk of sexually transmitted infection (STI) transmission and should therefore be recommended as a risk-reduction strategy.

B A causal relationship between progestogen-only injectable contraception and HIV transmission/acquisition has not been established but cannot be completely excluded.

✓ Women who experience unscheduled bleeding during use of a progestogen-only injectable and who are medically eligible can be offered a combined oral contraceptive (COC) for 3 months. This can be taken in the usual cyclic manner or continuously without a hormone-free interval (outside product licence). Longer-term use of the injectable and COC has not been studied and is a matter of clinical judgement.

B Women with unscheduled bleeding during use of a progestogen-only injectable contraceptive can be offered 500 mg mefenamic acid up to three times daily for 5 days.

Faculty of Sexual & Reproductive Healthcare
Clinical Effectiveness Unit

A unit funded by the FSRH and supported by NHS Greater Glasgow & Clyde to provide guidance on evidence-based practice

FSRH Guidance (December 2014, amended July 2023)

Progestogen-only Injectable Contraception

(Revision due by December 2019)

1 Purpose and Scope

This document provides clinical guidance, evidence-based recommendations and good practice points on use of progestogen-only injectable contraception. Unless otherwise stated, the guidance will refer to depot medroxyprogesterone acetate (DMPA) injectable contraception. Information on norethisterone enantate (NET-EN) will be included where relevant.

The guidance is intended for any health professional or service providing contraception or contraceptive advice in the UK. The document updates and replaces previous Faculty of Sexual & Reproductive Healthcare (FSRH) guidance on progestogen-only injectable contraception.[1] The main changes from the previous guidance are:

- Updated *UK Medical Eligibility Criteria for Contraceptive Use* (UKMEC)[2]
- Inclusion of information relating to subcutaneous DMPA
- Updated advice in relation to the dosing interval for DMPA (FSRH recommends 13 weeks)
- Updated advice on switching between contraceptive methods
- Updated advice on the upper age limit for use.

The recommendations included in this document should be used to guide clinical practice but they are not intended to serve alone as a standard of medical care or to replace clinical judgement in the management of individual cases. A key to the Grading of Recommendations, based on levels of evidence, is provided on the inside front cover of this document. Details of the methods used by the Clinical Effectiveness Unit (CEU) in developing this guidance are outlined in Appendix 1 and in the CEU section of the FSRH website (www.fsrh.org).

2 Background

Long-acting reversible contraceptives (LARCs) are those that are administered less frequently than once a month.[3,4] Both DMPA and NET-EN are long-acting progestogens; the combined contraceptive injectable is not available in the UK. DMPA is formulated for deep intramuscular (IM) injection as Depo-Provera® (150 mg medroxyprogesterone acetate in 1 ml)[5] and subcutaneous (SC) injection as Sayana Press® (104 mg MPA in 0.65 ml).[6] NET-EN is less commonly used in the UK. It is available as Noristerat® (200 mg in 1 ml),[7] administered by IM injection. NET-EN is licensed for short-term use by women whose partners have undergone vasectomy until successful vasectomy is confirmed, and after rubella immunisation.

3 What is the Mode of Action of the Progestogen-only Injectable and How Effective is it?

Progestogen-only injectable contraception works primarily by inhibiting ovulation.[8–10] There is also an effect on cervical mucus, resulting in poor cervical mucus scores and limited sperm penetration.[11,12] In the majority of women an effect on cervical mucus occurs within the first few days,[11,12] but in some women this may take up to 7 days or more.[13] Therefore, additional precautions are required for 7 days when starting after Days 1–5 to allow time for ovulation suppression and the cervical mucus effects of the progestogen-only injectable to become established.

In addition, changes to the endometrium make it an unfavourable environment for implantation.[14–16]

In a multinational randomised controlled trial (RCT) cumulative pregnancy rates for DMPA users were 0.7% at 1 year of use.[17] Similar results were reported in two cohort studies (0.4%[18] and 0.3%[19]) at 1 year of use. An RCT that compared pregnancy rates for NET-EN and DMPA users found 1-year cumulative pregnancy rates of 0.4% (NET-EN) and 0.1% (DMPA). At 2 years, cumulative pregnancy rates were <0.4% (<4 in 1000).[17] A large prospective study compared failure rates at 1–3 years in LARC users [implant/copper intrauterine device (Cu-IUD), *n*=5781] versus a group of combined pill, patch and ring users (*n*=1527) and a group of DMPA users (*n*=124). The reported cumulative pregnancy rates for those in the DMPA group (0.1%, 0.7% and 0.7%, respectively) did not differ significantly from those in the Cu-IUD/implant group (0.3%, 0.6% and 0.9%, respectively) (*p*=0.96). The failure rate per 100 participant years for DMPA was calculated as 0.22 in those women who returned for their injections (i.e. perfect use).[20]

Estimates from the USA[21] suggest that the percentage of women experiencing an unintended pregnancy within the first year of using the progestogen-only injectable is 0.2% with perfect use (used consistently and correctly) but 6% with typical use (includes incorrect/inconsistent use). The typical failure rates observed are higher than with other long-acting methods, perhaps due to the relative frequency with which repeat injections have to be administered. The injectable is therefore less cost-effective than the progestogen-only implant, the Cu-IUD and the levonorgestrel intrauterine system (LNG-IUS).[3,22] However, progestogen-only injectables are more cost-effective than combined oral contraception (COC), even after 1 year of use.[3,22]

A When administered at the recommended dosing interval the failure rate of progestogen-only injectable contraception is approximately 0.2% in the first year of use. With typical use the failure rate is approximately 6%.

4 Who is Eligible to Use the Progestogen-only Injectable?

The *UK Medical Eligibility Criteria for Contraceptive Use* (UKMEC)[2] is a document that provides evidence-based recommendations on the use of contraceptive methods in the presence of a range of medical conditions and social factors. Health professionals should take a medical history as outlined in FSRH *Service Standards for Record Keeping*[23] and should refer to UKMEC[2] when assessing an individual's eligibility for any contraceptive method including the progestogen-only injectable. Unless specifically stated, UKMEC[2] does not take account of multiple conditions. There are no formal rules for assessing multiple UKMEC categories. Assessing an individual's eligibility in the presence of multiple medical and social factors requires clinical judgement based on the evidence available. SC DMPA was not available in the UK when UKMEC was last published;[2] however, the FSRH would advise that UKMEC categories for IM DMPA can be applied to SC DMPA.

The definitions of the UKMEC categories are given in Table 1.

Table 1 Summary of *UK Medical Eligibility Criteria for Contraceptive Use* (UKMEC) categories

UKMEC Category	Definition
1	A condition for which there is no restriction for the use of the contraceptive method.
2	A condition for which the advantages of using the method generally outweigh the theoretical or proven risks.
3	A condition where the theoretical or proven risks usually outweigh the advantages of using the method. The provision of a method requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use of the method is not usually recommended unless other more appropriate methods are not available or not acceptable.
4	A condition which represents an unacceptable health risk if the method is used.

✓ Health professionals should be familiar with the most up-to-date *UK Medical Eligibility Criteria* for progestogen-only injectable contraception.

5 Non-contraceptive Benefits, Health Concerns and Side Effects Associated with Use of the Progestogen-only Injectable

5.1 Non-contraceptive benefits

5.1.1 Bleeding and dysmenorrhoea

The majority of progestogen-only injectable users become amenorrhoeic with time[18,19] (see page 10). Some women may view this as an adverse effect; others may view it as a benefit, particularly if they have menstrual problems.[24,25] The progestogen-only injectable is listed within National Institute for Health and Care Excellence (NICE) guidelines[26] as a possible treatment for the management of heavy menstrual bleeding. DMPA has also been shown to help improve dysmenorrhoea and the symptoms of endometriosis[27–30] and is listed as a possible treatment option within the European Society for Human Reproduction and Embryology guideline on the management of women with endometriosis.[31]

B Amenorrhoea or reduced bleeding is common in progestogen-only injectable users and may benefit women with menstrual problems.

A DMPA use may reduce pain associated with endometriosis.

✓ Women should be advised about changes in bleeding patterns.

5.1.2 Ovarian and endometrial cancers

Data from observational studies suggest that there is no increased risk of ovarian cancer[32–35] or endometrial cancer[33] associated with DMPA use, and that use of DMPA may confer some protection against these conditions.[33]

B Use of DMPA is not associated with an increased risk of ovarian or endometrial cancer and may offer some protection.

5.1.3 Sickle cell disease

Data on the benefits of DMPA in women with sickle cell disease are limited in terms of quantity and quality.[36–38] There is no evidence to date that suggests an increased risk of clinical complications associated with its use, and there is some evidence to suggest that DMPA may actually confer some benefits with regard to severity of sickle crisis pain.[36–38] However, a systematic review[36] has indicated that there is insufficient evidence to recommend DMPA over other contraceptives. No assessment can be made about the risk of thrombosis associated with DMPA use in women with sickle cell disease due to the lack of evidence (see section 5.2.3/page 7).

B DMPA is a contraceptive option for women with sickle cell disease and may reduce the severity of sickle crisis pain.

5.2 Health concerns

5.2.1 Bone mineral density

Suppression of ovulation with use of DMPA can lead to a decrease in estradiol and estrone levels. Although estradiol levels are similar to those seen in the early phase of the menstrual cycle, there is evidence that use of DMPA results in loss of bone mineral density (BMD).

A systematic review undertaken by NICE concluded that DMPA use is associated with a small loss of BMD, which is largely recovered when DMPA is discontinued.[3] Another systematic review of 10 observational studies, published between 1996 and 2006, found that following discontinuation of DMPA, BMD returned towards baseline or to baseline values in women of all ages.[39] Further published data from observational studies have not changed the findings of the NICE review.[40,43]

Findings of studies examining the impact of duration of use or number of DMPA injections on BMD have differed. A cross-sectional study of postmenopausal women who had used DMPA without a break for between 1 and 15 years were compared to an age-matched group of Cu-IUD users. As duration of use increased, so too did differences in the BMD at the ultra-distal radius. The difference became statistically significant after 13–15 years of use.[44] A 7-year matched cohort study of women aged 25–35 years found that at all time points in the 240-week treatment period the loss of BMD was significantly greater amongst DMPA users than Cu-IUD users; the greatest decline was in the first year of use.[45] Other studies similarly report that the rate of bone loss may be greatest initially but then tapers off with time.[46–48]

The clinical significance of changes in BMD with use of DMPA is unclear and it is not known whether this translates to an increased risk of fracture. There has been particular concern about use of DMPA in women aged <18 years (who have not yet attained their peak bone mass) and among older women who are approaching the menopause when additional BMD loss will occur.[3]

A Cochrane review of RCTs[49] concluded that the risk of fracture associated with DMPA use could not be determined from existing data. A Cochrane review of observational studies[50] concluded that data suggest use of DMPA might increase a woman's risk of fracture. Three observational studies; one case-control and one cohort study utilising the same UK dataset, and a case-control study of Danish women,[51] reported that women who have used DMPA may be at a modest increased risk of fracture compared with those who have not.[52,53] However, none of the studies were adequately powered to control for potential confounding factors such as smoking, body mass index (BMI), participation in sports, or physical risk-taking behaviour. In addition, one study[53] using a UK dataset reported that while DMPA users did experience more fractures than those who did not use DMPA, users appeared to have a higher background risk of fracture at the time of starting DMPA. Additionally, the increased risk was in relation to appendicular and miscellaneous fractures (i.e. fingers, toes, face, skull, multiple trauma, and unspecified fractures) rather than axial fractures (i.e. hip, pelvic fractures). DMPA users did not have an increase in risk after starting DMPA. The authors therefore suggested that the observed increased incidence of fracture compared to non-users may be a result of an inherent background risk in those who had chosen the method rather than an effect of DMPA use.

The FSRH supports guidance from the Medicines and Healthcare Products Regulatory Agency (MHRA)[54] which advises that:

- In women aged under 18 years DMPA may be used as first-line contraception after all options have been discussed and considered unsuitable or unacceptable.
- A re-evaluation of the risks and benefits of treatment for all women should be carried out every 2 years in those who wish to continue use.
- For women with significant lifestyle and/or medical risk factors for osteoporosis other methods of contraception should be considered.

Risk factors (both inherited and modifiable) for osteoporosis are outlined in guidance published by the National Osteoporosis Guideline Group.[55] There is insufficient evidence to make recommendations on bone densitometry, for example, dual energy X-ray absorptiometry (DEXA) scanning in progestogen-only injectable users. Clinicians should consult local protocols for referral criteria.

For women with complex health needs, who may be at increased risk of osteoporosis, the potential risks should be considered in the context of the potential benefits (e.g. menstrual suppression). The decision is a matter of clinical judgement.

For women over the age of 40 years, the advantages of using DMPA generally outweigh the theoretical or proven risks. Several observational studies have specifically examined the effects of DMPA use (past or present) on BMD in women aged over 40 years.[44,56–59]A small prospective study was identified that included a control group and two groups of women who used DMPA until the menopause: one group underwent subsequent hormone replacement, the other did not. Whereas bone loss was rapid in those women who did not use DMPA, in those who did and who did not use hormone replacement therapy, BMD changed very little.[56] Other studies have suggested there is no significant worsening of BMD in postmenopausal women who had used DMPA until the menopause compared with non-users.[44,56–59] It has been postulated that rather than worsen skeletal outcomes, women using DMPA until the menopause do not experience further significant bone loss because they have already undergone loss associated with the hypoestrogenic effects of DMPA.[44,56]

UKMEC[2] advises that use of the injectable in women aged over 45 years is a UKMEC category 2 (i.e. the advantages of using the method generally outweigh the theoretical or proven risks). In the UK, it has been advised that women using the injectable switch to another method at age 50 years because of concerns about the impact on skeletal health and the theoretical risk of osteoporotic fracture in the menopause.[60] However, if a woman prefers to continue or start the method at the age of 50 years or over, this would not be an unacceptable health risk and the benefits may outweigh the risks for some women.

B Progestogen-only injectable use is associated with a small loss of BMD, which is usually recovered after discontinuation.

C In women aged under 18 years progestogen-only injectable contraception can be used after consideration of alternative methods.

✓ Women using DMPA who wish to continue use should be reviewed every 2 years to assess individual situations, and to discuss the benefits and potential risks.

C Women are generally advised to switch to another method at age 50 years. If a woman does not wish to stop using DMPA, consideration may be given to continuation, providing the benefits and risks have been assessed and the woman informed of the potential risks.

5.2.2 Breast cancer

The limited available evidence is not consistent, but suggests that current or recent use of DMPA could be associated with a small increase in breast cancer risk. Causal association is not, however, clearly established and the absolute risk of breast cancer amongst users of hormonal contraception, including DMPA remains very low.

The evidence

When interpreting the evidence, there are the following important considerations. The available evidence derives from observational studies, some of which have found no effect of progestogen-only injectables on breast cancer risk or reduced incidence while others have reported a small increased risk. The number of incident breast cancers amongst women of reproductive age is very small, which makes effect of hormonal contraception on risk difficult to study. The observational, database-based nature of the studies that we do have means that findings could be affected by confounding factors that are not recorded or not considered. For example, a group of individuals that choose to use hormonal contraception may make other choices (e.g. lifestyle choices) that are different to those made by people that choose not to use hormonal contraception. There may be prescribing bias based on individuals' other risks. Individuals currently or recently using a given contraceptive method could have been using a different method prior to that and this is not always accounted for.

A case-control study[159] using UK database data for 1996-2017 compared current or recent use of hormonal contraception by individuals aged <50 years with incident invasive breast cancer with use by matched controls who had no history of invasive or in situ breast cancer. 308 people with incident invasive breast cancer were currently using or had recently used a progestogen-only injectable (they could have used other hormonal contraceptives previously). The study reported a statistically significant increased risk of invasive breast cancer for current or recent users of a progestogen-only injectable compared to individuals that had not used hormonal contraception during the study period (adjusted OR 1.25 (95% CI 1.07 to 1.45; p = 0.004). Adjustment was made for time since last birth, number of recorded births, BMI, and alcohol intake.

A cohort study[160] using the Swedish nationwide register included women aged 15-34 in 2005 and those that turned 15 thereafter, until the end of 2017 or age 45. During 127,259 person years of use of DMPA, 50 breast cancers occurred. Compared to individuals that did not use hormonal contraception during the study period, current users of DMPA had a statistically significantly reduced risk of incident invasive or in situ breast cancer (adjusted relative risk 0.74 (95% CI 0.56-0.97); p=0.03). Adjustment was made for age, education, place of birth, parity, age at first term pregnancy, but not for factors such as BMI, smoking and alcohol. The authors urge caution in interpretation of this finding of apparent reduced risk, highlighting the relatively small numbers involved.

A database study[161] using information from Danish national databases for the 1.8 million Danish women aged 15–49 years between 1995 and 2012 found that after adjustment for age, calendar year, level of education, parity, PCOS, endometriosis, and family history of premenopausal breast or ovarian cancer, current and recent users of hormonal contraception (all methods combined) were at 20% increased risk of developing breast cancer compared to never-users of hormonal contraceptives (adjusted RR 1.20; 95% CI 1.14–1.26). Current or recent use of the progestogen-only injectable was not found to be associated with increased risk of breast cancer (RR 0.95 (95% CI 0.4-2.29) – the wide CI reflects the very small number of incident breast cancers in this group.

A pooled analysis[61] of two case-control studies[62,63] reported that ever-use of DMPA was associated with a non-statistically significant increased risk of breast cancer (RR 1.1, 95% CI 0.97–1.4). Subgroup analysis[61] suggested that the risk of breast cancer may be increased in women who have started use within the previous 5 years (RR 2.0, 95% CI 1.5–2.8) but not in those who had used DMPA more than 5 years previously regardless of the duration of use.

The Collaborative Group on Hormonal Factors in Breast Cancer undertook a re-analysis of 54 studies to investigate the relationship between breast cancer and hormonal contraceptives. Although few women used progestogen-only methods, limiting the strength of the findings, a non-statistically significant increased risk of breast cancer was observed for injectable progestogens.[64] A case-control study[65] of women (n=919 controls and n=1028 cases) aged 20–44 years reported a 2.2-fold [odds ratio (OR) 2.2, 95% CI 1.2–4.2] increase in risk of invasive breast cancer amongst those who had recently used DMPA (within 5 years of diagnosis) for 12 months or longer compared to non-users of DMPA.

A meta-analysis carried out by Fitzpatrick et al[159] combined data from their UK database study with data from eight other observational studies,[64,65,160–165] some of which are described above. Some of these studies considered individuals that had last used DMPA up to 10 years ago and compared them to individuals that had never used a progestogen-only injectable (rather than to those that had never used hormonal contraception). The meta-analysis[159] suggested a small but statistically significant increased breast cancer risk (RR 1.18, 95% CI 1.07-1.30) for current or recent users of the progestogen-only injectable compared to individuals that had never used a progestogen-only injectable or had never used hormonal contraception. This was similar to risk associated with current or recent use of other hormonal contraceptives.

B The available evidence suggests a possible association between current or recent use of hormonal contraception (including progestogen-only injectables) and a small increase in risk of breast cancer; absolute risk remains very small.

5.2.3 Cardiovascular health

Venous thromboembolism

Few studies have been large enough to evaluate the risk of venous thromboembolism (VTE) associated with use of progestogen-only contraceptives but available studies do not show an increased risk for progestogen-only contraceptives collectively.[66–69]

A small, prospective, non-randomised pilot study[70] was conducted to examine the effects of SC or IM DMPA on coagulation and inflammatory factors that may be indicative of an increased risk of thrombosis. Following four injections (i.e. 12 months of use), coagulation and inflammation factors were not adversely affected. The concentration of D-dimer was noted as being significantly reduced from baseline at 6 and 12 months.[70] The study was limited by small numbers and lack of a control group, making the findings unreliable. However, the findings were not indicative of DMPA having a negative affect on possible markers of thrombosis.[70]

A case-control study conducted by the World Health Organization (WHO) found a small non-statistically significant increased risk of venous thrombosis in the small number of DMPA users included.[66] Two subsequent papers; a meta-analysis of five case-control and three retrospective cohorts,[68] and a large case-control study[71] have reported a statistically significant increased risk of VTE associated with use of the progestogen-only injectable. More research is required before a causal relationship can be confirmed or excluded and the long-term consequences of any cardiovascular effects can be established.

UKMEC indicates that a history of VTE or known thrombogenic mutations are conditions where the advantages of using the progestogen-only injectable outweigh the theoretical or proven risks (UKMEC 2) and are therefore a potential option for women with these conditions.[2]

Women with systemic lupus erythematosus (SLE) are at increased risk of a number of cardiovascular conditions such as ischaemic heart disease, stroke and VTE. It is for this reason

that greater caution is advised in women with SLE and positive or unknown antiphospholipid antibodies (UKMEC 3) than women who have a history of VTE (UKMEC 2).[2] A UKMEC category 3 does not exclude use of the method, but the provision requires expert clinical judgement and/or referral to a specialist contraceptive provider, since use is not usually recommended unless other more appropriate methods are not available or not acceptable.[2]

Cardiometabolic parameters

A small, 18-week prospective study[72] designed to examine the short-term effects of SC DMPA on cardiometabolic markers in obese and normal weight women reported that amongst obese women there was a significantly greater decline in beta-cell compensation for insulin resistance (1.88 vs –2.86, p=0.04). Limitations of the study included the small sample size (n=15) and a control group who were not using contraception. A Cochrane review[73] examined data from 31 RCTs to examine whether hormonal contraceptive use affected carbohydrate metabolism in healthy women and overweight women at risk of diabetes. There were few data available for progestogen-only injectables, and one study showed a higher mean fasting glucose, glucose 2-hour response, and fasting insulin level amongst DMPA users compared to those using NET-EN. Overall the review suggested that there was little evidence on which to draw conclusions about the impact of hormonal contraceptives in women with diabetes. In women without diabetes, there did not appear to be any major differences in terms of carbohydrate metabolism.

No studies were identified comparing SC and IM DMPA with regard to cardiovascular parameters.

Lipids

DMPA has been shown to negatively affect lipid profiles in the few studies that have prospectively followed women starting DMPA, while taking into account possible confounders such as diet.[74,75] A prospective cohort study[75] of 703 women of different ethnicities, who self-selected either DMPA, a COC or a non-hormonal contraceptive, found that levels of high-density lipoprotein cholesterol (HDL-C) initially decreased and the ratio of low-density lipoprotein cholesterol to HDL-C increased from baseline to the 6-month measurement. However, the levels returned to baseline values over 24 months of DMPA use.

Myocardial infarction and stroke

Progestogen-only injectable use does not appear to be associated with an increased risk of myocardial infarction (MI) or stroke. An international hospital-based case-control study[66] comparing progestogen-only injectable users and non-users reported that current use did not affect risk of combined cardiovascular disease, risk of stroke, or MI.

Stroke or ischaemic heart disease (current/history) are UKMEC 3 conditions for use of the progestogen-only injectable[2] (see Table 1 on page 3).

B A causal association between DMPA and venous thrombosis has not been demonstrated in the small number of studies that have investigated this relationship.

B From the limited evidence available it is not possible to confirm or exclude an association between progestogen-only injectable use and MI or stroke.

5.2.4 Cervical cancer

The primary cause of the most common types of cervical cancer is the human papillomavirus (HPV), with persistent exposure increasing a woman's risk of developing precancerous conditions or cervical cancer. Numerous observational studies have investigated whether an association between DMPA use and cervical cancer or cervical dysplasia exists.[76–83]

A systematic review[84] that pooled analysis from three case-control studies suggested that with less than 5 years of DMPA use there was no statistically significant increased risk of developing cervical cancer. Pooled analysis from two case-control studies suggested a possible increased risk with use of 5 years or more (RR 1.2, 95% CI 1.0–1.6). A reanalysis of epidemiological data[85] also found a small significant increased risk of invasive cervical cancer (RR 1.22, 95% CI 1.01–1.46) in those women who had used DMPA for more than 5 (mean 8.8) years; this was lower than for women in the same studies who had used COCs (RR 1.54, 95% CI 1.39–1.71), and lower than the RR calculated for COCs from a pooled analysis of 24 observational studies worldwide (RR 1.90, 95% CI 1.69–2.13).

A population-based cohort[80] of over 12 000 women reported, after controlling for confounding factors such as age and number of sexual partners, that no evidence was found of an association between use of hormonal contraception or length of use and increased risk of high-grade cervical intraepithelial neoplasia (CIN) lesions or high-risk HPV infection. It was suggested that any observed risk may be a consequence of differences in lifestyle and sexual behaviours between users of hormonal contraceptives and non-users. Conversely, a smaller case-control study[76] reported that hormonal contraception, including DMPA use on its own, conferred some risk of cervical dysplasia but that factors such as sexual partners, alcohol consumption and parity may modify or confound the effect.

Two case-control studies reported that among women who were positive for oncogenic HPV, use of DMPA was not associated with an increased risk of CIN1 or greater.[86]

Use of the progestogen-only injectable (DMPA or NET-EN) is a UKMEC category 2 in women with CIN or cervical cancer (awaiting treatment) (i.e. the advantages of using the method generally outweigh the theoretical or proven risks).[2]

B There is a weak association between cervical cancer and use of DMPA for 5 years or longer. Any increased risk appears to reduce with time after stopping and could be due to confounding factors.

✓ Health professionals should check that women requesting DMPA are up-to-date with cervical cytology screening and, if relevant, have completed the HPV vaccination programme.

✓ Women should be informed about the link between HPV and cervical cancer, and advised about strategies that reduce the risk such as condom use, smoking cessation, regular cervical screening and, where appropriate, vaccination against HPV.

5.3 Side effects

Informing women about potential side effects may help continuation rates. In a study[87] of 430 women starting DMPA it was found that those who were informed of efficacy and potential side effects, such as bleeding changes, and advised to return to the clinic if they had any problems, were more likely to continue the method than those who were not informed.

This document highlights a selection of side effects that are important or may be of particular concern to women. It is not exhaustive. The Summary of Product Characteristics (SPC)[5,7] for each contraceptive product lists a number of undesirable effects that were noted in a large clinical trial. Side effects are also listed in the manufacturer's patient information leaflets (available at http://www.medicines.org.uk/emc/). Side-effect profiles for subcutaneous DMPA are broadly similar to those of intramuscular DMPA.[88]

5.3.1 *Altered bleeding patterns*

Altered bleeding patterns (amenorrhoea, infrequent bleeding, spotting, prolonged bleeding) are commonly experienced by women using DMPA[89–91] but there is a trend towards less bleeding and amenorrhoea with increased duration of use.[89,90] In a multicentre Phase III RCT comparing two doses of DMPA administered every 3 months, 1156 women provided a menstrual diary. Amenorrhoea, as defined as no bleeding or spotting in 90 days, increased from 9% and 10% of women at 3 months to 41% and 47% at 1 year for the 100 and 150 mg doses, respectively.[90] Altered bleeding patterns are commonly cited as a reason for DMPA discontinuation,[91–95] therefore as a matter of good practice women should be informed that changes to bleeding patterns are common. Advice on the management of unscheduled bleeding is provided later in this document (page 19) and within existing FSRH guidance.[96]

The SPCs for IM and SC DMPA[5,6] indicate that DMPA should be used with caution in the puerperium because of the potential to alter bleeding. Two low-quality, non-randomised studies have reported an increased number of bleeding days in women using DMPA in the puerperium.[97,98] Only one of the studies used an appropriate control group.[97] In that study the bleeding was not considered heavy and was not associated with anaemia.[97] Further evidence is required to substantiate an association between DMPA and altered bleeding in the puerperium. FSRH guidance advises that women should be informed of the potential for troublesome bleeding but use of DMPA in the postpartum period should not be restricted for this reason.[2,99]

5.3.2 *Weight gain*

DMPA use can be associated with weight gain, and this is often reported as a reason for method discontinuation.[92,94,95,100] Higher initial BMI is predictive of weight gain with DMPA use in adolescents (aged <18 years).[101] Significantly greater weight gain has been observed in new adolescent users of progestogen-only injectables compared to COC users, non-hormonal contraception users and discontinuers of any of the methods studied.[102] The association between weight gain and higher BMI at initiation of DMPA has not been observed in adult women.[103]

The available evidence suggests that women who experience an increase of more than 5% of their starting weight within the first 6 months of use are likely to continue to experience weight gain.[87,88]

Unlike some other guidelines[104,105] that differentiate between young women with a BMI under or over 30 kg/m^2, UKMEC does not advise any restriction on the use of the progestogen-only injectable in women with obesity.[2]

B Use of DMPA appears to be associated with weight gain, particularly in women under 18 years of age with a BMI ≥30kg/m^2.

C Women who gain more than 5% of their baseline body weight in the first 6 months of DMPA use are likely to experience continued weight gain.

5.3.3 *Injection site reactions*

Injection site reaction is listed as a commonly reported undesirable effect in the SPC for both IM[5] and SC DMPA.[6] Injection site reactions appear to be more common in SC than in IM users.[88] With SC DMPA reaction rates ranging from 1.6% to 21% have been reported.[9,88,106,107] These reactions were generally regarded as mild to moderate. In a pilot study examining the feasibility of self-administration of SC DMPA, skin changes, including indurations, scarring and atrophy, were observed in 9% of participants.[106]

B Injection site reactions appear to be more common with use of SC DMPA than with use of IM DMPA.

5.3.4 *Diffuse hair loss (alopecia)*

Diffuse hair loss may be associated with hormonal changes and certain drugs. No studies were identified that investigated the risk of hair loss associated with use of DMPA; however, hair loss has been cited as a side effect/reason for discontinuation of DMPA.[93,108,109] The SPC[5] for Depo-Provera indicates that alopecia was a commonly (≥1% and <10%) reported undesirable effect noted in a large clinical trial.

5.3.5 *Headache*

Headaches are common among the general population, making it difficult to assess the impact of any hormonal contraceptive on their development. A number of studies have reported headache as a possible side effect with use of the injectable contraceptive.[91,93,110,111] In an early comparative study by WHO[110] headaches were reported in around 11% of DMPA users, and the proportion of DMPA users complaining of headache at each study visit was statistically significantly increased over the 1-year study period from 8.5% at the first visit to 15.7% at the fourth visit ($p<0.01$).

5.3.6 *Mood change*

A prospective cohort study[112] of DMPA users ($n=183$) and non-users ($n=274$) sought to examine depressive symptoms over a 3-year period. Compared to non-users, those who used DMPA but discontinued were more likely to have experienced depressive symptoms (OR 1.66, 95% CI 1.03–2.48). However, those who continued to use DMPA were also more likely than non-users to have experienced such symptoms in the past (OR 1.44, 95% CI 1.00–2.07). Those who discontinued use of DMPA had increased depressive symptoms immediately before (OR 2.30, 95% CI 1.42–3.70) and after (OR 2.46, 95% CI 1.46–4.14) discontinuation.[112]

Another cohort study[113] of 495 women reported that baseline depressive symptom scores were higher amongst those women who discontinued DMPA or were lost to follow-up compared to those who continued to use the method. No increase in depressive symptoms was reported, even amongst those who were the most depressed at baseline; in fact there appeared to have been a slight improvement.

A case-control study[114] of 39 adolescent DMPA users and 24 non-hormonal contraceptive users did not demonstrate an increase in depressive symptoms amongst DMPA users or any significant changes in mood, either positive or negative, as measured using standardised tools.

In a nested cohort study[115] of 328 adolescents, higher levels of negative mood in users of DMPA were noted when compared to periods of no use. There was no difference observed in positive mood. Another cohort study[116] reported no significant differences or changes in the incidence of depression in adolescents using DMPA.

5.3.7 *Vasomotor symptoms*

No evidence was identified examining the effect of SC or IM DMPA on vasomotor symptoms.

5.3.8 *Libido and sexual function*

Decreased sexual interest[111,115] has been noted in clinical trials but a causal association has not been demonstrated.

5.3.9 *Vaginitis*

Although listed as a common undesirable effect within the SPC for IM DMPA,[5] no evidence was identified to confirm an association.

C Whilst there is little evidence available to demonstrate causation, a number of possible side effects such as acne, decreased libido, mood swings, headache, hot flushes and vaginitis have been reported with use of DMPA.

6 How Long Can Women Use Progestogen-only Injectable Contraceptives?

There is no upper limit for duration of use of the progestogen-only injectable.

Progestogen-only injectable users should be advised to return on the date their next injection is due, or sooner if they experience any adverse reactions or intolerable side effects. In line with other contraceptive methods, an annual prescription can be given. At each visit the health professional administering the injectable should assess the time since last injection, bleeding pattern, changes in sexual health, and check that women still fulfil the medical eligibility criteria. Long-term users should be reviewed at least every 2 years by a prescriber. In deciding whether continued use is appropriate the prescriber should assess risks, benefits and user preferences.(see BMD section on page 4).

7 How Should Progestogen-only Injectables be Administered?

IM DMPA is an aqueous suspension that usually comes in a pre-filled syringe. The syringe should be shaken vigorously before use to ensure the dose being given represents a uniform suspension.[5]

The SPC for IM DMPA states that it should be administered by deep IM injection into muscle tissue, preferably the gluteus maximus but other muscle such as the deltoid (upper arm) may be used.[5] Traditionally the dorsogluteal site (upper outer quadrant of the buttock) has been used. The ventrogluteal site (lateral thigh) has been investigated as an alternative site because the risk of sciatic nerve injury is reduced[117,118] and the fat layer is thinner than in the dorsogluteal area. However, in women who are classified as overweight or obese it may be difficult to ensure IM administration in either the dorso- or ventrogluteal region. A retrospective study of 100 adults reported that using standard-length 'green' 21-gauge needles into the ventrogluteal site resulted in 12% of injections being SC rather than IM, and that in the dorsogluteal site 43% of injections failed to reach the muscle. For standard-length 'blue' 23-gauge needles the proportions were higher (26% and 72%, respectively).[119]

If a clinician has been trained to administer IM injection in the ventrogluteal region this site may be considered in order to reduce the risk of sciatic nerve injury. If there are concerns about the ability to administer a deep IM injection due to body weight then the deltoid muscle in the upper arm may also be considered as an alternative site,[3,5] or SC DMPA would be a suitable alternative.

NET-EN is a thick, oily fluid. The manufacturer suggests that the ampoule is immersed in warm water before use to reduce viscosity.[7] Administration via fine-gauge needles should be avoided and the injection must be administered extremely slowly. The SPC states that NET-EN should always be injected deep into the gluteal muscle.

SC DMPA[6] is supplied in a pre-filled injector and according to the manufacturer's instructions should be administered at room temperature. It should be injected into the anterior thigh or abdomen, avoiding bony areas or the umbilicus.[6] The single-dose container should be shaken vigorously before use. Health professionals should refer to the manufacturer's advice for detailed instructions on administration (www.medicines.org.uk/emc).[6]

Data from cohort studies suggest that self-administration of SC DMPA is feasible[106,107,120,121], convenient[107] and acceptable to women.[106,107] A small pilot study[106] reported that there was no significant difference in continuation rates at 12 months when self-administration was compared with health professional administration, although injection site reactions may be greater.

SC DMPA can now be self-administered by women who have been appropriately trained. While rare, anaphylactic reaction is possible with both first and subsequent exposures to Sayana Press. It is therefore recommended that users are advised to ensure there is a competent adult present at the time of self-administration who is aware that they should call for emergency help at the time of onset of any relevant symptoms.

C The gluteal muscle in the buttock is the preferred site for IM DMPA administration but it can be administered into the deltoid muscle of the upper arm. In women with deep adipose tissue in the gluteal area, standard-length needles may not reach the muscle layer and SC DMPA or deltoid administration of IM DMPA should be considered.

C SC DMPA should be injected into the abdomen or anterior thigh.

7.1 What clinical assessment and documentation is required?

The FSRH *Standards for Sexual Health Services*[23,122] detail the appropriate recommendations for training, resuscitation and record-keeping in relation to progestogen-only injectable contraception. Assessment of BMI should be undertaken in order to make decisions about site of administration and needle length (see page 9).

8 When in the Menstrual Cycle Can Progestogen-only Injectable Contraceptives be Started?

The SPC[5] advises that DMPA can be started up to Day 5 without additional contraceptive precautions. This advice may be overcautious, as there is evidence to suggest that ovulation is suppressed when DMPA is started up to Day 7 of the menstrual cycle.[11,12,123]

If quick starting beyond Day 5 a woman may start progestogen-only injectable contraceptives at any time if it is reasonably certain that she is not pregnant (Box 1). Women requesting the progestogen-only injectable following emergency contraception (EC) should ideally be offered an oral contraceptive as a temporary bridging method.[124] However, if such methods are not appropriate or not acceptable, immediate start of the progestogen-only injectable after levonorgestrel 1.5mg or start of the progestogen-only injectable 5 days after ulipristal acetate 30mg for emergency contraception (UPA- C) can be considered.[124] See Table 2. After quick starting, pregnancy testing no sooner than 3 weeks after the last episode of unprotected sexual intercourse (UPSI) is important to avoid any potential delay in diagnosis of pregnancy that may occur if amenorrhoea is assumed to be due to the contraceptive method, or if bleeding caused by the method is mistaken for a period. Further information on quick starting is provided in the FSRH *Quick Starting Contraception* guidance.[124]

For the purposes of excluding pregnancy, the CEU would advise that hormonal, intrauterine and barrier methods can be considered reliable providing they have been used consistently and correctly on every incidence of intercourse. This should be assessed on an individual basis.

Box 1 Criteria for excluding pregnancy

Health professionals can be 'reasonably certain' that a woman is **not currently pregnant** if any one or more of the following criteria are met **and** there are no symptoms or signs of pregnancy:

- She has not had intercourse since the start of her last normal (natural) menstrual period, since childbirth, abortion, miscarriage, ectopic pregnancy or uterine evacuation for gestational trophoblastic disease.
- She has been correctly and consistently using a reliable method of contraception. (For the purposes of being reasonably certain that a woman is not currently pregnant, barrier methods of contraception can be considered reliable providing that they have been used consistently and correctly for every episode of intercourse.)
- She is within the first 5 days of the onset of a normal (natural) menstrual period.
- She is less than 21 days postpartum (non-breastfeeding women).
- She is fully breastfeeding, amenorrhoeic **AND** less than 6 months postpartum.
- She is within the first 5 days after abortion, miscarriage, ectopic pregnancy or uterine evacuation for gestational trophoblastic disease.
- She has not had intercourse for 21 days **AND** has a negative high-sensitivity urine pregnancy test (able to detect hCG levels around 20 mIU/ ml).

Table 2 Faculty of Sexual & Reproductive Healthcare advice on starting progestogen-only injectable contraception

Circumstances	Starting day	Additional contraceptive protection required?	Any additional information
Women having menstrual cycles	Day 1-5 of cycle	**No**	It is advisable to check that the menstrual period is typical of the woman s usual bleeding pattern in terms duration, heaviness and timing.
	After Day 5 of cycle	**Yes** (7 days)	If there has been a risk of pregnancy consider EC and quick starting (see below)[c]
Women who are amenorrhoeic	Any time if it is reasonably certain she is not pregnant	**Yes** (7 days)	If there has been a risk of pregnancy consider EC and quick starting (see below)[c]
Postpartum[a]	≤21 days postpartum	**No**	
	>21 days if menstrual cycles have returned	Start as for other women having menstrual cycles	If there has been a risk of pregnancy consider EC and quick starting (see below)[c]
	>21 days postpartum if menstrual cycles have not returned	**Yes** (7 days)	If there has been a risk of pregnancy consider EC and quick starting (see below)[c]
Post first- or second-trimester abortion	Up to and including Day 5[b]	**No**	The injectable can be initiated after the first part of a medical abortion[125–127] (please see FSRH guideline Contraception After Pregnancy)
	At any other time if it is reasonably certain she is not pregnant	**Yes** (7 days)	
Quick starting after oral EC **OR** in other situations in which pregnancy cannot be excluded[c]	If pregnancy cannot be excluded ideally use a bridging method until negative PT at 3 weeks. If bridging method inappropriate or unacceptable consider quick starting injectable with advice to use additional precaution for 7 days after injection and pregnancy test no sooner than 3 weeks after most recent UPSI. Note that after UPA-EC, quick start should be delayed for 5 days.		

[a]Prior to 6 weeks postpartum use of DMPA in breastfeeding women is UKMEC 2.
[b]The FSRH advises that women ideally start on the day or day after a first- or second-trimester abortion.
[c]See FSRH guidance on *Quick Starting Contraception*.[124]
EC, emergency contraception; LNG, levonorgestrel; UPA, ulipristal acetate; UPSI, unprotected sexual intercourse.

8.1 Switching from another method

Advice on starting the injectable and switching from other methods of contraception is summarised in Tables 2 and 3, respectively. Consideration of EC and a pregnancy test no sooner than 3 weeks after the most recent incidence of UPSI may be required if there has been a risk of pregnancy.

8.2 When should repeat injections be administered?

The dosing intervals advised in the SPCs of IM DMPA, SC DMPA and NET-EN are 12 weeks,[5] 13 weeks[6] and 8 weeks,[7] respectively. When administered every 12 weeks the failure rate of DMPA is very low (<4/1000 over 2 years).[17–19] The failure rate is lower with DMPA than NET-EN.[17] Even when DMPA is administered every 16 weeks the rate of pregnancy is less than 1%.[126]

The FSRH has advised that injections can be administered up to 14 weeks and 10 weeks from the last DMPA and NET-EN injections respectively (Table 4).[1,127] The SPC for Sayana Press advises that SC DMPA can be given 1 week late (up to 14 weeks).[6] WHO recommendations changed in 2008 to advise that the injectable can be given up to 16 weeks after the last injection without any effect on efficacy.[128]

The guideline development group preferred to take a more cautious approach than WHO and to leave FSRH advice on late IM DMPA and NET-EN unchanged. The group agreed for consistency to recommend a dosing interval of 13 weeks for both IM DMPA (outside terms of product licence) and SC DMPA.

Table 3 Faculty of Sexual & Reproductive Healthcare advice when switching from another contraceptive to progestogen-only injectable contraception

Situation	Starting	Additional contraceptive protection required?	Additional information
Switching from CHC (if taken correctly)	Day 1-2 of the HFI	**No**	
	Day 3-7 of HFI **OR** week 1 following the HFI	**Yes** (7 days). If UPSI has occurred after Day 2 of the HFI, advise continuing the CHC method for at least 7 days	When switching after a 7-day HFI there are no data to confirm that suppression of ovulation is maintained
	Week 2–3 of pill/ring/patch	**No**, providing the CHC method has been used consistently and correctly for 7 consecutive days before switching	There is evidence to suggest that taking hormonally active pills for 7 consecutive days prevents ovulation. Therefore as long as there have been 7 days of CHC use, 7 hormone-free days can occur without any effect on contraceptive efficacy
Switching from traditional POP (if taken correctly) **OR** LNG-IUS	Any time	**Yes** (7 days) **AND** If UPSI in last 7 days, retain LNG IUS for 7 days after starting injectable	The continuing method provides contraceptive cover while the effects of the injectable are established
Switching from desogestrel POP (if taken correctly) **OR** progestogen-only implant (3 years since implant insertion)	Any time	**No**	
>3 years since implant insertion	Any time	**Yes** (7 days)	If there has been a risk of pregnancy consider the need for EC and a PT no sooner than 3 weeks after the most recent incidence of UPSI
Switching from Cu-IUD	Day 1–5 of menstrual cycle Any other time	**No** **Yes (**7 days). If UPSI in last 7 days, retain Cu-IUD for 7 days	

CHC, combined hormonal contraception; Cu-IUD, copper intrauterine device; EC, emergency contraception; HFI, hormone free interval; POP, progestogen-only pill; PT, pregnancy test; UPSI, unprotected sexual intercourse

If the timing of a woman's previous DMPA injection is unknown, the injection can be given if it is reasonably certain that the woman is not pregnant. Additional contraceptive protection or avoidance of sex should be advised for the next 7 days. If there is a risk of pregnancy, the woman can be offered EC, a bridging method or quick started on the injectable, as appropriate[124] (see section on quick starting on page 12). A pregnancy test should be advised no sooner than 3 weeks after the most recent episode of UPSI.

Repeat injections can be given early if necessary.[127,129]

✓ Women should be advised to return every 13 weeks for a repeat injection of IM or SC DMPA (outside the product licence for IM DMPA).

B An injection of DMPA can be administered up to 7 days late (up to 14 weeks after the last injection) without the need for additional contraceptive precautions (outside the product licence for IM DMPA).

C If necessary, an early repeat injection of DMPA can be administered from 10 weeks and from 6 weeks for NET-EN (outside product licence).

Table 4 Faculty of Sexual & Reproductive Healthcare advice in relation to late progestogen-only contraceptive injections

Timing of injection	Has UPSI occurred?	Is there a risk of pregnancy?	Can EC be offered?	Can the injection be given?	Is additional contraception required?	Is a pregnancy test required?
Up to 14 weeks since last DMPA injection **OR** Up to 10 weeks since last NET-EN injection	**Yes**	**No**	**NA**	**Yes**	**No**	**No**
14 weeks + 1 day or more since last IM or SC DMPA injection **OR** 10 weeks + 1 day or more since last NET-EN injection	**No** (no sex or used barrier method)	**No**	**NA**	**Yes**	**Yes** (7 days after injection)	**No**
	Yes, but only in the last 5 days (sex that occurs up to Week 14 or Week 10 is protected)	**Yes**	**Yes.** Consider Cu-IUD or LNG EC. The effectiveness of UPA EC could theoretically be reduced by residual circulating progestogen.[a]	**Yes*** (if bridging method not acceptable).[a] * After LNG EC injection can be given immediately. After UPA EC, delay injection for 5 days.[a]	**Yes**(until 7 days after injection)	**Yes** ≥3 weeks since last episode of UPSI
	Yes – multiple episodes <5 days ago and >5 days ago	**Yes**	**Yes.** The effectiveness of UPA EC could theoretically be reduced by residual circulating progestogen.[a]	**Yes***(if bridging method not acceptable).[a] * After LNG EC injection can be given immediately. After UPA EC, delay injection for 5 days.[a]	**Yes** (until 7 days after injection)	**Yes**, prior to administering the injection and ≥3 weeks since last episode of UPSI
	Yes – multiple episodes >5 days ago and ≤3 weeks ago	**Yes**	**No**	**Yes** (if bridging method not acceptable).	**Yes** (until 7 days after injection)	**Yes**, prior to administering the injection and ≥3 weeks since last episode of UPSI
	Yes – multiple episodes >3 weeks ago	**Yes**	**No**	Perform a pregnancy test and if negative administer injectable	**Yes** (until 7 days after injection)	**Yes**, prior to administering the injection

[a] See FSRH guidance on Emergency Contraception[139]
CHC, combined hormonal contraception; Cu-IUD, copper intrauterine device; DMPA, depot medroxyprogesterone acetate; EC, emergency contraception; IM, intramuscular; LNG, levonorgestrel; NA, not applicable; NET-EN, norethisterone enantate; POP; progestogen-only pill; SC, subcutaneous; UPA, ulipristal acetate; UPSI, unprotected sexual intercourse.

9 What Advice Should be Given Regarding Exposure to Progestogen-only Injectable Contraception in Pregnancy?

The SPC for Depo-Provera[5] states that infants born from accidental pregnancies that occur 1–2 months after injection may be at increased risk of low birth weight and neonatal death. This is based on an observational study[130] of Thai DMPA users in which the authors acknowledge the difficulties of adjusting for confounding variables such as differences in antenatal care, socioeconomic status, smoking and alcohol use among DMPA users and controls. Longer-term follow-up of the same group of children showed no evidence of any adverse effects on their growth or pubertal development.[131] Other observational data have not shown any adverse effects on physical, intellectual, sexual or social development of children exposed to DMPA *in utero* and followed to adolescence.[132]

NICE LARC guidelines[3] recommend that if a pregnancy occurs while using progestogen-only injectable contraception women should be advised that there is no evidence of harm to the pregnancy or fetus. No studies were identified examining the risk of ectopic pregnancy associated with use of SC or IM DMPA.

10 Are there Any Factors that Would Affect the Efficacy of Progestogen-only Injectables?

10.1 Drug interactions

The SPCs for Depo-Provera[5] and Sayana Press[6] state that the clearance of DMPA is approximately equal to the rate of hepatic blood flow. For this reason, it is unlikely that drugs that induce hepatic enzymes will significantly affect serum levels of DMPA. Pharmacokinetic data from studies of antiretroviral drugs support this theory[133,134] and a non-systematic review of drug interactions between HIV medications and contraception has also concluded that the contraceptive efficacy of injectable DMPA is not affected.[135] Consequently the usual injection intervals for DMPA do not need to be reduced when using enzyme-inducing drugs.

FSRH guidance on *Drug Interactions with Hormonal Contraception*[136] recommends that NET-EN can be used with enzyme-inducing drugs without additional contraception or alteration of the dosing interval. UKMEC 2009[2] and WHOMEC[104] give more cautious advice for NET-EN than for DMPA based on the product licence.

Ulipristal acetate (UPA) is a progesterone receptor modulator that is licensed for use as an emergency contraceptive or in the management of uterine fibroids.[137,138] Because UPA has predominantly inhibitory effects on the progesterone receptor, it could in theory reduce the efficacy of progestogen-containing contraceptives or vice versa.[137,138] imited evidence from biomedical studies suggests that effectiveness of oral hormonal contraception is not affected by use of ulipristal acetate 30mg for emergency contraception. The effectiveness of ulipristal acetate 30mg for emergency contraception could however be reduced by concomitant use of progestogen. See FSRH guideline Emergency Contraception[139]. The SPC for UPA for the management of uterine fibroids[138] advises against concomitant use with progestogen-containing contraceptives.

B The efficacy of DMPA is not reduced with concurrent use of enzyme-inducing drugs.

10.2 Weight

Very few studies have specifically examined the effectiveness of progestogen-only injectables in women who are classified as obese or 'heavy' as compared with women of 'normal' BMI or of lighter weight. An early comparative study of 'thin' and obese users of progestogen-only injectables did not find any difference between the groups of women in terms of rate of return of ovarian activity or hormone serum levels.[140] However, in this study the greatest BMI was approximately 37 kg/m^2 and the average weight in the DMPA group was 79.2 kg (range 69–98 kg). A subsequently published pharmacokinetic study conducted in eight women found no correlation between the time when hormone levels from a single dose of 150 mg DMPA became undetectable and obesity index as measured by weight (kg)/height (cm) x100. Women weighed between 59 and 78 kg.[141] Results from a 26-week prospective study[142] reported that levels of MPA, although high enough to suppress ovulation, were lower in obese women, particularly those with a BMI ≥40 kg/m^2 compared with women of 'normal weight' (BMI 18.5–24.9 kg/m^2) after receiving an injection of SC DMPA. In one extremely obese woman, levels were found to be just below the therapeutic level during the first 2 months following her first injection. The authors called for more research as the study was limited by its small sample size.

B No increased risk of pregnancy has been demonstrated in progestogen-only injectable users with higher body weight, although data are limited in women with a BMI ≥40 kg/m^2.

11 Other Considerations

11.1 Return of fertility

Non-comparative studies[141,143–146] have reported evidence of ovulation within 6 months after the last DMPA injection. A pharmacokinetic study[9] using serum progestogen levels as a marker of ovulation found that the majority of women (38/39 and 18/19, respectively) following a single injection of either SC or IM DMPA had ovulated by 12 months. The median time to return of ovulation for those who ovulated during the 12-month follow-up was 212 (range 106–358) days for the SC DMPA group and 183 (range 70–315) days for the IM DMPA group.[9] The difference was not statistically significant.[9]

Although a large cohort study[147] identified a mean delay from discontinuation of DMPA to conception of 5.5 months (compared to 4.5 months for Cu-IUD users), there were no significant differences in cumulative pregnancy rates 2 years after stopping the methods.

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.[3] As there is wide inter-individual variation in return of fertility, women who do not wish to conceive should be advised to start another contraceptive method before or at the time of the next scheduled injection. No evidence was identified that examined whether duration of use influenced return of ovulation.

✓ Women who discontinue their progestogen-only injectable and who do not wish to conceive should be advised to start another contraceptive method before or at the time of their next scheduled injection even if amenorrhoeic.

C Women should be informed that there can be a delay of up to 1 year in the return of fertility after discontinuation of IM or SC DMPA.

11.2 Emergency contraception

EC may need to be considered if a woman does not follow the relevant advice in relation to additional precautions when starting the progestogen-only injectable or if a woman does not receive a repeat injection until 14 weeks after the last injection (10 weeks for NET-EN) (Table 4). A copper IUD can be inserted for EC up to 5 days after earliest UPSI or 5 days from expected date of ovulation. A copper IUD can therefore be inserted within 5 days of the first UPSI. The earliest date of ovulation after a missed injection cannot be accurately estimated.

For advice regarding choice of oral emergency contraception and administration of DMPA after ulipristal acetate 30mg for emergency contraception (UPA-EC), please see Table 2 and Table 4. See also FSRH Guideline Emergency Contraception.[139]

11.3 Sexually transmitted infections and testing

Assessment of women attending for progestogen-only injectable contraception should include a sexual history and sexually transmitted infection (STI) risk assessment.[148] An STI screen should be offered, and should be advised if there has been a risk of STI exposure or symptoms such as altered bleeding.

Several observational studies[149,150] have reported a statistically significant increased risk of HIV acquisition and transmission associated with use of the progestogen-only injectable or worsening of HIV outcomes; others[151–153] have not. Following an extensive systematic review and consultation, the WHO's position is that a causal relationship cannot be entirely excluded but that there is currently insufficient evidence to change their current medical eligibility criteria for women at high risk of HIV or living with HIV.[154] Women requesting the progestogen-only injectable should be informed about safer sex and that the consistent and correct use of condoms provides an effective means of protecting against HIV and other STIs.[154]

B The consistent and correct use of condoms (male or female) can reduce the risk of STI transmission and should therefore be recommended as a risk-reduction strategy.

B A causal relationship between progestogen-only injectable contraception and HIV transmission/acquisition has not been established but cannot be completely excluded.

12 How Should Common Problems Associated with DMPA Use be Managed?

12.1 Problematic bleeding

In addition to consideration of STIs, women with persistent problematic bleeding (or with bleeding after a period of amenorrhoea) should have gynaecological pathology excluded.[96] Health professionals should enquire about the woman's cervical screening history and if appropriate (based on national screening guidelines) perform a cervical cytology test.

Although regimens such as estrogen supplementation or tranexamic acid may help to reduce bleeding induced by progestogen-only contraceptives in the short term,[151–153] there is insufficient evidence to support routine use long-term.[136]

Guidance on the *Management of Unscheduled Bleeding in Women using Hormonal Contraception*[96] is available from the FSRH. It states that women who are medically eligible can be offered a COC for 3 months or that mefenamic acid 500 mg can be given up to three times a day for 5 days. There is no evidence looking at the benefits/risks of COC use long-term in conjunction with DMPA. If unscheduled bleeding recurs after 3 months of COC, the decision to restart COC is a matter of clinical judgement.

No studies were identified that examined whether or not reducing the injection interval helps with unscheduled bleeding. However, for women who experience bleeding towards the end of the injection interval, FSRH guidance would suggest that the injection can be given from 10 weeks after the last injection (see section on early administration on page 15).[96]

✓ Women who experience unscheduled bleeding during use of a progestogen-only injectable and who are medically eligible can be offered a COC for 3 months. This can be taken in the usual cyclic manner or continuously without a hormone-free interval (outside product licence). Longer-term use of the injectable and COC has not been studied and is a matter of clinical judgement.

B Women with unscheduled bleeding during use of a progestogen-only injectable contraceptive can be offered 500 mg mefenamic acid up to three times daily for 5 days.

12.2 Injectable contraception and women with epilepsy, a learning disability, or HIV

For women taking antiepileptic or antiretroviral drugs that induce liver enzymes DMPA may be an appropriate method of contraception because its efficacy is unaffected.

However, in 2009 the MHRA[155] highlighted that women who take carbamazepine, phenytoin, primidone or sodium valproate long term and who are immobilised for long periods and have inadequate sun exposure or dietary calcium may be at an increased risk of developing osteopenia, osteoporosis and fractures: NICE recommends vitamin D supplementation for such women. Therefore, whilst DMPA is a useful and effective contraceptive for women using antiepileptic medications, the individual benefits and risks and the availability/suitability of other options will need to be considered carefully in those individuals who are immobile or have other risk factors.

Individuals living with HIV have been reported to be more prone to lower BMD and osteopenia compared with those who do not have HIV.[156] The European AIDS Clinical Society Guidelines[157] quote prevalence figures of around 60% for osteopenia and 10–15% for osteoporosis. The aetiology is thought to be multifactorial. Initiation of highly active antiretroviral therapy has been shown to be associated with an initial loss in BMD, which is thought to stabilise thereafter.[158] Such factors may need to be taken into account when deciding on the most appropriate contraceptive option for women living with HIV, or when assessing continued use long-term.

DMPA is commonly prescribed in women with learning disabilities, often because of use of antiepileptic drugs or to reduce menstrual bleeding. Contraceptive options for women with a disability are as for other women. For those with a learning disability the primary additional consideration will be the woman's capacity to consent to use of her chosen contraceptive. Her ability to comply with her chosen regimens may also be a factor.

References

1 Faculty of Sexual & Reproductive Health Care. *Progestogen-only Injectable Contraception*. 2008. http://www.fsrh.org/admin/uploads/CEUGuidanceProgestogenOnlyInjectables09.pdf [Accessed 27 November 2014].

2 Faculty of Sexual & Reproductive Health Care. *UK Medical Eligibility Criteria for Contraceptive Use* (UKMEC 2009). 2009. http://www.fsrh.org/pdfs/UKMEC2009.pdf [Accessed 27 November 2014].

3 National Institute for Health and Clinical Excellence (NICE). *Long-acting Reversible Contraception: The Effective and Appropriate Use of Long-acting Reversible Contraception*. 2005. http://www.nice.org.uk/pdf/CG030fullguideline.pdf [Accessed 27 November 2014].

4 National Institute for Health and Care Excellence (NICE). *Long-acting Reversible Contraception* (Update). 2014. http://www.nice.org.uk/guidance/cg30/resources/guidance-longacting-reversible-contraception-update-pdf [Accessed 27 November 2014].

5 Pfizer Limited. Depo-Provera 150mg/ml Injection. 2014. https://www.medicines.org.uk/emc/medicine/11121 [Accessed 27 November 2014].

6 Pfizer Limited. SAYANA PRESS 104 mg/0.65 ml suspension for injection: Summary of Product Characteristics. 2014. https://www.medicines.org.uk/emc/medicine/27798/SPC/SAYANA+PRESS+104+mg+0.65+ml+suspension+for+injection/ [Accessed 27 November 2014].

7 Bayer plc. Noristerat: Summary of Product Characteristics. 2009. http://www.emc.medicines.org.uk [Accessed 27 November 2014].

8 Mishell DR Jr. Pharmacokinetics of depot medroxyprogesterone acetate contraception. *J Repod Med* 1996; **41:** 381–390.

9 Jain J, Dutton C, Nicosia A, Wajszczuk C, Bode FR, Mishell DR Jr. Pharmacokinetics, ovulation suppression and return to ovulation following a lower dose subcutaneous formulation of Depo-Provera. *Contraception* 2004; **70:** 11–18.

10 Ortiz A, Hirol M, Stanczyk FZ, Goebelsmann U, Mishell DR. Serum medroxyprogesterone acetate (MPA) concentrations and ovarian function following intramuscular injection of depo-MPA. *J Clin Endcrinol Metab* 1977; **44:** 32–38.

11 Petta CA, Faundes A, Dunson TR, Ramos M, DeLucio M, Faundes D, *et al*. Timing of the onset of contraceptive effectiveness in Depo-Provera users. II Effects on ovarian function. *Fertil Steril* 1998; **70:** 817–820.

12 Kapp N, Gaffield ME. Initiation of progestogen-only injectables on different days of the menstrual cycle and its effect on contraceptive effectiveness and compliance: a systematic review. *Contraception* 2013; **87:** 576–582.

13 Petta CA, Faundes A, Dunson TR, Ramos M, DeLucio M, Faundes D, *et al*. Timing of the onset of contraceptive effectiveness in Depo-Provers users; Part I. Changes in cervical mucus. Fertil Steril 1998; **69:** 252–257.

14 Gold MA. Contraception update: implantable and injectable methods. *Pediatr Ann* 1995; **24:** 203–207.

15 Fraser IS, Weisberg EA. A comprehensive review of injectable contraception with special emphasis on depot medroxyprogesterone acetate. *Med J Aust* 1981; **24:** 3–19.

16 Bhathena RK. The long-acting progestogen-only contraceptive injections: an update. *BJOG* 2001; **108:** 3–8.

17 Task Force on Long-Acting Systemic Agents for Fertility Regulation Special Programme of Research, Development and Research Training in Human Reproduction. Multinational comparative trial of long-acting injectable contraceptives: norethisterone enanthate given in two dosage regimens and depot-medroyproegesterone acetate. Final Report. *Contraception* 1983; **28:** 1–20.

18 Chinnatamby S. A comparison of the long-acting contraceptive agents norethisterone oenanthate and medroyprogesterone acetate. *Aust N Z J Obstet Gynaecol* 1971; **11:** 233–236.

19 Sekadde-Kigondu C, Mwathe EG, Ruminjo JK, Nichols D, Katz K, Jessencky K, *et al*. Acceptability and discontinuation of Depo-Provera, IUCD and combined pill in Kenya. *East Afr Med J* 1996; **73:** 786–794.

20 Winner B, Peipert JF, Zhao Q, Buckel C, Madden T, Allsworth JE, *et al*. Effectiveness of long-acting reversible contraception. *N Engl J Med* 2012; **366:** 1998–2007.

21 Trussell J. Contraceptive failure in United States. *Contraception* 2011; **83:** 397–404.

22 Mavranezouli I. The cost-effectiveness of long-acting reversible contraceptive methods in the UK: analysis based on a decision-analytic model developed for a NICE clinical practice guideline. *Hum Reprod* 2008; **23:** 1338–1345.

23 Faculty of Sexual & Reproductive Healthcare Clinical Standards Committee. *Service Standards for Record Keeping*. 2010. http://www.fsrh.org/pdfs/ServiceStandardsRecordKeeping.pdf [Accessed 27 November 2014].

24 Wanyonyi SZ, Stones WR, Sequeira E. Health-related quality of life changes among users of depot medroxyprogesterone acetate for contraception. *Contraception* 2012; **84:** e17–e22.

25 Adaji SE, Shittu SO, Sule ST. Attitude of Nigerian women to abnormal menstrual bleeding from injectable progestogen-only contraceptive. *Ann Afr Med* 2005; **4:** 144–149.

26 National Institute for Health and Clinical Excellence (NICE). *Heavy Menstrual Bleeding*. 2007. http://www.nice.org.uk/guidance/cg44/resources/guidance-heavy-menstrual-bleeding-pdf [Accessed 27 November 2014].

27 Crosignani PG, Luciano A, Ray A, Bergqvist A. Subcutaneous depot medroxyprogesterone acetate versus leuprolide acetate in the treatment of endometriosis-associated pain. *Hum Reprod* 2006; **21:** 248–256.

28 Vercellini P, De Giorgi O, Oldani S, Cortesi I, Panazza S, Crosignani PG. Depot medroxyprogesterone acetate versus oral contraceptive combined with very-low dose danazol for long-term treatment of pelvic pain associated with endometriosis. *Am J Obstet Gynecol* 1996; **175:** 396–401.

29 Wong AYK, Tang LCH, Chin RKH. Levonorgestrel-releasing intrauterine system (Mirena) and depot medroxyprogesterone acetate (Depoprovera) as long-term maintenance therapy for patients with moderate and severe endometriosis: a randomised controlled trial. *Aust N Z J Obstet Gynaecol* 2010; **50:** 273–279.

30 Walch K, Unfried G, Huber J, Kurz C, van Trotsenburg M, Pernicka E, *et al*. Implanon versus medroxyprogesterone acetate: effects on pain scores in patients with symptomatic endometriosis – a pilot study. *Contraception* 2009; **79:** 29–34.

31 European Society for Human Reproduction and Embryology. Guideline on the management of women with endometriosis. *Hum Reprod* 2014; **29:** 400–412.

32 Wilailak S, Vipupinyo C, Suraseranivong V, Chotivanich K, Kietpeerakool C, Tanapat Y, *et al*. Depot medroxyprogesterone acetate and epithelial ovarian cancer: a multicentre case-control study. *BJOG* 2012; **119:** 672–677.

33 Silpisornkosol S, Pardthaisong T, Sahapong V, Theetranont C, Boosiri B, Chutivongse S, *et al*. Depot-medroxyprogesterone acetate (DMPA) and risk of endometrial cancer. The WHO Collaborative Study of Neoplasia and Steroid Contraceptives. *Int J Cancer* 1991; **49:** 186–190.

34 Liang AP, Levenson AG, Layde PM, Shelton JD, Hatcher RA, Potts M, *et al*. Risk of breast, uterine corpus, and ovarian cancer in women receiving medroxyprogesterone injections. *JAMA* 1983; **249:** 2909–2912.

35 Cuevas HR, Salazar SB, Palet A, Ontiveros P, Silpisornkosol S, Pardthaisong T, *et al*. Depot-medroxyprogesterone acetate (DMPA) and risk of epithelial ovarian cancer. The WHO Collaborative Study of Neoplasia and Steroid Contraceptives. *Int J Cancer* 1991; **49:** 191–195.

36 Haddad LB, Curtis KM, Legardy-Williams JK, Cwiak C, Jamieson DJ. Contraception for individuals with sickle cell disease: a systematic review of the literature. *Contraception* 2012; **85:** 527–537.

37 Legardy JK, Curtis KM. Progestogen-only contraceptive use among women with sickle cell anemia: a systematic review. *Contraception* 2006; **73:** 195–204.

38 Manchikanti A, Grimes DA, Lopez LM, Schulz KF. Steroid hormones for contraception in women with sickle cell disease. *Cochrane Database Syst Rev* 2007; **2:** CD006261.

39 Kaunitz AM, Arias R, McClung M. Bone density recovery after depot medroxyprogesterone acetate injectable contraception use. *Contraception* 2008; **77:** 67–76.

40 Albertazzi P, Bottazzi M, Steel SA. Bone mineral density and depot medroyprogesterone acetate. *Contraception* 2006; **73:** 577–583.

41 Shaarawy M, El-Mallah SY, Seoudi S, Hassan M, Mohsen IA. Effects of the long-term use of depot medroxyprogesterone acetate as hormonal contraceptive on bone mineral density and biochemical markers of bone remodeling. *Contraception* 2006; **74:** 297–302.

42 Cromer BA, Stager M, Bonny A, Lazebnik R, Rome E, Ziegler J, *et al*. Depot medroxyprogesterone acetate, oral contraceptives and bone mineral denisty in a cohort of adolescent girls. *J Adolesc Health* 2004; **35:** 434–441.

43 Gai L, Zhang J, Zhang H, Gai P, Zhou L, Liu Y. The effect of depot medroxyprogesterone acetate (DMPA) on bone mineral density (BMD) and evaluating changes in BMD after discontinuation of DMPA in Chinese women of reproductive age. *Contraception* 2011; **83:** 218–222.

44 Viola AS, Castro S, Marchi NM, Bahamondes MV, Viola CF, Bahamondes L. Long-term assessment of forearm bone mineral density in postmenopausal former users of depot medroxyprogesterone acetate. *Contraception* 2011; **84:** 122–127.

45 Harel Z, Johnson CC, Gold MA, Cromer B, Peterson E, Burkman R, *et al*. Recovery of bone mineral density in adolescents following the use of depot medroxyprogesterone acetate contraceptive injections. *Contraception* 2010; **81:** 281–291.

46 Scholes D, Lacroix AZ, Ichikawa LE, Barlow WE, Ott SM. Change in bone mineral density among adolescent women using and discontinuing depot medroxyproegesterone acetate contraception. *Arch Pediatr Adolesc Med* 2005; **159:** 139–144.

47 Clark MK, Sowers MF, Levy B, Nichols S. Bone mineral density loss and recovery during 48 months in first-time users of depot medroxyprogesterone acetate. *Fertil Steril* 2006; **86:** 1466–1474.

48 Tang OS, Tang G, Yip PS, Li B. Further evaluation on long-term depot-medroxyprogesterone acetate use and bone mineral density: a longitudinal cohort study. *Contraception* 2000; **62:** 161–164.

49 Lopez LM, Grimes DA, Schulz KF, Curtis KM, Chen M. Steroidal contraceptives: effect on bone fractures in women. *Cochrane Database Syst Rev* 2014; **6:** CD006033.

50 Lopez LM, Chen M, Mullins S, Curtis KM, Helmerhorst FM. Steroidal contraceptives and bone fractures in women: evidence from observational studies . *Cochrane Database Syst Rev* 2012; **8:** CD009849.

51 Vestergaard P, Rejnmark L, Mosekilde L. Fracture risk in very young women using combined oral contraceptives. *Contraception* 2008; **78:** 358–364.

52 Meier C, Brauchli YB, Jick SS, Kraenzlin ME, Meier CR. Use of depot medroxyprogesterone acetate and fracture risk. *J Clin Endocrinol Metab* 2010; **95:** 4909–4916.

53 Lanza LL, McQuay LJ, Rothman KJ, Bone HG, Kaunitz AM, Harel Z, *et al*. Use of depot medroxyprogesterone acetate contraception and incidence of bone fracture. *Obstet Gynecol* 2013; **121:** 593–600.

54 Medicines and Healthcare Products Regulatory Agency (MHRA). *Updating Prescribing Advice on the Effects of Depo-provera Contraception on Bones*. London, UK: MHRA; 2004.

55 National Osteoporosis Guideline Group. *Guideline for the Diagnosis and Management of Osteoporosis in Postmenopausal Women and Men from the Age of 50 Years in the UK*. 2014. http://www.shef.ac.uk/NOGG/NOGG_Pocket_Guide_for_Healthcare_Professionals.pdf [Accessed 27 November 2014].

56 Cundy T, Cornish J, Roberts H, Reid IR. Menopausal bone loss in long-term users of depot medroxyprogesterone acetate contraception. *Am J Obstet Gynecol* 2002; **186:** 978–983.

57 Walsh JS, Eastell R, Peel NF. Depot medroxyprogesterone acetate use after peak bone mass is associated with increased bone turnover but no decrease in bone mineral density. *Fertil Steril* 2010; **93:** 697–701.

58 Sanches L, Marchi NM, Castro S, Juliato CT, Villarroel M, Bahamondes L. Forearm bone mineral density in postmenopausal former users of depot medroxyprogesterone acetate. *Contraception* 2008; **78:** 365–369.

59 Beksinska ME, Smit JA, Kleinschmidt I, Farley TMM, Mbatha F. Bone mineral density in women aged 40–49 years using depotmedroyprogesterone acetate, norethisterone enanthate or combined oral contraceptives for contraception. *Contraception* 2005; **71:** 170–175.

60 Faculty of Sexual & Reproductive Healthcare. *Contraception for Women Aged Over 40 Years*. 2010. http://www.fsrh.org/pdfs/ContraceptionOver40July10.pdf [Accessed 27 November 2014].

61 Skegg DC, Noonan EA, Paul C, Spears GF, Meirik O, Thomas DB. Depot medroxyprogesterone acetate and breast cancer. A pooled analysis of the World Health Organization and New Zealand studies. *JAMA* 1995; **273:** 799–804.

62 Paul C, Skegg DC, Spears GF. Depot medroxyprogesterone acetate (Depo Provera) and risk of breast cancer. *BMJ* 1989; **299:** 759–762.

63 Breast cancer and depot-medroxyprogesterone acetate: a multinational study. WHO Collaborative Study of Neoplasia and Steroid Contraceptives. *Lancet* 1991; **338:** 833–838.

64 Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. *Lancet* 1996; **347:** 1713–1727.

65 Li CI, Beaber EF, Tang MT, Porter PL, Daling JR, Malone KE. Effect of depo-medroxyprogesterone acetate on breast cancer risk among women 20 to 44 years of age. *Cancer Res* 2012; **72:** 2028–2035.

66 World Health Organization. Cardiovascular disease and use of oral and injectable progestogen only contraceptives and combined injectable contraceptives. Results of an international, multicentre, case control study. *Contraception* 1998; **57:** 315–324.

67 Lidegaard O, Nielson L, Skovlund CW, Lokkegaard E. Venous thrombosis in users of non-oral hormonal contraception: follow-up study, Denmark 2001–10. *BMJ* 2012; **344:** e2990.

68 Mantha S, Karp R, Raghavan V, Terrin N, Bauer KA, Zwicker JI. Assessing the risk of venous thromboembolic events in women taking progestin-only contraception: a meta-analysis. *BMJ* 2012; **345:** e4944.

69 Lidegaard O, Nielson LH, Skovlund CW, Skedlestad FE, Lokkegaard E. Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001–9. *BMJ* 2011; **343**(d6423).

70 Goldstein J, Cushman M, Badger GJ, Johnson JV. Effect of depomedroxyprogesterone acetate on coagulation parameter: a pilot study. *Fertil Steril* 2007; **87:** 1267–1270.

71 van Hylckama V, Helmerhorst FM, Rosendaal FR. The risk of deep venous thrombosis associated with injectable depot-medroxyprogesterone acetate contraceptives or a levonorgestrel intrauterine device. *Arterioscler Thromb Vasc Biol* 2010; **30:** 2297–2300.

72 Segall-Gutierrez P, Du J, Niu C, Ge M, Tilley I, Mizraji K, *et al*. Effect of subcutaneous depo-medroxyprogesterone acetate (DMPA-SC) on serum androgen markers in normal-weight, obese, and extremely obese women. *Contraception* 2012; **86:** 739–745.

73 Lopez LM, Grimes DA, Schulz KF. Steroidal contraceptives: effect on carbohydrate metabolism in women without diabetes mellitus. *Cochrane Database Syst Rev* 2014; **4:** CD006133.

74 Sonmezer M, Atabekoglu C, Cengiz B, Dokmeci F, Cengiz SD. Depot-medroxyprogesterone acetate in anticoagulated patients with previous hemorrhagic corpus luteum. *Eur J Contracept Reprod Health Care* 2005; **10:** 9–14.

75 Berenson AB, Rahman M, Wilkinson G. Effect of injectable and oral contraceptives on serum lipids. *Am Coll Obstet Gynecol* 2009; **114:** 786–794.

76 McFarlane-Anderson N, Bazuaye PE, Jackson MD, Smikle M, Fletcher HM. Cervical dysplasia and cancer and the use of hormonal contraceptives in Jamaican women. *BMC Womens Health* 2008; **8:** 9.

77 Thomas DB, Ye Z, Ray RM, WHO Collaborative Study of Neoplasia and Steroid Contraceptives. Cervical carcinoma *in situ* and use of depot-medroxyprogesterone acetate (DMPA). *Contraception* 1995; **51:** 25–31.

78 La Vecchia C. Depot-medroxyprogesterone acetate, other injectable contraceptives, and cervical neoplasia. Contraception 1994; **49:** 223–230.

79 Depot-medroxyprogesterone acetate (DMPA) and risk of invasive squamous cell cervical cancer. The WHO Collaborative Study of Neoplasia and Steroid Contraceptives. *Contraception* 1992; **45:** 299–312.

80 Longatto-Filho A, Hammes LS, Sarian LO, Roteli-Martins C, Derchain SFM, Erzen M, *et al*. Hormonal contraceptive and the length of their use are not independent risk factors for high-risk HPV infections or high-grade CIN. *Gynecol Obstet Invest* 2011; **71:** 93–103.

81 Ghanem KG, Datta SD, Unger ER, Hagensee M, Shlay JC, Kerndt P, *et al*. The association of current hormonal contraceptive use with type-specific HPV detection. *Sex Trans Infect* 2011; **87:** 385–388.

82 Thomas DB, Ray RM. Depot medroxyprogesterone acetate (DMPA) and risk of invasive adenocarcinomas and adenosquamous carcinomas of the uterine cervix. WHO Collaborative Study of Neoplasia and Steroid Contraceptives. *Contraception* 1995; **52:** 307–312.

83 Shapiro S, Rosenberg L, Hoffman M, Kelly JP, Cooper DD, Carrara H, *et al*. Risk of invasive cancer of the cervix in relation to the use of injectable progestogen contraceptives and combined estrogen/progestogen oral contraceptives (South Africa). *Cancer Causes Control* 2003; **14:** 485–495.

84 Smith JS, Green J. Cervical cancer and use of hormonal contraception:a systematic review. *Lancet* 2003; **361:** 1159–1167.

85 International Collaboration of Epidemiological Studies of Cervical Cancer, Appleby P, Beral V, Berrington de Gonzalez A, Colin D, Franceschi S, *et al*. Cervical cancer and hormonal contraceptives: collaborative reanalysis of individual data for 16,573 women with cervical cancer and 35,509 women without cervical cancer from 24 epidemiological studies. *Lancet* 2007; **370:** 1609–1621.

86 Harris TG, Miller L, Kulasingam SL, Feng Q, Kiviat NB, Schwartz SM, *et al*. Depot-medroxyprogesterone acetate and combined oral contraceptive use and cervical neoplasia among women with oncogenic human papillomavirus infection. *Am J Obstet Gynecol* 2009; **200:** 489.e1–e8.

87 Hubacher D, Goco N, Gonzalez B, Taylor D. Factors affecting continuation rates of DMPA. *Contraception* 1999; **60:** 345–351.

88 Kaunitz AM, Darney PD, Ross D, Wolter KD, Speroff L. Subcutaneous DMPA vs. intramuscular DMPA: a 2-year randomized study of contraceptive efficacy and bone mineral density. *Contraception* 2009; **80:** 7–17.

89 Canto De Cetina TE, Canto P, Luna MO. Effect of counselling to improve compliance in Mexican women receiving depot-medroxyprogesterone acetate. *Contraception* 2001; **63:** 143–146.

90 Said S, Omar K, Koetsawang S, Kiriwat O, Srisatayapan Y, Kazi A, *et al*. A multicentred phase III comparative clinical trial of depot-medroxyprogesterone acetate given three-monthly at doses of 100 mg or 150 mg: II. The comparison of bleeding patterns. World Health Organization Task Force on Long-Acting Systemic Agents for Fertility Regulation Special Programme of Research, Development and Research Training in Human Reproduction. *Contraception* 1987; **35:** 591–610.

91 Aktun H, Moroy P, Cakmak P, Yalcin HR, Mollamahmutoglu L, Danisman N. Depo-Provera: use of a long-acting progestin injectable contraceptive in Turkish women. *Contraception* 2005; **72:** 24–27.

92 Polaneczky M, Guarnaccia M, Alon J, Wiley J. Early experience with the contraceptive use of depot medroxyprogesterone acetate in an inner-city clinic population. *Fam Plann Perspect* 1996; **28:** 174–178.

93 Sangi-Haghpeykar H, Poindexter AN, Bateman L, Ditmore JR. Experiences of injectable contraceptive users in an urban setting. *Obstet Gynecol* 1996; **88:** 227–233.

94 Schwallie PC, Assenzo JR. Contraceptive use – efficacy study utilizing medroxyprogesterone acetate administered as an intramuscular injection once every 90 days. *Fertil Steril* 1972; **24:** 331–339.

95 Potter LS, Dalberth BT, Cañamar R, Betz M. Depot medroxyprogesterone acetate pioneers. *Contraception* 1997; **56:** 305–312.

96 Faculty of Sexual & Reproductive Health Care. *Management of Unscheduled Bleeding in Women Using Hormonal Contraception*. 2009. http://www.fsrh.org/pdfs/UnscheduledBleedingMay09.pdf [Accessed 27 November 2014].

97 Murphy HM. Effect of depot medroxyprogesterone acetate on vaginal bleeding in the puerperium. *BMJ* 1979; **2:** 1400–1401.

98 Sapire KE. A study of bleeding patterns with two injectable contraceptives given postpartum and the effect of two non-hormonal treatments. *Adv Contracept* 1991; **7:** 379–387.

99 Faculty of Sexual & Reproductive Healthcare. *Postnatal Sexual and Reproductive Health*. 2009. http://www.fsrh.org/pfds/Ceuguidancepostnatal09.pdf [Accessed 27 November 2014].

100 Paul C, Skegg DC, Williams S. Depot medroxyprogesterone acetate. Patterns of use and reasons for discontinuation. *Contraception* 1997; **56:** 209–214.

101 Curtis KM, Ravi A, Gaffield ML. Progestogen-only contraceptive use in obese women. *Contraception* 2009; **80:** 346–354.

102 Beksinska ME, Smit JA, Kleinschmidt I, Milford C, Farley TMM. Propsective study of weight change in new adolescent users of DMPA, NET-EN, COCs, nonusers and discontinuers of hormonal contraception. *Contraception* 2010; **81:** 30–34.

103 Pantoja M, Medeiros T, Baccarin MC, Morais SS, Bahamondes L, dos Santos Fernandes AM. Variations in body mass index of users of depot-medroxyprogesterone acetate as a contraceptive. *Contraception* 2010; **81:** 107–111.

104 World Health Organization. *Medical Eligibility Criteria for Contraceptive Use* (4th edn). 2010. http://whqlibdoc.who.int/publications/2010/9789241563888_eng.pdf [Accessed 27 November 2014].

105 Centre for Disease Control and Prevention. U.S. Medical Eligibility Criteria for Contraceptive Use 2010. *MMWR Morb Mortal Wkly Rep* 2010; **59**(RR4): 1–85.

106 Cameron ST, Glasier A, Johnstone A. Pilot study of home self-administration of subcutaneous depo-medroxyprogesterone acetate for contraception. *Contraception* 2012; **85:** 458–464.

107 Prabhakaran S, Sweet A. Self-administration of subcutaneous depot medroxyprogesterone acetate for contraception: feasibility and acceptability. *Contraception* 2012; **85:** 453–457.

108 Polaneczky M, Liblanc M. Long-term depot medroxyprogesterone acetate (Depo-Provera) use in inner-city adolescents. *J Adolesc Health* 1998; **23:** 81–88.

109 Sobande AA, Al-Bar HM, Archibong EI, Sadek AA. Efficacy and acceptability of depo-medroxyprogesterone acetate injection as a method of contraception in Saudi Arabia. *Saudi Med J* 2000; **21:** 348–351.

110 Benagiano G, Diczfalusy E, Diethelm P, Goldzieher JW, Gray R, Apelo R, *et al*. Multinational comparative clinical evaluation of two long-acting injectable contraceptive steroids: noresthisterone oenanthate and medroxyprogesterone acetate. 2. Bleeding patterns and side effects. *Contraception* 1978; **17:** 395–406.

111 Matson SC, Henderson KA, McGrath GJ. Physical findings and symptoms of depot medroxyprogesterone acetate use in adolescent females. *J Pediatr Adolesc Gynecol* 1997; **10:** 18–23.

112 Civic D, Scholes D, Ichikawa L, Lacroix AZ, Yoshida CK, Ott SM, *et al*. Depressive symptoms in users and non-users of depot medroxyprogesterone acetate. *Contraception* 2000; **61:** 385–390.

113 Westhoff C, Truman C, Kalmuss D, Cushman L, Davidson A, Rulin M, *et al*. Depressive symptoms and Depo-Provera. *Contraception* 1998; **57:** 237–240.

114 Gupta N, O'Brien R, Jacobsen LJ, Davis A, Zuckerman A, Supran S, *et al*. Mood changes in adolescents using depot-medroxyprogesterone acetate for contraception: a prospective study. *J Pediatr Adolesc Gynecol* 2001; **14:** 71–76.

115 Ott MA, Shew ML, Ofner S, Tu W, Fortenberry JD. The influence of hormonal contraception on mood and sexual interest among adolescents. *Arch Sex Behav* 2008; **37:** 605–613.

116 Cromer BA, Smith RD, Blair JM, Dwyer J, Brown RT. A prospective study of adolescents who choose among levonorgestrel implant (Norplant), medroxyprogesterone acetate (Depo-Provera), or the combined oral contraceptive pill as contraception. *Pediatrics* 1994; **94:** 687–694.

117 Cocoman A, Murray J. Recognizing the evidence and changing practice on injection sites. *Br J Nurs* 2010; **19:** 1170–1174.

118 Small SP. Preventing sciatic nerve injury from intramuscular injections: literature review. *J Adv Nurs* 2004; **47:** 287–296.

119 Nisbet AC. Intramuscular gluteal injections in the increasingly obese population: retrospective study. BMJ 2006; **332:** 637–638.

120 Williams RL, Hensel DJ, Fortenberry JD. Self-administration of subcutaneous depot medroxyprogesterone acetate by adolescent women. *Contraception* 2013; **88:** 401–407.

121 Beasley A, White KO, Cremers S, Westhoff C. Randomized clinical trial of self versus clinical administration of subcutaneous depot medroxyprogesterone acetate. *Contraception* 2014; **89:** 352–356.

122 Faculty of Sexual & Reproductive Health Care. *Service Standards for Resuscitation in Sexual Health Services*. 2010. http://www.fsrh.org/pdfs/ServiceStandardsResuscitationSHServices.pdf [Accessed 27 November 2014].

123 Siriwongse T, Snidvongs W, Tantayaporn W, Leepipatpaiboon S. Effect of depo-meroxyprogesterone acetate on serum progesterone levels when administered on various cycle days. *Contraception* 1982; **26:** 487–493.

124 Faculty of Sexual & Reproductive Healthcare. *Quick Starting Contraception*. 2010. http://www.fsrh.org/pdfs/CEUGuidanceQuickStartingContraception.pdf [Accessed 27 November 2014].

125 World Health Organization. *Safe Abortion: Technical and Policy Guidance for Health Systems* (2nd edn). Geneva, Switzerland: World Health Organization, 2012.

126 Paulen ME, Curtis KM. When can a woman have repeat progestogen-only injectables-depot medroxyprogesterone acetate or norethisterone enantate? *Contraception* 2009; **80:** 391–408.

127 Faculty of Sexual Reproductive Healthcare. 2017. https: www.fsrh.org standards-and-guidance documents contraception-after-pregnancy-guideline-january-2017 [Accessed 6 February 2019.

128 World Health Organization. *Selected Practice Recommendations for Contraceptive Use*: 2008 Update. 2008. http://whqlibdoc.who.int/hq/2008/WHO_RHR_08.17_eng.pdf?ua=1 [Accessed 27 November 2014].

129 World Health Organization. *Selected Practice Recommendations for Contraceptive Use* (2nd edn). 2004. http://whqlibdoc.who.int/publications/2004/9241562846.pdf [Accessed 27 November 2014].

130 Pardthaisong T, Yenchit C, Gray R. The long-term growth and development of children exposed to Depo-Provera during pregnancy or lactation. *Contraception* 1992; **45:** 313–324.

131 Jaffe B, Shye D, Harlap S, Baras M, Belmaker E, Gordon L, *et al*. Health, growth and sexual development of teenagers exposed in utero to medroxyprogesterone acetate. *Paediatr Perinat Epidemiol* 1990; **4:** 184–195.

132 Gray RH, Pardthaisong T. In utero exposure to steroid contraceptives and survival during infancy. *Am J Epidemiol* 1991; **134:** 804–811.

133 Watts DH, Park JG, Cohn SE, Yu S, Hitti J, Stek A, *et al*. Safety and tolerability of DMPA among HIV infected women on antireteroviral therapy. *Contraception* 2008; **72:** 84–90.

134 Nanda K, Amaral E, Hays M, Viscola MAM, Mehta N, Bahamondes L. Pharmacokinetic interactions between depot medroxyprogesterone acetate and combination antiretroviral therapy. *Fertil Steril* 2008; **90:** 965–971.

135 Robinson JA, Jamshidi R, Burke AE. Contraception for the HIV-positive woman: a review of interactions between hormonal contraception and antiretroviral therapy. *Infect Dis Obstet Gynecol* 2012; doi:10.1155/2012/890160.

136 Faculty of Sexual & Reproductive Health Care. *Drug Interactions with Hormonal Contraception*. 2011. http://www.fsrh.org/pdfs/CEUguidancedruginteractionshormonal.pdf [Accessed 27 November 2014].

137 HRA Pharma UK Ltd. ellaOne: Summary of Product Characteristics. 2011. http://www.medicines.org.uk/emc [Accessed 27 November 2014].

138 Preglem UK a Division of Gedeon Richter (UK) Ltd. Esmya 5 mg Tablets (ulipristal acetate): Summary of Product Characteristics. 2013. http://www.medicines.org.uk/EMC/medicine/26068/SPC/ [Accessed 27 November 2014].

139 Faculty of Sexual & Reproductive Health Care. *Emergency Contraception*. 2011. http://www.fsrh.org/pdfs/CEUguidanceEmergencyContraception11.pdf [Accessed 27 November 2014].

140 Fotherby K, Koetsawang S. Metabolism of injectable formulations of contraceptive steroids in obese and thin women. *Contraception* 1982; **26:** 51–58.

141 Lan PT, Aedo AR, Landgren BM, Johannisson E, Diczfalusy E. Return of ovulation following a single injection of depo-medroxyprogesterone acetate: a pharmokinetic and pharmacodynamic study. *Contraception* 1984; **29:** 1–18.

142 Segall-Gutierrez P, Taylor D, Liu X, Stanzcyk F, Azen S, Mishell DR Jr. Follicular development and ovulation in extremely obese women receiving depo-medroxyprogesterone acetate subcutaneously. *Contraception* 2010; **81:** 487–495.

143 Fotherby K, Saxena BN, Shrimanker K, Hingorani V, Takker D, Diczafalusy E, *et al*. A preliminary pharmacokinetic and pharmacodynamic evaluation of depot-medroyprogesterone acetate and norethisterone oenanthate. *Fertil Steril* 1980; **34:** 131–139.

144 Bassol S, Garza-Flores J, Cravioto MC, Diaz-Sanchez V, Fotherby K, Lichtenberg R, *et al*. Ovarian function following a single administration of depo-medroxyprogesterone acetate (DMPA) at different doses. *Fertil Steril* 1984; **42:** 216–222.

145 Saxena BN, Dusitsin N, Tankeyoon M, Chaudhury RR. Return of ovulation after the cessation of depot-medroxy progesterone acetate treatment in Thai women. *J Med Assoc Thai* 1980; **63:** 66–69.

146 Garza-Flores J, Cardenas S, Rodriguez V, Cravoioto MC, Diaz-Sanchez V, Perez-Palacios G. Return to ovulation following the use of long-term acting reversible injectable contraceptives: a comparative study. *Contraception* 1985; **31:** 361–366.

147 Pardthaisong T, Gray RH, McDaniel EB. Return to fertility after the discontinution of depot medroxyprogesteone acetate and intrauterine devices in Northern Thailand. *Lancet* 1980; **1:** 509–512.

148 Medical Foundation and Sexual Health, British Association for Sexual Health and HIV (BASHH). *Standards for the Management of Sexually Transmitted Infections (STIs)*. 2010. http://www.bashh.org/documents/2513.pdf [Accessed 27 November 2014].

149 Heffron R, Donnell D, Rees H, Celum C, Mugo N, Were E, *et al*. and Partners in Prevention HSV/HIV Transmission Study Team. Use of hormonal contraceptives and risk of HIV-1 transmission: a prospective cohort study. [Erratum appears in *Lancet Infect Dis* 2012; **12:** 98]. *Lancet Infect Dis* 2012; **12:** 19–26.

150 Wand H, Ramjee G. The effects of injectable hormonal contraceptives on HIV seroconversion and on sexually transmitted infections. *AIDS* 2012; **26:** 375–380.

151 Morrison CS, Richardson BA, Mmiro F, Chipato T, Celentano DD, Luoto J, *et al*. and Hormonal Contraception and the Risk of HIV Acqusition (HC-HIV) Study Group. Hormonal contraception and the risk of HIV acquisition. *AIDS* 2007; **21:** 85–95.

152 Kleinschmidt I, Rees H, Delany S, Smith D, Dinat N, Nkala B, *et al*. Injectable progestin contraceptive use and risk of HIV infection in a South African family planning cohort. *Contraception* 2007; **75:** 461–467.

153 Myer L, Denny L, Wright TC, Kuhn L. Prospective study of hormonal contraception and women's risk of HIV infection in South Africa. *Int J Epidemiol* 2007; **36:** 166–174.

154 World Health Organization. *Hormonal Contraception and HIV: Technical Statement*. 2012. http://whqlibdoc.who.int/hq/2012/WHO_RHR_12.08_eng.pdf [Accessed 27 November 2014].

155 Medicines and Healthcare Products Regulatory Agency. *Antiepileptics: Adverse Effects on Bone*. 2009. http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON087970 [Accessed 27 November 2014].

156 Brown TT, Qaqish RB. Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review. *AIDS* 2006; **20:** 2165–2174.

157 European AIDS Clinical Society (EACS). *Guidelines. Version 7.02 June 2014*. 2014. http://www.eacsociety.org/Portals/0/140601_EACS%20EN7.02.pdf [Accessed 27 November 2014].

158 Bolland MJ, Wang TKM, Grey A, Gamble GD, Reid IR. Stable bone density in HAART-treated individuals with HIV: a meta-analysis. *J Clin Endocrinol Metab* **96**: 2721–2731.

159 Fitzpatrick D, Pirie K, Reeves G, Green , Beral (2023) Combined and progestagen-only hormonal contraceptives and breast cancer risk: A UK nested case–control study and meta-analysis. P oS Med 20(3): e1004188.

160 Hultstrand , Gemzell-Danielsson K, Kallner HK, indman H, Wikman P, Sundstr m-Poromaa I. Hormonal contraception and risk of breast cancer and breast cancer in situ among Swedish women 15–34 years of age: a nationwide register-based study. The ancet Regional Health– urope. 2022;21.

161 M rch S, Skovlund CW, Hannaford PC, et al. Contemporary hormonal contraception and the risk of breast cancer. ngl Med 2017;377:2228–39.

162 Urban M, Banks , gger S, Canfell K, O Connell D, Beral , Sitas F. Injectable and oral contraceptive use and cancers of the breast, cervix, ovary, and endometrium in black South African women: case–control study. P oS medicine. 2012 Mar 6;9(3):e1001182.

163 Strom B , Berlin A, Weber A , orman SA, Bernstein , Burkman RT, Daling R, Deapen D, Folger SG, Malone K , Marchbanks PA. Absence of an effect of injectable and implantable progestin-only contraceptives on subse uent risk of breast cancer. Contraception. 2004 May 1;69(5):353-60.

164 Shapiro S, Rosenberg , Hoffman M, Truter H, Cooper D, Rao S, Dent D, Gudgeon A, yl , Katzenellenbogen , Bailie R. Risk of breast cancer in relation to the use of injectable progestogen contraceptives and combined estrogen progestogen contraceptives. American ournal of pidemiology. 2000 Feb 15;151(4):396-403.

165 Sweeney C, Giuliano AR, Baumgartner KB, Byers T, Herrick S, dwards S , Slattery M . Oral, injected and implanted contraceptives and breast cancer risk among US Hispanic and non-Hispanic white women. International journal of cancer. 2007 Dec 1;121(11):2517-23.

APPENDIX 1: DEVELOPMENT OF CEU GUIDANCE

GUIDELINE DEVELOPMENT GROUP

Dr Louise Melvin – Director, Clinical Effectiveness Unit

Ms Julie Craik – Researcher, Clinical Effectiveness Unit

Dr Lucy Caird – Consultant Obstetrician and Gynaecologist; Raigmore Hospital, NHS Highland, Inverness

Dr Sharon Cameron – Consultant in Sexual and Reproductive Health, Chalmers Centre, NHS Lothian, Edinburgh

Mr Christopher Dodd – Superintendent Pharmacist, Molineux Pharmacy, Molineux Primary Care Centre, Newcastle-upon-Tyne

Dr Lucinda Farmer – Specialty Doctor, Sexual and Reproductive Healthcare; Bristol Sexual Health Services, Tower Hill, Bristol

Mr Babatunde A Gbolade – Consultant Gynaecologist and Director of Fertility Control Unit, Department of Obstetrics and Gynaecology, St James's University Hospital, The Leeds Teaching Hospitals NHS Trust, Leeds

Dr Lynne Gilbert – FSRH Clinical Standards Committee representative; Associate Specialist in Sexual and Reproductive Healthcare, CASH, The Laurels, Cambridge

Dr Fiona Hassall – Long-term GP locum, Ashton Medical Practice, Glasgow

Ms Lynn Hearton – Former Clinical and Information Lead, Family Planning Association (FPA), London

Ms Carol McQuillian – Osteoporosis Nurse Specialist; Southern General Hospital, Glasgow

Ms Shelley Mehigan – FSRH Clinical Effectiveness Committee representative; Nurse Specialist, Contraception, Bournemouth

Ms Tina Proctor – Nurse Consultant in Contraception and Sexual Health; East Laith Gate House, Doncaster

INDEPENDENT PEER REVIEWER

Professor Martha Hickey – Professor of Obstetrics and Gynaecology, University of Melbourne, Melbourne, Australia/Adjunct Professor of Obstetrics, Gynaecology and Reproductive Sciences, Yale University, New Haven, CT, USA

Declared Interests

Dr Sharon Cameron has received research funding from HRA Pharma (France) and Sayana (USA), has given lectures on behalf of HRA Pharma (France), and is a scientific advisor to Sayana (UK) and Exelgyn (France).

Dr Lucinda Farmer has received payment from MSD for providing training sessions on the insertion of Nexplanon.

Mr Babatunde Gbolade was a consultant to MSD during 2011 and received an honorarium from Nordic Pharma Limited for chairing and organising a meeting.

Ms Lynn Hearton declared that the FPA has received funding to provide an enquiry service from five pharmaceutical companies.

Ms Shelley Mehigan has undertaken paid consultancy work for pharmaceutical companies involved in contraception including MSD, Bayer and Pfizer.

Ms Tina Proctor received payment from HRA Pharma for participation in consensus meetings on emergency contraception.

Patient Consultation

A questionnaire on the proposed guidance content was completed by a sample of potential users.

Clinical Effectiveness Unit (CEU) Guidance is developed in collaboration with the Clinical Effectiveness Committee (CEC) of the Faculty of Sexual & Reproductive Healthcare (FSRH). The CEU guidance development process employs standard methodology and makes use of systematic literature review and a multidisciplinary group of professionals. The multidisciplinary group is identified by the CEU for their expertise in the topic area and typically includes clinicians working in family planning, sexual and reproductive health care, general practice, other allied specialities, and user representation. In addition, the aim is to include a representative from the FSRH CEC, the FSRH Meetings Committee and FSRH Council in the multidisciplinary guidance development group.

Evidence is identified using a systematic literature review and electronic searches are performed for: MEDLINE (CD Ovid version) (1996–2014); EMBASE (1996–2014); PubMed (1996–2014); The Cochrane Library (to 2014) and the US National Guideline Clearing House. The searches are performed using relevant medical subject headings (MeSH), terms and text words. The Cochrane Library is searched for relevant systematic reviews, meta-analyses and controlled trials relevant to progestogen-only injectable contraception. Previously existing guidelines from the FSRH (formerly the Faculty of Family Planning and Reproductive Health Care), the Royal College of Obstetricians and Gynaecologists (RCOG), the World Health Organization (WHO) and the British Association for Sexual Health and HIV (BASHH), and reference lists of identified publication, are also searched. Similar search strategies have been used in the development of other national guidelines. Selected key publications are appraised using methodological checklists. The clinical recommendations within this guidance are based on evidence whenever possible. Summary evidence tables are available on request from the CEU. The process for the development of CEU guidance is detailed in the CEU section of the FSRH website (www.fsrh.org). The methods used in the development of this guidance (CEU Process Manual version 2.0) have been accredited by NHS Evidence.

Questions for Continuing Professional Development

The following questions have been developed for continuing professional development (CPD).

The answers to the questions and information on claiming CPD points can be found in the 'members-only section' of the FSRH website (www.fsrh.org), which is accessible to all Diplomates, Members, Associate Members and Fellows of the FSRH.

[NB. Questions 3 and 5 have been amended subsequent to the publication of this guidance in December 2014.]

1 The main mode of action of progestogen-only injectable contraceptives is by:

a. Inhibiting ovulation
b. Preventing implantation
c. Thickening the cervical mucus
d. Thinning the endometrium

2 Norethisterone enantate is given by:

q. Intramuscular (IM) injection
b. Intravenous injection
c. Subcutaneous (SC) injection
d. Subdermal injection

3 If a woman has had intercourse with no additional contraception, emergency contraception may need to be considered in which of the following situations?

a. 11–12 weeks after her last DMPA injection
b. 12–13 weeks after her last DMPA injection
c. 13–14 weeks after her last DMPA injection
d. More than 14 weeks after her last DMPA injection

4 A 17-year-old woman presents with a body mass index (BMI) of 32 kg/m^2. She is requesting the progestogen-only injectable but wonders if there are any considerations as a result of her weight. What is the single most appropriate advice to offer her from the list below?

a. A causal association between weight and DMPA has not been established
b. She should return every 10 weeks due to concerns about efficacy in women with a higher BMI
c. The use of the progestogen-only injectable is not advised in women with a BMI >30 kg/m^2
d. Use of DMPA appears to be associated with weight gain, particularly in women under 18 years of age with a BMI ≥30 kg/m^2

5 Women who use progestogen-only injectable contraception should have a medical review by the prescriber:

a. Every 6 months
b. Every 12 months
c. Every 24 months
d. None required

6 A woman attends requesting her regular repeat progestogen-only injection at the correct time. She says she has had irregular bleeding since her last injection. She had been amenorrhoeic before this. Which of the following should you do?

a. Advise stopping the method and changing to another
d. Assess her sexually transmitted infection risk and other pathology, and give the injection
c. Give her azithromycin in case she has chlamydia infection
b. Give her the injection and tell her the bleeding will settle down again

7 With regard to bone health, which of the following is true?

a. DMPA decreases bone mineral density
b. DMPA has no effect on bones
c. DMPA increases fracture risk
d. DMPA should not be given to teenagers

8 How long can a woman continue with progestogen-only injectables?

a. 2 years
b. 5 years
c. Until age 50 years
d. Until the menopause or age 55 years

9 A woman has painful periods and wants to know if depot medroxyprogesterone acetate (DMPA) injection will help. What does the evidence suggest in relation to this?

a. There is no evidence to suggest that DMPA reduces dysmenorrhoea
b. Use of DMPA can reduce dysmenorrhoea and can reduce endometriosis-associated pain
c. Use of DMPA can reduce dysmenorrhoea but has not been shown to reduce pain as a result of pelvic pathology
d. Use of SC DMPA is preferable to IM DMPA in women with dysmenorrhoea

10 A woman presents reporting that she is using phenytoin for epilepsy. She wishes to continue to use IM DMPA. What is the single most appropriate advice to offer her from the list below?

a. She can continue IM DMPA and have repeat injections at the same interval
b. She can continue IM DMPA but she should have repeat injections every 8 weeks
c. She can continue IM DMPA but she should have repeat injections every 10 weeks
d. The efficacy of IM DMPA may be affected and she should consider an intrauterine device

What learning needs did this guidance address and how will it change your practice? (Please write below)

Auditable Outcomes for Progestogen-only Injectable Contraception

The following auditable outcomes have been suggested by the FSRH Clinical Standards Committee.

Auditable Outcomes

1 Percentage of women aged under 18 years who have a documented discussion about alternative methods of contraception prior to commencing the progestogen-only injectable [Auditable standard 97%]

2 Percentage of women who have used depot medroxyprogesterone acetate for a continuous period of more than 2 years who are reviewed by a prescriber to discuss the benefits and potential risks of longer-term use [Auditable standard 97%]

3 Percentage of women who have a documented assessment of risk factors for osteoporosis or osteopenia prior to commencement of the method [Auditable standard 97%]

4 Percentage of women who, prior to commencing progestogen-only injectable contraception, are advised of a possible delay of up to a year in the return of fertility after discontinuation [Auditable standard 97%]

COMMENTS AND FEEDBACK ON PUBLISHED GUIDANCE

All comments on published this guideline can be sent directly to the Clinical ffectiveness Unit (C U) of the Faculty of Sexual Reproductive Healthcare (FSRH) via the FSRH website (www.fsrh.org).

The C U may not respond individually to all feedback. However, the C U will review all comments and provide an anonymised summary of comments and responses, which are reviewed by the Clinical ffectiveness Committee (C C) and any necessary amendments made subse uently.

www.fsrh.org