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## Abbreviations used

<b>ATE</b>	arterial thromboembolism
<b>BMD</b>	bone mineral density
<b>BMI</b>	body mass index
<b>CEU</b>	Clinical Effectiveness Unit
<b>CHC</b>	combined hormonal contraception/contraceptive
<b>CI</b>	confidence interval
<b>COC</b>	combined oral contraception/contraceptive
<b>Cu-IUD</b>	copper intrauterine device
<b>DMPA</b>	depot medroxyprogesterone acetate
<b>EC</b>	emergency contraception
<b>ENG</b>	etonogestrel
<b>FSRH</b>	Faculty of Sexual & Reproductive Healthcare
<b>GDG</b>	guideline development group
<b>HCP</b>	healthcare practitioner
<b>HMB</b>	heavy menstrual bleeding
<b>IMP</b>	implant
<b>IUS</b>	intrauterine system
<b>LARC</b>	long-acting reversible contraception/contraceptive
<b>LNG</b>	levonorgestrel
<b>LNG-IUS</b>	levonorgestrel-releasing intrauterine system
<b>MHRA</b>	Medicines and Healthcare products Regulatory Agency
<b>PCOS</b>	polycystic ovary syndrome
<b>POP</b>	progestogen-only pill
<b>RCT</b>	randomised controlled trial
<b>RP</b>	reference period
<b>RR</b>	relative risk
<b>SRH</b>	sexual and reproductive healthcare
<b>UKMEC</b>	United Kingdom Medical Eligibility Criteria
<b>UPA</b>	ulipristal acetate
<b>UPSI</b>	unprotected sexual intercourse
<b>VTE</b>	venous thromboembolism
<b>WHO</b>	World Health Organization



## Grading of recommendations

Refer to [Appendix 1](#) for a full explanation of the classification of evidence level and grading of recommendations.

<b>A</b>	<p><b>At least one meta-analysis, systematic review or randomised controlled trial (RCT) rated as 1++, and directly applicable to the target population;</b></p> <p><i>or</i></p> <p><b>A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results.</b></p>
<b>B</b>	<p><b>A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results;</b></p> <p><i>or</i></p> <p><b>Extrapolated evidence from studies rated as 1++ or 1+.</b></p>
<b>C</b>	<p><b>A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results;</b></p> <p><i>or</i></p> <p><b>Extrapolated evidence from studies rated as 2++.</b></p>
<b>D</b>	<p><b>Evidence level 3 or 4;</b></p> <p><i>or</i></p> <p><b>Extrapolated evidence from studies rated as 2+.</b></p>
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### Information box

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## Executive summary of recommendations

### What is the progestogen-only implant?

#### Key information



The etonogestrel implant (ENG-IMP) is currently the only progestogen-only contraceptive subdermal implant available in the UK.



The ENG-IMP is a highly effective long-acting reversible method of contraception, licensed for 3 years of use for contraception.

### How effective is the etonogestrel implant for contraception?

#### Key information



The first year contraceptive failure rate for the ENG-IMP has been estimated at 0.05%. Cases of apparent true contraceptive failure have, however, been reported.

### Contraceptive effectiveness during extended use of the etonogestrel implant

#### Key information



The limited available evidence indicates that the risk of pregnancy during the fourth year of use of an ENG-IMP is likely to be very low.

#### Clinical recommendations



Healthcare practitioners (HCPs) can advise individuals who present after unprotected intercourse during the fourth year of use of an ENG-IMP that pregnancy risk is likely to be very low and emergency contraception is unlikely to be required.



*Routine* use of the ENG-IMP for longer than 3 years is not currently recommended. This is because available evidence is too limited to enable users to be given accurate information about effectiveness during extended use.

### What drug interactions are important to consider?

#### Enzyme-inducing drugs

#### Clinical recommendations



Individuals using enzyme-inducing drugs should be informed that the contraceptive effectiveness of the ENG-IMP could be reduced during use of the enzyme-inducer and for 28 days after stopping the enzyme-inducer.



Individuals using enzyme-inducing drugs should be offered a reliable contraceptive method that is unaffected by enzyme-inducers.

### Ulipristal acetate (UPA)

#### Key information



The ability of ulipristal acetate oral emergency contraception (UPA-EC) to delay ovulation could be reduced if an ENG-IMP is inserted within 5 days of taking the UPA.



The ability of UPA-EC to delay ovulation could theoretically be reduced if a woman has an ENG-IMP in situ (even if it has been in situ for longer than 3 years).

*Clinical recommendation***D**

Individuals should be advised to wait 5 days after taking UPA-EC before insertion of the ENG-IMP. They should be made aware that they must use condoms reliably or abstain from sex during the 5 days waiting and then for 7 days after implant insertion.

**What is the effect of weight/body mass index on contraceptive effectiveness?***Key information***C**

The available evidence suggests that contraceptive effectiveness of the ENG-IMP is not affected by body weight or body mass index.

**Assessing suitability of the etonogestrel implant for an individual***Key information*

✓

The FSRH supports the use of the ENG-IMP by medically eligible individuals between menarche and age 55 years.

**D**

Breast cancer, arterial thromboembolism, decompensated cirrhosis, hepatocellular tumours and unexplained vaginal bleeding are UKMEC3 or UKMEC 4 conditions for use of the ENG-IMP.

**Non-contraceptive benefits associated with use of the etonogestrel implant***Key information***C**

Most individuals with dysmenorrhoea at baseline report improvement in dysmenorrhoea with use of the ENG-IMP. A few individuals report new onset or worsening of dysmenorrhoea with ENG-IMP use.

**D**

Available evidence is too limited to allow conclusions to be drawn regarding the effect of use of the ENG-IMP on heavy menstrual bleeding.

**D**

The very limited available evidence suggests that use of the ENG-IMP could be associated with improvement in endometriosis-associated pain, but the evidence is limited to the first year after ENG-IMP insertion.

*Clinical recommendation*

✓

Induction of withdrawal bleeding is not required in ENG-IMP users with polycystic ovary syndrome who are amenorrhoeic during the licensed duration of use of the ENG-IMP.

**Risk of adverse health events associated with use of the etonogestrel implant***Key information***C**

The very limited available evidence suggests no significant increase in risk of venous or arterial thromboembolic events associated with current use of the ENG-IMP.

**C**

The available evidence is too limited to confirm or exclude an association between ENG-IMP use and reduction in bone mineral density.





- D** The available evidence suggests a possible association between current or recent use of hormonal contraception (including progestogen-only implants) and a small increase in risk of breast cancer; absolute risk remains very small.
- D** The available evidence is too limited to inform whether there is any association between use of the ENG-IMP and risk of ovarian, endometrial or cervical cancer.
- C** The absolute risk of ectopic pregnancy during use of the ENG-IMP is extremely small.

**Side effects associated with use of the etonogestrel implant**

**Unpredictable bleeding patterns**

*Key information*

- ✓** Mechanisms underlying irregular bleeding with progestogen-only contraception are incompletely understood.
- C** Irregular, unpredictable bleeding is common during use of the ENG-IMP.
- C** Bleeding pattern may change at any time during use of an ENG-IMP.
- C** The median number of days of bleeding/spotting during use of the ENG-IMP is lower than or comparable to that during natural menstrual cycles or standard use of combined contraception, but the pattern is less predictable.
- C** Individuals with ‘unfavourable’ bleeding patterns in the first few months after ENG-IMP insertion may have about a 50% chance that bleeding will improve over time.

*Clinical recommendations*

- ✓** Individuals considering use of the ENG-IMP should be:
  - ▶ Advised that a change in bleeding pattern is likely;
  - ▶ Advised that bleeding pattern is unpredictable, often irregular and may change during use; and
  - ▶ Made aware how to access support for management of problematic bleeding.
- ✓** After exclusion of other causes of bleeding, ENG-IMP users with problematic bleeding *who are medically eligible* can be offered a 3-month trial of additional use of combined oral contraception (outside the product licence) or a 5-day course of mefenamic acid.

**Other side effects**

*Key information*

- C** Headache is commonly reported during ENG-IMP use; evidence is, however, too limited to confirm or exclude any causative association.
- C** Observational studies suggest that during ENG-IMP use a minority of users experience new onset acne or worsening of existing acne while others have improvement in existing acne.

- C** The available evidence is too limited to confirm or exclude a causative association between ENG-IMP use and depression.
- C** The available evidence is too limited to confirm or exclude a causal association between ENG-IMP use and weight gain.

### When can the etonogestrel implant be inserted?

#### Key information



The ENG-IMP can be inserted on days 1–5 of a natural menstrual cycle, by day 5 after abortion or by day 21 after childbirth without requirement for additional contraceptive precautions.

At any other time, the ENG-IMP can be quick started according to [Quick Starting Guidance](#), with advice to use additional contraceptive precautions for 7 days and to take a follow-up pregnancy test (if required) (see [Table 2](#)).

### Nexplanon insertion

#### Clinical recommendations



Nexplanon should only be inserted and removed by HCPs trained in these techniques.



Nexplanon must be inserted subdermally in the inner upper arm, avoiding the sulcus between biceps and triceps. In line with manufacturer instructions, the point of insertion should be identified by measuring 8–10 cm proximally from the medial epicondyle along the sulcal line and then 3–5 cm posteriorly (over triceps), perpendicular to the sulcal line.



An existing, in-date ENG-IMP located at another site in the arm should not be replaced on the basis of its position alone.

### Etonogestrel implant removal

#### Clinical recommendations



The ENG-IMP can be removed at any time until 3 years after insertion without requirement for abstinence or additional contraception prior to removal.

### Complications of implant insertion and removal

#### Implant migration

#### Key information



Cases of local migration of the ENG-IMP have been reported.



Rare cases of intravascular insertion of the ENG-IMP and subsequent distant vascular migration have occurred.



*Clinical recommendations*

- ✓ Individuals considering use of the ENG-IMP should be advised that intravascular insertion and distant migration are rare complications of the Nexplanon insertion procedure.
- ✓ ENG-IMP users should be advised to feel for the implant in their arm once the insertion wound has healed to check that it is in situ. If they cannot feel their implant at any time, users should have its presence confirmed by an HPC.
- ✓ HCPs should consider the possibility of implant migration if the implant is not palpable near to the insertion site.

**Impalpable and deeply sited etonogestrel implants**

*Clinical recommendations*

- ✓ No attempt should be made to remove an impalpable ENG-IMP that has not been localised.
- ✓ If an ENG-IMP is impalpable, additional contraceptive precautions should be advised and investigation to locate the implant should be decided in consultation with local specialist services.
- ✓ Removal of an ENG-IMP that is deeply sited in the arm should only be undertaken by a specialist trained in complex implant removal techniques.

**Cost-effectiveness of the etonogestrel implant**

*Key information*

- D** Evidence suggests that the ENG-IMP is highly cost-effective for services compared to use of no contraception or oral contraception.

# FSRH Guideline (February 2021) Progestogen-only Implant (Revision due by February 2026)

## 1 Purpose and scope

This document updates previous Faculty of Sexual & Reproductive Healthcare (FSRH) guidance and aims to summarise the available evidence and expert opinion relating to the etonogestrel subdermal contraceptive implant. The guideline is intended for use by healthcare practitioners (HCPs) providing or giving information about etonogestrel implants.

## 2 Identification and assessment of the evidence

This guideline was developed in accordance with standard methodology for developing FSRH clinical guidelines. The recommendations made within this document are based on the best available evidence and the consensus opinion of experts and the guideline development group (GDG). The methodology used in developing this guideline and a list of GDG members and other contributors can be found in [Appendix 1](#).

The recommendations included should be used to guide clinical practice but are not intended to serve alone as a standard of medical care or to replace clinical judgement in the management of individual cases.

## 3 Introduction

The guideline will consider only the etonogestrel subdermal implant (ENG-IMP) as this is the only progestogen-only implant currently available in the UK. At the time of writing, Nexplanon is the only available ENG-IMP; recommendations in this guideline relate to evidence from studies of the ENG-IMP Nexplanon and its predecessor, Implanon. Implanon had a different insertion device and did not contain the barium sulphate that renders Nexplanon radio-opaque.

## 4 Summary, including changes to existing guidance

The ENG-IMP is a single-rod subdermal contraceptive implant that releases the progestogen etonogestrel (ENG). It acts by suppressing ovulation, with additional effects on endometrium and cervical mucus. The contraceptive effect is lost rapidly after removal.

### **Contraceptive effectiveness**

The ENG-IMP provides very effective contraception for 3 years and is not user-dependent during this time. True implant failures have been reported, but it is estimated that only 0.05% of users have unplanned pregnancies in the first year of ENG-IMP use. Very limited evidence suggests



that risk of pregnancy is likely to be very low during the fourth year of use of an ENG-IMP, thus emergency contraception (EC) is unlikely to be required. Routine extended ENG-IMP use is not yet recommended as evidence is too limited to enable users to be given accurate information about fourth-year effectiveness.

Effectiveness could be affected by use of enzyme-inducing drugs, and (theoretically) by daily use of ulipristal acetate (UPA) for management of fibroids, but does not appear to be significantly affected by body weight or body mass index (BMI).

### **Assessment of suitability of the etonogestrel implant for an individual**

FSRH supports use of the ENG-IMP from menarche until age 55 years (use under the age of 18 years and over 40 years is outside the product licence). There are few medical conditions that contraindicate ENG-IMP use (see [Section 8.1](#) and UK Medical Eligibility Criteria for Contraceptive Use (UKMEC 2016)) and no investigations are routinely required prior to commencement. A drug history is required to identify any potential drug interactions.

### **Non-contraceptive benefits**

Most ENG-IMP users that have dysmenorrhoea at baseline report improvement during use; new onset and worsening dysmenorrhoea are uncommon. Heavy menstrual bleeding (HMB) is not commonly reported during ENG-IMP use. There may be benefit for endometriosis-associated symptoms.

### **Health risks**

The limited available evidence suggests no increased risk of venous (VTE) or arterial thromboembolism (ATE) associated with ENG-IMP use, but a possible small increase in breast cancer risk (absolute risk remains very small). The evidence is too limited to inform effect of ENG-IMP use on risk of gynaecological cancers. An association between use of the ENG-IMP and reduction in bone mineral density (BMD) cannot be confirmed or excluded (note that this is a more cautious interpretation of the evidence than that in existing FSRH guidance). Risk of any pregnancy (including ectopic pregnancy) is very low during ENG-IMP use.

Potential users should be made aware that complications associated with ENG-IMP insertion include local migration (only occasionally more than about 2 cm) and, very rarely, distant intravascular migration. Users should be advised how to feel the implant in situ. Other possible complications of insertion and removal procedures include local reaction, nerve damage, and deep or intramuscular insertion.

### **Side effects**

Potential users should be made aware that unpredictable bleeding is common with the ENG-IMP and bleeding pattern may change at any time during use. Although not usually a cause for concern, erratic or persistent bleeding may be unacceptable to the user. Many users will have irregular episodic bleeding; for a minority, these bleeding/spotting episodes may be frequent or prolonged. Some users experience amenorrhoea. Users with problematic bleeding should be assessed for other potential causes. To manage problematic bleeding, a 3-month trial of additional combined oral contraception (COC) or a 5-day course of mefenamic acid can be considered for medically eligible individuals. Safety and effectiveness of adding a desogestrel progestogen-only pill (POP) to manage problematic bleeding with the ENG-IMP is not known.

Headache is commonly reported during use of the ENG-IMP, but causation is not established. Existing acne may worsen or improve during ENG-IMP use and a minority of users report new onset acne during use. Limited evidence suggests a possible association between ENG-IMP use and

depression, but causation is not established. Some users may gain weight during use, but evidence does not establish that the ENG-IMP *causes* weight gain.

### **Timing of implant insertion**

The ENG-IMP can be inserted at any time on days 1–5 of a natural menstrual cycle, by day 21 after childbirth or by day 5 after medical or surgical abortion with no requirement for additional contraception. At any other time, the ENG-IMP can be quick started according to FSRH guidance with advice to use condoms for 7 days and to have a follow-up pregnancy test if appropriate. The ENG-IMP may be quick started immediately following levonorgestrel oral emergency contraception (LNG-EC) or 5 days after ulipristal acetate oral emergency contraception (UPA-EC), with advice to use condoms for 7 days and to have a follow-up pregnancy test. When switching from another contraceptive method, see [Table 2](#) and [Table 3](#).

### **Pre-insertion checklist**

See [Section 13](#) for *minimum* criteria that should be met prior to insertion.

### **Nexplanon insertion and removal**

Nexplanon should only be inserted and removed by HCPs trained in these techniques.

The recommended Nexplanon insertion site is updated in this guideline to align with new instructions from the manufacturer. Insertion *must* be subdermal (do not rely on the insertion device alone to avoid deep insertion), avoiding the sulcus between biceps and triceps.

With the individual lying on their back with the arm (usually the non-dominant arm) abducted to 90°, the elbow flexed and the hand behind the head, the point of insertion is identified by measuring 8–10 cm proximally from the medial epicondyle along the sulcal line and then 3–5 cm posteriorly from that point over triceps, perpendicular to the sulcal line. The inserter is advanced proximally from this insertion point, parallel to the sulcal line and in the subdermal layer.

The revised insertion site advice is based on the anatomical site at which insertion/removal procedures are theoretically least likely to result in neurovascular injury or intravascular insertion; clinical studies do not inform the insertion site that is safest in practice. There is no standard requirement to change the arm in which the ENG-IMP is inserted after any given number of previous ENG-IMP insertions.

Suggested insertion and removal procedures are given in [Appendix 2](#) and [Appendix 3](#), respectively, and should be used in conjunction with [manufacturer audiovisual resources](#).

Management of impalpable, deeply sited, bent or broken implants is considered in [Section 19](#) and [Section 20](#). Do not proceed with their removal until the information in [Sections 19](#) and [20](#) has been reviewed, as referral to specialist services may be necessary.

### **Switching from the etonogestrel implant to other contraceptive methods**

See [Table 6](#) and [Table 7](#) for information about switching from the ENG-IMP to another contraceptive method. Note that when switching from an ENG-IMP in its fourth year of use to a levonorgestrel-releasing intrauterine system (LNG-IUS), the LNG-IUS may be inserted if a pregnancy test is negative even if there has been unprotected sexual intercourse (UPSI) in the previous 21 days. A follow-up pregnancy test is required 21 days after the last UPSI. This is a change to existing guidance, reflecting the fact that the risk of pregnancy in the fourth year of use of the ENG-IMP appears to be very low and contraceptive effectiveness is likely to compare favourably with that of user-dependent contraceptive methods.

**Cost-effectiveness**

Weighing costs associated with ENG-IMP provision, insertion, removal and with management of ENG-IMP-associated problems against provision of other contraceptive methods and management of unplanned pregnancy, the evidence suggests that the ENG-IMP is cost-effective for services compared to use of no contraception and oral contraception.

## 5 What is the progestogen-only implant?

### Key information



The ENG-IMP is currently the only progestogen-only contraceptive subdermal implant available in the UK.



The ENG-IMP is a highly effective long-acting reversible method of contraception, licensed for 3 years of use for contraception.

The ENG-IMP is currently the only progestogen-only contraceptive implant available in the UK. It is a long-acting reversible contraceptive (LARC) method, licensed for 3 years of use for contraception. It is a single, flexible, non-biodegradable, radio-opaque<sup>1,2</sup> plastic rod, 4 cm in length and 2 mm in diameter, supplied preloaded in a sterile, single-use insertion device. The ENG-IMP has an ethylene vinyl acetate copolymer skin and core; the core contains 68 mg ENG (the active metabolite of desogestrel, a 19-nortestosterone derivative) and barium sulphate for radio-opacity. The implant is inserted subdermally in the upper arm. ENG release rate reduces gradually over time, from 60–70 µg/day in weeks 5–6 to 35–45 µg/day at the end of the first year, and 25–30 µg/day at the end of the third year.

## 6 How does the etonogestrel implant work for contraception?

The primary mechanism of action of the ENG-IMP is prevention of ovulation. Serum ENG reaches ovulation-inhibiting concentrations (estimated at 90 pg/ml)<sup>3,4</sup> within a day after insertion. Maximum serum concentrations are achieved within 2 weeks and decline rapidly over the first few months, reducing to an average of 156 pg/ml (111–202 pg/ml) after 3 years.<sup>5</sup> In a cohort study<sup>6</sup> 223 women extended ENG-IMP use to 4 years and 102 women to 5 years; median serum ENG levels remained well above 90 pg/ml at 3, 4 and 5 years after insertion (although the range of serum levels was wide). There was no clear correlation between serum ENG levels and BMI.

During use of the ENG-IMP, ovulation is infrequent,<sup>7,8</sup> but ovarian activity is not completely suppressed; follicular development is common.<sup>4,7–9</sup> Serum estradiol levels fluctuate<sup>8</sup> but are not suppressed<sup>3,8,10</sup> below levels typical during the follicular phase of natural menstrual cycles.

There may be additional mechanisms of contraceptive action. The ENG-IMP renders the endometrium thin and inactive or weakly proliferative,<sup>11</sup> and its effect on cervical mucus impedes passage of sperm into the upper genital tract.<sup>4</sup>

### **Resumption of ovulation after removal of the etonogestrel implant**

After removal of the ENG-IMP, serum ENG levels fall rapidly. A study of 16 women using the ENG-IMP for up to 3 years reported serum ENG levels below the detection level by 7 days after removal and

return of ovulation within 6 weeks in almost all subjects.<sup>8</sup> Pregnancies have been conceived within 14 days of removal of the ENG-IMP.<sup>12</sup>

## 7 How effective is the etonogestrel implant for contraception?

### Key information

**C**

**The first-year contraceptive failure rate for the ENG-IMP has been estimated at 0.05%. Cases of apparent true contraceptive failure have, however, been reported.**

The ENG-IMP provides highly effective contraception that is not user-dependent for 3 years after insertion. The rate of unplanned pregnancy in the first year of use has been estimated at 0.05% for both perfect and typical use.<sup>13</sup> However, true ENG-IMP failures (pregnancies conceived during correct use of the ENG-IMP and not associated with drug interaction) have been reported in the literature.<sup>14</sup>

### The evidence

Most clinical studies<sup>2,7,12,15–27</sup> have reported no on-treatment pregnancies with the ENG-IMP. Some studies with no on-treatment pregnancies reported higher Pearl Indices because they included pregnancies that occurred within 14 days of implant removal.<sup>28</sup> In a multicentre randomised controlled trial (RCT),<sup>29</sup> three pregnancies (one in the first year of use and two in the third year) were observed amongst the 717 women randomised to use of the ENG-IMP who completed 3 years of use. This corresponds to a pregnancy rate of 0.4 (95% confidence interval (95% CI) 0.1–1.4) per 100 users over 3 years. No additional information was reported around the circumstances of the observed pregnancies.

Evidence level 2+

Postmarketing data and case studies also include pregnancies reported during ENG-IMP use.<sup>12</sup> Most of these pregnancies were conceived prior to the implant being inserted or becoming effective, or during concomitant use of enzyme-inducing drugs; in some cases, the implant had not in fact been successfully inserted.<sup>30–34</sup> However a small number of cases of apparent true contraceptive failure have been documented.<sup>14,30,35–40</sup>

Evidence level 3

### 7.1 Contraceptive effectiveness during extended use of the etonogestrel implant

#### Key information

**C**

**The limited available evidence indicates that the risk of pregnancy during the fourth year of use of an ENG-IMP is likely to be very low.**

#### Clinical recommendations



**HCPs can advise individuals who present after unprotected intercourse during the fourth year of use of an ENG-IMP that pregnancy risk is likely to be very low and EC is unlikely to be required.**



**Routine use of the ENG-IMP for longer than 3 years is not currently recommended. This is because available evidence is too limited to enable users to be given accurate information about effectiveness during extended use.**





In some centres outside the UK, use of each ENG-IMP for contraception is routinely extended beyond the licensed 3 years. The limited available evidence suggests that risk of pregnancy in the fourth year of use of a single ENG-IMP is likely to be very low. The evidence is, however, too limited to inform whether contraceptive effectiveness during the fourth year of use of an ENG-IMP is as high as that during the first 3 years.

### The evidence

A 2019 systematic review<sup>41</sup> identified five observational studies of extended use. These studies recorded no pregnancies amongst a total of 783 women who chose to extend use of the ENG-IMP to 4 years and 306 women who continued use for 5 years. These study populations were small and may not be representative of the general population; use of additional contraception was not recorded. See also evidence relating to serum ENG levels during extended use ([Section 6](#)).

Evidence level 1-

The GDG recommends that an individual who presents after UPSI during the fourth year of use of the ENG-IMP can be advised that risk of pregnancy is likely to be very low and EC is unlikely to be required. So long as a pregnancy test is negative, an individual in this situation can quick start a suitable method of contraception (see [Table 6](#) and [Table 7](#)), with advice to use condoms until the new method becomes effective; they should have a follow-up pregnancy test 21 days after the last UPSI.

The GDG considers, however, that *routine* use of the ENG-IMP beyond the licensed 3 years cannot be recommended. This is because ENG-IMP users expect very high contraceptive effectiveness, and the available evidence is currently too limited to enable users to be given accurate information about contraceptive effectiveness during extended use. The contraceptive effectiveness of an ENG-IMP in its fourth year of use is, however, likely to compare favourably with typical use of user-dependent contraceptive methods.

## 7.2 What drug interactions are important to consider?

### 7.2.1 Enzyme-inducing drugs

#### Clinical recommendations



**Individuals using enzyme-inducing drugs should be informed that the contraceptive effectiveness of the ENG-IMP could be reduced during use of the enzyme-inducer and for 28 days after stopping the enzyme-inducer.**



**Individuals using enzyme-inducing drugs should be offered a reliable contraceptive method that is unaffected by enzyme-inducers.**

Drugs that induce hepatic enzymes increase the metabolism of progestogens and could reduce the contraceptive effectiveness of the ENG-IMP.<sup>42</sup> There are numerous case reports of pregnancy occurring during concomitant use of the ENG-IMP with enzyme-inducing drugs.<sup>14,43</sup> Although risk of pregnancy could still be relatively low, individuals in this situation should be offered an effective contraceptive method that is unaffected by enzyme-inducing drugs (depot medroxyprogesterone acetate (DMPA), the copper intrauterine device (Cu-IUD) or the LNG-IUS are suitable options if the individual is medically eligible) (see FSRH Clinical Guidance [Drug Interactions with Hormonal Contraception](#)<sup>42</sup>). If an individual declines these methods and opts to use the ENG-IMP for contraception during use of an enzyme-inducing drug, they should be advised that contraceptive effectiveness may be reduced and condoms should be used consistently and correctly in addition.

### 7.2.2 Ulipristal acetate (UPA)

#### Key information

**D** The ability of UPA-EC to delay ovulation could be reduced if an ENG-IMP is inserted within 5 days of taking the UPA.

**D** The ability of UPA-EC to delay ovulation could theoretically be reduced if a woman has an ENG-IMP in situ (even if it has been in situ for longer than 3 years).

#### Clinical recommendation

**D** Individuals should be advised to wait 5 days after taking UPA-EC before insertion of the ENG-IMP. They should be made aware that they must use condoms reliably or abstain from sex during the 5 days waiting and then for 7 days after implant insertion.

UPA is a selective progesterone receptor modulator. Biomedical studies<sup>44,45</sup> have demonstrated that starting a desogestrel POP or a combined oral contraceptive (COC) soon after UPA 30 mg given for emergency contraception (UPA-EC) reduces the ability of UPA-EC to delay ovulation and could therefore reduce the effectiveness of the EC.

Evidence level 1-

The FSRH Clinical Guideline **Emergency Contraception**<sup>46</sup> recommends that after UPA-EC, insertion of the ENG-IMP (and commencement of other hormonal contraceptives) is delayed for at least 120 hours after UPA-EC has been given. This ensures that the UPA-EC is as effective as possible in preventing pregnancy resulting from the episode(s) of UPSI for which it was taken. Condoms should be used during the 5 days waiting. After the 5 days waiting, the ENG-IMP can be inserted with advice to use additional contraceptive precautions for the following 7 days.

Evidence level 4

EC may be indicated if an individual has UPSI in the 7 days after quick start ENG-IMP insertion (see **Table 2** and **Table 3**) or after ENG-IMP expiry (see **Table 6** and **Table 7**). Theoretically, the ability of UPA-EC to delay ovulation could be reduced if an individual has an ENG-IMP in situ, even if expired (ENG release may persist for several years). See **Section 7.1** and **Table 6** for guidance on risk of pregnancy and requirement for EC following UPSI for an individual who has an ENG-IMP in its fourth year of use.

No studies have investigated whether contraceptive effectiveness of the ENG-IMP is affected by concomitant use of UPA-EC. However, limited biomedical evidence<sup>44</sup> suggests that effectiveness of the desogestrel POP is not reduced by concomitant use of single-dose UPA-EC.

Theoretically, there could be an interaction between the ENG-IMP and UPA taken for management of fibroids. In the absence of evidence regarding either the contraceptive effectiveness of the ENG-IMP or the effectiveness of the UPA for management of fibroids in this situation, users may wish to consider use of a non-hormonal method of contraception.

### 7.3 What is the effect of weight/body mass index on contraceptive effectiveness?

#### Key information

**C** The available evidence suggests that contraceptive effectiveness of the ENG-IMP is not affected by body weight or BMI.

**FSRH**

No studies have been specifically designed to assess how obesity impacts effectiveness of the ENG-IMP. Currently available pharmacokinetic and clinical data suggest that (for the 3-year licensed duration of use) the ENG-IMP is highly effective for contraception in individuals with raised BMI. However, data for those with BMI  $\geq 40$  kg/m<sup>2</sup> are still lacking. It is noted that in a cohort study that reported no pregnancies amongst 223 women who extended ENG-IMP use to 4 years and 102 women who extended use to 5 years, about half of the subjects had a BMI  $>30$  kg/m<sup>2</sup>.<sup>6</sup> Early replacement of the ENG-IMP on the basis of higher weight or BMI is not recommended (see FSRH Clinical Guideline [Overweight, Obesity and Contraception](#)<sup>47</sup>).

Evidence level 2+

**7.4 Contraceptive effectiveness of bent or broken implants**

Refer to [Section 20](#).

**7.5 Pregnancy diagnosed when there is an etonogestrel implant in situ**

Contraceptive failure is rare during use of the ENG-IMP, thus published evidence regarding outcomes in pregnancies exposed to ENG-IMP is limited to a few case reports.<sup>48</sup> There is, however, no evidence that suggests a teratogenic effect (see FSRH Clinical Guideline [Quick Starting Contraception](#)<sup>48</sup> Section 4.1.3: Fetal exposure to progestogen-only implant: pregnancy outcomes and risk of fetal abnormality).

If pregnancy is diagnosed in an individual with an ENG-IMP in situ and they opt to continue with the pregnancy, it is established practice that the implant should be removed. If they opt for abortion, the GDG recommends that the ENG-IMP can remain in situ during medical or surgical abortion to provide contraception afterwards; this guidance extrapolates from evidence indicating that success of medical abortion is not affected by ENG-IMP initiation at the time of mifepristone administration<sup>49</sup> (see FSRH Clinical Guideline [Contraception After Pregnancy](#)<sup>49</sup>). If the pregnancy was conceived during established use of the ENG-IMP (rather than prior to the ENG-IMP becoming effective), HCPs should check for drug interactions. If true contraceptive failure of the ENG-IMP is suspected, the user may wish to consider an alternative contraceptive method.

**8 Assessing suitability of the etonogestrel implant for an individual***Key information*

The FSRH supports the use of the ENG-IMP by medically eligible individuals between menarche and age 55 years.



Breast cancer, arterial thromboembolism, decompensated cirrhosis, hepatocellular tumours and unexplained vaginal bleeding are UKMEC3 or UKMEC4 conditions for use of the ENG-IMP.

**8.1 Medical eligibility****8.1.1 Age**

It is established practice and existing FSRH guidance that the ENG-IMP can be used from menarche until age 55 years.<sup>50,51</sup> Although few studies have formally assessed safety of use in individuals aged under 18 years and over 40 years, there is no indication of specific health

concerns associated with use by younger or older individuals. See FSRH Clinical Guideline **Contraception for Women Aged Over 40 Years** for information relating to use of the ENG-IMP during the perimenopause.<sup>50</sup>

### 8.1.2 Medical conditions

Few medical conditions contraindicate use of the ENG-IMP. The UK Medical Eligibility Criteria for Contraceptive Use 2016 (UKMEC 2016)<sup>51</sup> recommends that the ENG-IMP should not be used by those who currently have breast cancer (UKMEC4). UKMEC 2016 indicates that potential health risks associated with use of the ENG-IMP generally outweigh contraceptive benefits (UKMEC3) after breast cancer, for individuals who have had an arterial thrombotic event during use of the implant, and for individuals with hepatocellular adenoma or hepatocellular carcinoma (see **Table 1**). Note that UKMEC Category 3 does not absolutely contraindicate the method; use may be considered if safer effective contraceptive methods are unavailable or unacceptable.

Evidence level 4

### 8.1.3 Previous use of etonogestrel implant

There is no limit to the number of ENG-IMPs that a woman can use consecutively.

### 8.1.4 Investigations

No clinical examination or laboratory investigations are routinely required prior to insertion of the ENG-IMP. Although not essential, it is considered good practice to document blood pressure prior to

**Table 1: Medical conditions that are UKMEC3 or UKMEC4 for use of the etonogestrel subdermal implant**

Condition	UKMEC category for use of etonogestrel subdermal implant
Current and history of ischaemic heart disease	UKMEC3 for continuation (UKMEC2 for initiation)
History of stroke	UKMEC3 for continuation (UKMEC2 for initiation)
Unexplained vaginal bleeding (before evaluation)	UKMEC3
Current breast cancer	UKMEC4
Past breast cancer	UKMEC3
Severe (decompensated) cirrhosis	UKMEC3
Hepatocellular adenoma or carcinoma	UKMEC3

UKMEC	Definition of category
Category 1	A condition for which there is no restriction for the use of the method.
Category 2	A condition where the advantages of using the method generally outweigh the theoretical or proven risks.
Category 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.
Category 4	A condition which represents an unacceptable health risk if the method is used.



initiation of any method of contraception, and a baseline weight may be useful if there is perceived weight gain during use.<sup>52</sup> Sexually transmitted infection risk assessment and screening should be considered.

## 8.2 Assessment of factors that could affect contraceptive effectiveness

A drug history should identify any prescribed or non-prescribed drug that could affect the contraceptive effectiveness of the ENG-IMP or could itself be affected by ENG (see [Section 7.2](#)).

# 9 Non-contraceptive benefits associated with use of the etonogestrel implant

## 9.1 Dysmenorrhoea

*Key information*

**C**

**Most individuals with dysmenorrhoea at baseline report improvement in dysmenorrhoea with use of the ENG-IMP. A few individuals report new onset or worsening of dysmenorrhoea with ENG-IMP use.**

### *The evidence*

Some of the original manufacturer-sponsored clinical cohort trials<sup>18,53</sup> of the ENG-IMP collected data for rates and severity of dysmenorrhoea at baseline and at end of treatment. Combined analysis of dysmenorrhoea data for 647 women in five of these studies was presented by Mansour *et al* in 2008. Amongst the 49% of study participants who reported mild, moderate or severe dysmenorrhoea at baseline, 77% had complete resolution and 6% decreased severity at end of treatment. Some 5.5% of all participants reported new onset or worsening of dysmenorrhoea.<sup>54</sup> In a more recent manufacturer-sponsored cohort study of 301 women, 3.7% of women reported dysmenorrhoea during use of the ENG-IMP that was considered to be related to or possibly related to the implant.<sup>2</sup>

Evidence level 2+

Smaller studies indicate similar reduction in dysmenorrhoea associated with use of the ENG-IMP. A cohort study of 41 women in Turkey<sup>55</sup> reported dysmenorrhoea in 41.5% at baseline and only 2.4% after 6 months of use of the ENG-IMP. In Egypt, 23 women with pelvic pain considered to be due to pelvic congestion syndrome were randomised to use of the ENG-IMP (n=12) or no treatment (n=11).<sup>56</sup> Mean visual analogue scores for dysmenorrhoea fell significantly in the ENG-IMP group, but not in the control group over the 12-month study period. In a small prospective cohort study<sup>57</sup> of use of the ENG-IMP by 17 women with adenomyosis-associated dysmenorrhoea, all participants reported reduced dysmenorrhoea by 3 months after insertion; mean visual analogue pain score was statistically significantly lower at 3 months than at baseline, with the improvement maintained at 12 months. Almost a third of the participants were amenorrhoeic at 12 months and a quarter reported infrequent bleeding.

Evidence level 2-

## 9.2 Heavy menstrual bleeding

*Key information*

**D**

**Available evidence is too limited to allow conclusions to be drawn regarding the effect of use of the ENG-IMP on HMB.**

There is little published evidence relating to effect of use of the ENG-IMP on pre-existing HMB.

### The evidence

Amongst a cohort of 116 European women in a manufacturer-funded study, 48% reported “much less” or “less” bleeding intensity during ENG-IMP use compared to baseline.<sup>58</sup> In a second cohort study in Australia<sup>59</sup>, 16% of 149 subjects reported HMB at baseline but fewer than 10% reported HMB during ENG-IMP use.

Evidence level 2-

## 9.3 Endometriosis

### Key information

**D**

**The very limited available evidence suggests that use of the ENG-IMP could be associated with improvement in endometriosis-associated pain, but the evidence is limited to the first year after ENG-IMP insertion.**

Very limited evidence from small, short studies suggests that use of the ENG-IMP is associated with improvement in endometriosis-related pain in the first year of use. None of the identified studies compared ENG-IMP to no treatment or considered longer-term effectiveness for this indication.

### The evidence

A small Austrian study<sup>60</sup> randomised women with symptomatic endometriosis to either ENG-IMP (n=21) or DMPA (n=20). Six months after implant insertion, visual analogue pain scores had reduced by a mean of 68% (95% CI 53%–83%) from baseline and requirement for analgesia had fallen. Lower pain scores were maintained at 12 months. There was a slightly smaller reduction in pain scores in the DMPA group. Similarly, a study in Brazil that randomised 103 women with endometriosis-associated pelvic pain, dysmenorrhoea or both to use of an ENG-IMP or a 52 mg LNG-IUS reported significantly reduced visual analogue scores in both groups for pelvic pain and dysmenorrhoea over 6 months of use.<sup>61</sup>

Evidence level 2-

Two small, observational studies<sup>62,63</sup> also observed reduction in endometriosis pain with use of the ENG-IMP. Sansone *et al* (2018)<sup>62</sup> reported significant reduction in dysmenorrhoea and dyspareunia over 6 months of ENG-IMP use (maintained at 12 months) amongst 25 Italian women with endometriosis. In a short study<sup>63</sup> of 50 Thai women with symptomatic endometriosis, significant improvement in mean pain score was reported from baseline to 3 months of use of the ENG-IMP.

## 9.4 Endometrial protection in polycystic ovary syndrome

### Clinical recommendation

**✓**

**Induction of withdrawal bleeding is not required in ENG-IMP users with polycystic ovary syndrome who are amenorrhoeic during the licensed duration of use of the ENG-IMP.**

The FSRH Clinical Effectiveness Unit (CEU) is regularly asked about induction of withdrawal bleeding in women with polycystic ovary syndrome (PCOS) who are amenorrhoeic during use of progestogen-only contraception. Studies have not specifically assessed the effect of the ENG-IMP on the endometrium in individuals with PCOS; but in the general population, use of the ENG-IMP is associated with reduced endometrial thickness (see [Section 14.4](#)).



The GDG recommends that in line with established practice, induction of withdrawal bleeding is not required in individuals with PCOS who are amenorrhoeic during the first 3 years of use of an ENG-IMP.

## 10 Risk of adverse health events associated with use of the etonogestrel implant

### 10.1 Venous and arterial thromboembolism

#### Key information

**C**

The very limited available evidence suggests no significant increase in risk of venous or arterial thromboembolic events associated with current use of the ENG-IMP.

#### Venous thromboembolism

Evidence relating to risk of venous thromboembolism (VTE) during ENG-IMP use is extremely limited, but suggests no significant increased risk in the general population of implant users.<sup>64</sup>

##### The evidence

A Danish database study identified five confirmed first VTE events during 29 497 woman-years of exposure to the ENG-IMP. After adjustment for age, this represented a non-significant increased risk of confirmed VTE (relative risk (RR) 1.4; 95% CI 0.6–3.4) during use of the ENG-IMP compared with non-pregnant women using non-hormonal contraception.<sup>65</sup> A Swedish case-control study suggested no difference between users of the ENG-IMP and non-users of hormonal contraception in the general population, but the number of implant users in the study was very small.<sup>66</sup>

Evidence level 2+

Risk of VTE associated with use of the ENG-IMP by women who have already had a venous thromboembolic event is unknown.

#### Arterial thromboembolism

Evidence relating to risk of arterial thromboembolism (ATE) during use of the ENG-IMP is extremely limited, but suggests no significant increased risk in the general population of implant users.<sup>64</sup>

##### The evidence

A Danish database study<sup>67</sup> identified three incidents of thrombotic stroke and three of myocardial infarction during 24 954 woman years of use of the ENG-IMP. The study reported no significant increased risk of either outcome in ENG-IMP users (for ENG-IMP use relative to non-use of hormonal contraception the relative risk for thrombotic stroke was 0.88 (95% CI 0.28–2.72) and for myocardial infarction relative risk was 2.14 (95% CI 0.69–6.65).

Evidence level 2+

Risk of ATE associated with use of the ENG-IMP by women who have already had an arterial thromboembolic event is unknown.

## 10.2 Osteoporosis

### Key information

C

**The available evidence is too limited to confirm or exclude an association between ENG-IMP use and reduction in BMD.**

#### The evidence

The Summary of Product Characteristics (SPC) for Nexplanon suggests no significant effect of ENG-IMP use on BMD.<sup>5</sup> The SPC states that mean serum estradiol levels remain above those seen in the early follicular phase<sup>4</sup> and references one small prospective cohort study comparing BMD in 44 ENG-IMP users and 29 Cu-IUD users before and after 2 years of use.<sup>68</sup>

In a Brazilian cohort study<sup>69</sup> of 56 women using various methods of contraception at baseline, there was a small but significant loss of BMD at midshaft of ulna over 18 months of use of the ENG-IMP. There was, however, no significant change in BMD at distal radius. The study did not include a comparator group of women using no hormonal contraception. A later small Brazilian study<sup>70</sup> measured BMD at femoral neck and lumbar spine at baseline and after 12 months in 23 new users of the ENG-IMP and 25 similar new users of the Cu-IUD. At 12 months, the study reported a reduction in BMD at both sites in implant users, but this was not statistically significantly different from the change in BMD for Cu-IUD users. A cross-sectional study<sup>71</sup> reported significantly lower BMD at distal radius and ulna (but not at lumbar spine or femur) amongst 100 Thai women who had used the ENG-IMP for at least 2 years compared to 50 similar controls. None of these studies considered long-term ENG-IMP use or the clinical significance of the findings in terms of fracture risk.

Evidence level 2+

The GDG interprets the existing evidence more cautiously than it has done in previous FSRH guidance and considers that there is currently inadequate evidence to confirm or exclude an association between use of the ENG-IMP and reduction in BMD. There is, however, insufficient evidence of harm to warrant routine monitoring of BMD.

## 10.3 Breast cancer

### Key information

D

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

#### The evidence

A large database study<sup>72</sup> used information drawn from Danish national databases for the 1.8 million Danish women aged 15–49 years between 1995 and 2012 to assess the risk of breast cancer associated with use of hormonal contraception. 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 any progestogen-only implant (data for ENG and LNG implants are not separated) was not found to be associated with increased risk of breast cancer. When interpreting this evidence it should be noted that the number of person-years of exposure to implants in this study was small compared to, for example, combined hormonal contraception (CHC), and there were few incident breast cancers in this group. Evidence from earlier case-control studies relates to LNG rather than to ENG implants.<sup>73,74</sup>

Evidence level 2-





## 10.4 Gynaecological cancers

### Key information

**D**

**The available evidence is too limited to inform whether there is any association between use of the ENG-IMP and risk of ovarian, endometrial or cervical cancer.**

#### The evidence

A Danish database study<sup>75</sup> suggested lower risk of ovarian cancer associated with current or recent use of any progestogen-only contraception than with never-use of hormonal contraception (adjusted RR 0.72; 95% CI 0.55–0.95). The study did not inform risk of ovarian cancer associated specifically with use of the ENG-IMP.

Evidence level 2-

A small UK study published in 1998 randomised 60 women to use of an ENG or a LNG implant. Amongst the 26 ENG-IMP users that completed 24 months of ENG-IMP use, mean endometrial thickness reduced from 11.3 mm at baseline to 3.3 mm at month 12 and 3.2 mm at month 24. There was no change in cervical cytology (all samples were normal at baseline).<sup>11</sup> Similar findings were reported by a small Scandinavian study, although of the 16 women who commenced ENG-IMP use only nine completed 2 years and seven completed 3 years of use.<sup>8</sup>

## 10.5 Ectopic pregnancy

### Key information

**C**

**The absolute risk of ectopic pregnancy during use of the ENG-IMP is extremely small.**

The risk of any pregnancy (intrauterine or ectopic) during use of the ENG-IMP is extremely small (see [Section 7](#)). Note that previous ectopic pregnancy does not contraindicate use of the ENG-IMP.<sup>51</sup>

#### The evidence

A few individual cases of ectopic pregnancy during ENG-IMP use are reported in the literature.<sup>30–32,34,37,39,40,76</sup> A review of clinical trials and marketing data for the ENG-IMP reported a rate of 0.2 ectopic pregnancies per 100 000 implants sold. In this study, ectopic pregnancies represented 4.7% of all reported pregnancies associated with ENG-IMP use (not all of these were confirmed on-treatment pregnancies).<sup>12</sup> A review of postmarketing surveillance data submitted to Australia's drug regulatory agency reported five ectopic pregnancies in 218 unintended pregnancies associated with ENG-IMP use (2.3%).<sup>30</sup> For reference, in the UK about 1% of all pregnancies are ectopic.<sup>77</sup>

Evidence level 2+

## 11 Side effects associated with use of the etonogestrel implant

Unpredictable bleeding is a common side effect of the ENG-IMP that is often cited as a reason for discontinuation. Other side effects reported during ENG-IMP use may or may not be caused by the implant itself, but can still be a reason for some individuals to be dissatisfied with the method. For some possible side effects, evidence does not establish that the ENG-IMP is a cause. As with any contraceptive method, however, the GDG considers it important to acknowledge an individual's experience of the method and their resulting concerns.

## 11.1 Unpredictable bleeding patterns

### Key information

- ✓ **Mechanisms underlying irregular bleeding with progestogen-only contraception are incompletely understood.**
- C **Irregular, unpredictable bleeding is common during use of the ENG-IMP.**
- C **Bleeding pattern may change at any time during use of an ENG-IMP.**
- C **The median number of days of bleeding/spotting during use of the ENG-IMP is lower than or comparable to that during natural menstrual cycles or standard use of combined contraception, but the pattern is less predictable.**
- C **Individuals with 'unfavourable' bleeding patterns in the first few months after ENG-IMP insertion may have about a 50% chance that bleeding will improve over time.**

### Clinical recommendations

- ✓ **Individuals considering use of the ENG-IMP should be:**
  - ▶ **Advised that a change in bleeding pattern is likely;**
  - ▶ **Advised that bleeding pattern is unpredictable, often irregular and may change during use; and**
  - ▶ **Made aware how to access support for management of problematic bleeding.**
- ✓ **After exclusion of other causes of bleeding, ENG-IMP users with problematic bleeding *who are medically eligible* can be offered a 3-month trial of additional use of COC (outside the product licence) or a 5-day course of mefenamic acid.**

#### 11.1.1 Why are bleeding patterns unpredictable during use of the etonogestrel implant?

The mechanism of altered bleeding patterns during use of progestogen-only contraceptives is complex and incompletely understood.<sup>78–82</sup> The endometrial glands, stroma and vasculature are continuously exposed to progestogen and, at the same time, fluctuating levels of estrogen resulting from incomplete ovarian suppression. It is thought that this disturbs endometrial angiogenesis, resulting in thin-walled, distended, fragile superficial microvessels that bleed easily when subjected to minor stretching stresses. Progestogen exposure may cause the covering surface epithelium to detach from the underlying stroma, allowing subepithelial bleeds to become overt. Epithelial repair mechanisms may be defective, permitting light bleeding to persist.<sup>54,83</sup>

#### 11.1.2 What bleeding patterns are observed during use of the etonogestrel implant?

The GDG considers that based on the available evidence (set out below), the following broad conclusions can be drawn regarding bleeding patterns during use of the ENG-IMP.

- ▶ Bleeding pattern is unpredictable.
- ▶ Bleeding pattern can change at any time during use of an ENG-IMP.
- ▶ The median number of days of bleeding/spotting during use of the ENG-IMP is fewer than or equivalent to that with natural menstrual cycles or standard use of CHC, but bleeding is less regular in pattern.

**FSRH**

Looking (as most published studies do) at the experience of a group of ENG-IMP users over the last 90 days of use:

- ▶ Many users will have experienced intermittent (often irregular) bleeding/spotting episodes that average out to occurring the equivalent of once a month (about one in three users) or less (about one in three users).
- ▶ A small number of users will have experienced frequent bleeding/spotting episodes that average out to occurring more often than once a month.
- ▶ For a minority of users (one in five or fewer), bleeding/spotting episodes may have been prolonged, each lasting 14 days or more.
- ▶ Up to one in four users may have experienced amenorrhoea.

Individuals who experience each of these bleeding patterns in one 90-day period of time during ENG-IMP use may not, however, experience the same bleeding pattern in previous or subsequent 90-day time periods. See [Section 11.1.3](#) regarding what we know about predictability for existing users of future bleeding patterns during ongoing ENG-IMP use.

The GDG recommends that to ensure informed decision-making and reduce user concern if bleeding is irregular or changeable, it is important that information given to potential users highlights the unpredictability of bleeding for any individual (a spectrum from amenorrhoea to frequent or prolonged bleeding) and the fact that bleeding pattern may change at any time during 3 years of ENG-IMP use.

**The evidence****Introduction**

Findings from studies that report bleeding patterns with the ENG-IMP are difficult to bring together as they do not all use the same outcome measures or timeframes. Additionally, many of the studies are small with high rates of discontinuation (often because of bleeding) and wide variation in findings.<sup>23,24,84–88</sup>

In many studies, participants recorded their bleeding pattern for each 90-day interval during implant use; the data are reported as the proportion of women with each of the defined bleeding patterns in each 90-day period. However, the group of women reporting a particular bleeding pattern at one point in time are not necessarily the same group of women reporting that bleeding pattern at another time. Therefore the figures reflect the overall experience of the study groups over time rather than the individual experiences of the participants during their use of an ENG-IMP.

**The studies**

In 2008, Mansour *et al* published an analysis of data from the daily bleeding diaries of 889 ENG-IMP users in 11 manufacturer-funded clinical trials.<sup>54</sup> For each reference period (90-day time period) during implant use, each woman's bleeding was defined according to standard World Health Organization (WHO) definitions (see [Box 1](#)) as amenorrhoea, infrequent bleeding, normal frequency bleeding, frequent bleeding and/or prolonged bleeding.<sup>89</sup> It is noted that bleeding data were contributed by only about two-thirds of the original subjects in the second year of use and fewer than one-third in the third year of use, and that frequent and prolonged bleeding were important factors associated with implant discontinuation. No medical interventions for management of bleeding were allowed during the included trials.

Evidence level 2+

**Box 1: Clinically important bleeding patterns in women aged 15–44 years<sup>89</sup>**

- ▶ Bleeding/spotting episode: one or more consecutive days of bleeding/spotting bounded by bleed-free days.
- ▶ Amenorrhoea: no bleeding/spotting in the last 90 days.
- ▶ Normal frequency bleeding: three to five bleeding/spotting episodes starting in the last 90 days.
- ▶ Infrequent bleeding: fewer than three bleeding/spotting episodes starting in the last 90 days.
- ▶ Frequent bleeding: more than five bleeding/spotting episodes starting in the last 90 days.
- ▶ Prolonged bleeding: bleeding/spotting episode lasting 14 days or more.

In this analysis, the median number of days of bleeding/spotting per 90-day reference period (RP) during ENG-IMP use was fewer than or comparable with that reported in other studies for natural menstrual cycles or users of COC, respectively, but less regular in pattern.

Evidence level 2+

For RPs 2 to 6 (3 to 18 months after insertion), this analysis reports that the mean number of bleeding/spotting days per RP was 17.7 and the mean number of bleeding/spotting episodes starting in each RP was 2.4. The mean percentage of subjects in each of RPs 2 to 6 recording:

- ▶ Amenorrhoea = 22%
- ▶ Infrequent bleeding = 34%
- ▶ Normal frequency bleeding = 38%
- ▶ Frequent bleeding = 7%
- ▶ Prolonged bleeding = 18%\*.

\*Prolonged bleeding may be infrequent, normal frequency or frequent.

Amenorrhoea was recorded by 25% of ENG-IMP users at 6 to 9 months after insertion, declining thereafter to 12% by 3 years. Infrequent bleeding was recorded by around one-third of the women in each 90-day RP throughout the 3 years studied. Frequent bleeding was recorded by 12% of women in the first few months of use, but by only 2% of continuing users at 3 years. One-third of the women recorded prolonged bleeding in the first few months, but thereafter prolonged bleeding was recorded by fewer than 20% of the continuing users for each RP.

A 2007 Cochrane systematic review<sup>15</sup> identified eight randomised studies (seven were manufacturer-sponsored) comparing ENG-IMP with Norplant. Bleeding pattern data from these eight studies were defined according to the WHO definitions as above and combined for meta-analysis. The number of ENG-IMP users recording amenorrhoea increased over the first 9 months of use, then remained fairly constant, with approximately one-third of continuing users recording amenorrhoea in each 90-day RP for the remainder of the 3 years studied. Infrequent bleeding was recorded by almost 50% of users in the first few months, reducing to about one-quarter to one-third thereafter. Frequent bleeding was uncommon, reported by fewer than 5% of continuing users in most 90-day RPs. Around 20% of the women reported prolonged bleeding in the first few months of use, but this declined over time to below 10%.

Evidence level 1+



A more recent international multicentre trial<sup>90</sup> that randomised women requesting LARC to use of an ENG or LNG implant followed up almost 1000 ENG-IMP users at 3 and 6 months after insertion and then at 6-monthly intervals for up to 3 years. The trial was not designed specifically to report bleeding patterns. Almost half the women (48.7%) reported “irregular bleeding”, 22.6% “prolonged bleeding”, 18.7% amenorrhoea and 13% “heavy bleeding” at one or more follow-up visits.

Evidence level 1-

### 11.1.3 Can initial bleeding patterns with the etonogestrel implant predict subsequent bleeding?

The available evidence suggests that users with ‘favourable’ bleeding patterns in the first few months after ENG-IMP insertion are more likely to continue to have ‘favourable’ bleeding patterns during years 1 and 2 of use than to develop ‘unfavourable’ bleeding patterns (see definitions of ‘favourable’ and ‘unfavourable’ below). Individuals with ‘unfavourable’ bleeding patterns in the first few months after ENG-IMP insertion may have about a 50% chance that the bleeding pattern will improve over time.

The GDG notes that it is important to understand the definition in published studies of a ‘favourable’ bleeding pattern (see evidence section below). For example, an individual with five episodes of bleeding/spotting in a 90-day period, each lasting 13 days (a total of 65 days of bleeding or spotting in 90 days), would be defined as having ‘favourable’ bleeding, but might not necessarily consider such a bleeding pattern to be acceptable.

#### The evidence

Analysis of bleeding data from manufacturer-sponsored phase III trials explored whether bleeding pattern during early use of the ENG-IMP could be used to predict bleeding patterns during ongoing use.<sup>91</sup> Subjects with five or fewer episodes of bleeding in a 90-day period, each lasting less than 14 days, were classed as having ‘favourable’ bleeding in that RP; those with more than five episodes of bleeding in 90 days or episodes continuing for 14 consecutive days or more were classed as having ‘unfavourable’ bleeding.

Evidence level 2+

The 325 ENG-IMP users (60.5% of subjects) who had a ‘favourable’ bleeding pattern during months 2–4 of use were likely to continue to have a ‘favourable’ bleeding pattern during the first year of use; 60.6% of them recorded ‘favourable’ bleeding patterns for all three subsequent 90-day periods during the first year of use. Some 75%–85% of those with overall ‘favourable’ bleeding patterns in year 1 also recorded ‘favourable’ bleeding patterns in each 90-day period during the second year of use; almost half of them had ‘favourable’ bleeding in all four quarters of year 2. The authors concluded that women with a ‘favourable’ bleeding pattern in any 90-day period can be counselled that there is an 80% chance of this continuing into the next 90-day period.

Of the 212 users (39.5% of subjects) with an ‘unfavourable’ bleeding pattern in months 2–4 after insertion, around 55%, 40% and 40% had ‘unfavourable’ bleeding in the subsequent three 90-day periods in the first year of use, respectively. One-third to one-half of those with overall ‘unfavourable’ bleeding in year 1 RPs recorded a change to ‘favourable’ bleeding *at some point* during year 2. The authors concluded that women with an initial ‘unfavourable’ bleeding pattern can be counselled that there is an approximately 50% chance that it will improve over time.

### 11.1.4 Discontinuation of the etonogestrel implant due to bleeding problems

Dissatisfaction with bleeding pattern is a common reason for ENG-IMP discontinuation.<sup>18,29,55,59,84,86–88,92,93</sup> Observed rates of removal due to bleeding problems vary between studies and between study settings. Larger observational studies report removal rates due to bleeding problems of 16%–20% over 2–3 years of use.<sup>18,20,29,84</sup> Analysis of data from manufacturer-funded phase II, III and IV international trials indicates discontinuation due to bleeding problems of 10%–11%.<sup>54,85,91</sup> In Mansour and colleagues' 2019 analysis, discontinuation due to bleeding was significantly more common amongst subjects with 'unfavourable' bleeding patterns than those with 'favourable' bleeding patterns.<sup>91</sup> It is noted that data from these older, international studies may not represent current discontinuation rates in UK clinical settings.

Evidence level 2+

Despite discontinuation due to bleeding problems, studies that measure user satisfaction with the ENG-IMP indicate that the majority of users are satisfied with their implant. Three studies (including over 1200 subjects) reported 65% to >80% of users being 'satisfied' or 'very satisfied'.<sup>58,59,84</sup>

### 11.1.5 Giving information about bleeding before etonogestrel implant insertion

It is established practice that when choosing and starting their contraceptive method, individuals should receive information about possible changes in bleeding pattern.<sup>94,95</sup> For the ENG-IMP, as stated in Section 11.1.2, potential users should be made aware that:

- ▶ Bleeding patterns are unpredictable.
- ▶ The median number of days of bleeding/spotting is equivalent to or less than with natural menstrual cycles or standard use of CHC, but bleeding occurs in a less predictable pattern.
- ▶ Bleeding is intermittent and irregular for many users but can be anywhere on a spectrum from amenorrhoea to frequent, persistent bleeding.
- ▶ Bleeding pattern may change at any time during ENG-IMP use.

### 11.1.6 How does giving information about bleeding affect acceptability and continuation rates?

There is not clear, consistent, published evidence as to how the information that is given about bleeding patterns or the way that it is delivered affects acceptability and continuation rates for the ENG-IMP in general, and in the current UK setting in particular.<sup>15,96–98</sup>

#### *The evidence*

A 2019 Cochrane review of strategies to support continuation with shorter-acting hormonal methods<sup>99</sup> identified weak evidence suggesting that giving relevant information prior to commencement of the contraception could reduce discontinuation of these methods due to menstrual disturbance. Small, qualitative studies have suggested that women may be unprepared for changes in bleeding despite being told about them<sup>100,101</sup> and would value individualised counselling.<sup>102</sup> One proposed counselling tool prompts providers to explain that changes to bleeding pattern are normal with hormonal contraception, that other methods offering different bleeding patterns are available, that there are non-contraceptive benefits, that lack of menses does not indicate pregnancy or that menses will not return when the method is stopped, and that if bleeding is problematic there are interventions that can be used; the tool has yet to be assessed in the UK setting.<sup>103</sup> A small, qualitative UK study suggested that failure to give information about side effects that are then experienced could be associated with future distrust of the provider.<sup>101,104</sup>



### 11.1.7 Investigation of problematic bleeding

While unpredictable bleeding is common during use of the ENG-IMP, other causes of bleeding should always be considered and excluded where appropriate. The decision to examine, investigate and/or treat will depend on clinical history (see **Box 2**). Also see FSRH Clinical Guideline **Problematic Bleeding with Hormonal Contraception**.<sup>105</sup>

### 11.1.8 Management options for problematic bleeding during etonogestrel implant use

Relatively few studies have investigated management of problematic bleeding associated with use of the ENG-IMP. The studies that *have* been done (all double-blind RCTs, most small in size) have only considered short interventions and short-term outcomes. For management of problematic bleeding during use of the ENG-IMP it has become established practice (and FSRH guidance – see Clinical Guideline **Problematic Bleeding with Hormonal Contraception**<sup>105</sup>) to trial use of a COC for 3 months unless the woman has medical contraindications. Users should be made aware that this is an off-label indication for COC and that safety of concurrent long-term use of COC and the ENG-IMP has not been studied. Longer-term use of COC for this indication could be considered on an individual basis depending on the provider's clinical judgement. If COC is contraindicated, a trial of oral mefenamic acid 500 mg three times daily for 5 days may be considered. The GDG considers that there is currently inadequate evidence to recommend any other management option, including addition of a POP, although this is often used in practice. Further research would be welcomed.

#### The evidence

The evidence suggests that a short course of COC (14 or 28 days)<sup>106,107</sup> or mefenamic acid (5 days)<sup>108</sup> could help to arrest a bleeding episode and/or reduce the number of bleeding days in the month following the start of the intervention. This is also true for tamoxifen (7 days),<sup>109</sup> mifepristone (single dose)<sup>110,111</sup> or UPA (7 days)<sup>112</sup> but their effect on the contraceptive effectiveness of the implant is unknown (no ovulations were observed in the tamoxifen and UPA RCTs described above).<sup>109,112</sup> Findings relating to use of doxycycline (5 days) are conflicting.<sup>110,111</sup>

Studies of mefenamic acid, COC and UPA only followed up most subjects for a few weeks after the start of the short intervention; therefore, the effect of these interventions on subsequent bleeding

#### Box 2: Points to cover in the clinical history from an etonogestrel implant user who presents with problematic bleeding

Clinical history taking should include assessment of:

- ▶ The individual's own concerns (a particular bleeding pattern may be acceptable to one user, but not to another)
- ▶ Duration of use of the etonogestrel implant (ENG-IMP)
- ▶ Use of any medications (including over-the-counter preparations) which may interact with the ENG-IMP
- ▶ Cervical screening history
- ▶ Risk of sexually transmitted infections (highest risk in those aged <25 years, or at any age with a new partner, or more than one partner in the last year, but consider testing for all those with problematic bleeding)
- ▶ Bleeding pattern before starting hormonal contraception, since starting and currently
- ▶ Other symptoms suggestive of an underlying cause (for example, abdominal or pelvic pain, postcoital bleeding, dyspareunia, heavy menstrual bleeding)
- ▶ Possibility of pregnancy.

patterns is not evidenced. The studies of tamoxifen, mifepristone and doxycycline demonstrated no effect of the short intervention on longer-term bleeding patterns.

The published literature does not include studies evaluating use of progestogens (widely used in practice), non-steroidal anti-inflammatory drugs other than mefenamic acid and tranexamic acid for management of bleeding associated with the ENG-IMP.

## 11.2 Headache

### Key information

**C**

**Headache is commonly reported during ENG-IMP use; evidence is, however, too limited to confirm or exclude any causative association.**

Reported incidence of headache as a side effect of ENG-IMP varies between studies. It is noted that headache reported during ENG-IMP use is not necessarily caused by the implant. The available evidence is set out below.

#### The evidence

An international, multicentre study<sup>29</sup> that randomised women seeking LARC to use of an ENG or LNG implant also had a non-randomised comparator group of Cu-IUD users. Similar percentages (31.3% of the 995 ENG-IMP users and 33.6% of the 971 Cu-IUD users) reported headache as a side effect on at least one occasion. No information is given as to the nature or frequency of headache. In integrated analysis of data from 11 manufacturer-sponsored phase II, III and IV clinical trials,<sup>28,85</sup> headache was reported by 24.7% of the 942 subjects, but only 15.3% of subjects had headache that was considered to be related to or possibly related to use of the ENG-IMP. Headache was cited as a reason for discontinuation by only 1.6% of subjects.

Evidence level 2+

More recently, amongst a cohort of 310 ENG-IMP users taking part in a manufacturer-sponsored prospective 3-year multicentre study, 18.6% reported headache (9% reported headache that was considered ENG-IMP-related).<sup>2</sup>

## 11.3 Acne

### Key information

**C**

**Observational studies suggest that during ENG-IMP use a minority of users experience new onset acne or worsening of existing acne while others have improvement in existing acne.**

While a minority of subjects in observational studies reported new onset or worsening acne during ENG-IMP use, others experienced improvement in existing acne. The studies do not report severity or persistence of the acne reported during ENG-IMP use or use prior to study enrolment of hormonal contraception that could affect acne.





### The evidence

In a comparative trial<sup>29</sup> with a LNG implant, acne was reported by significantly more of the 995 women randomised to use of the ENG-IMP than by the 971 women in a non-randomised comparator group of Cu-IUD users (17.3% vs 13.1%, respectively).

Evidence level 2+

A manufacturer-sponsored multicentre prospective cohort study of 635 women using the ENG-IMP over 2 years asked subjects about acne symptoms at baseline and at the end of the study. Some 12.8% reported an improvement in acne during implant use and 12.6% reported new onset or worsening of acne.<sup>18</sup> Amongst 231 subjects in a manufacturer-sponsored American cohort study<sup>53</sup> who reported no acne at baseline, 84% reported no change and 16% reported acne during ENG-IMP use; of the 84 subjects with acne at baseline, 61% reported an improvement, 31% no change and 8% worsening acne. Some 1.5% of all participants cited acne as a reason for discontinuation. In integrated analysis that included data from these studies, 11.8% of the 942 ENG-IMP users reported acne that was considered to be due to the implant, and 1.3% discontinued use because of acne.<sup>28,85</sup>

More recently, a manufacturer-sponsored multicentre study<sup>2</sup> of 301 ENG-IMP users reported acne that was potentially implant-related in 12.3% of participants; 4% cited acne as a reason for discontinuation.

## 11.4 Depression

### Key information

**C**

**The available evidence is too limited to confirm or exclude a causative association between ENG-IMP use and depression.**

### The evidence

Amongst 942 new users of the ENG-IMP in manufacturer-sponsored phase II and III trials, 3.5% reported depression that was considered to be associated (or potentially associated) with use of the implant.<sup>85</sup> Some 1% of these women cited depression and 2.3% cited emotional lability as their reason for discontinuation of the implant.<sup>28</sup>

Evidence level 1-

A 2018 systematic review of studies that used externally validated measures of depression<sup>113</sup> concluded that the identified data did not support a clear, general association between progestogen-only contraceptives and depression scores or incident depression diagnoses.

A study using data from Danish national databases<sup>114</sup> reported significantly greater risk of first use of antidepressant medication for women using a progestogen-only implant compared with women who had not recently used hormonal contraception (RR 2.1; 95% CI 2.01–2.24); the study included 28 867 woman-years of implant use. In a second database study the same authors reported significantly greater risk of first suicide attempt amongst young Danish women using the progestogen-only implant than non-users of hormonal contraception.<sup>115</sup> An earlier Swedish prescription database study<sup>116</sup> that included 17 860 implant users aged 16–31 years reported an odds ratio for use of antidepressant medication of 1.69 (95% CI 1.61–1.77) for users of the ENG-IMP compared with non-users of hormonal contraception. In all these studies significant confounding factors cannot be excluded and causative association is not established.

## 11.5 Weight change

### Key information

**C**

**The available evidence is too limited to confirm or exclude a causal association between ENG-IMP use and weight gain.**

### The evidence

In 2019, the FSRH CEU systematically reviewed the evidence relating to use of the ENG-IMP and weight change to support the FSRH statement 'Contraception and weight gain'.<sup>117</sup> Studies identified compared weight change in ENG-IMP users with Cu-IUD users; none of the studies included non-users of contraception as a comparator. Weight change varied widely between individual women in the studies, but on average women gained weight during use of both the ENG-IMP and the Cu-IUD. Most studies reported no statistically significant difference in weight change between the methods.

Evidence level 2+

A 2017 prospective cohort study<sup>118</sup> comparing 33 ENG-IMP, 85 LNG-IUS and 31 Cu-IUD users found that changes in body composition and weight did not significantly differ among those who continued their method for 12 months. Weight increases were 0.1, 0.5 and 0.4 kg, respectively; the difference between these was not statistically significant ( $p=0.97$ ). The study used validated measures of eating behaviour and body composition and adjusted for confounding. An earlier analysis of this cohort<sup>119</sup> evaluating weight gain over 12 months as the primary outcome found that ENG-IMP use ( $n=130$ ) was not associated with significantly greater weight increase when compared to Cu-IUD use ( $n=100$ ) (2.12 kg for ENG-IMP and 0.16 kg for Cu-IUD; the difference was not statistically significant). One study<sup>70</sup> of body composition changes over 12 months among 23 ENG-IMP and 25 Cu-IUD users found that ENG-IMP users compared with Cu-IUD users had statistically significant increases in body weight (+4.1 vs -0.1 kg) and fat mass (+2.4 vs 0.2 kg). This study was, however, limited by very high losses to follow-up and no adjustment for possible confounding factors.

## 11.6 Other side effects

Integrated analysis of data from 942 women in 11 manufacturer-sponsored phase II, III and IV clinical trials<sup>85</sup> records the following side effects that could potentially relate to ENG-IMP use: mastalgia (10.2% of subjects), abdominal pain (5.2%), dizziness (4.9%), emotional lability (5.7%), nervousness (3.5%) and nausea (2.5%).

## 12 When can the etonogestrel implant be inserted?

### Key information

✓

**The ENG-IMP can be inserted on days 1–5 of a natural menstrual cycle, by day 5 after abortion or by day 21 after childbirth without requirement for additional contraceptive precautions.**

**At any other time, the ENG-IMP can be quick started according to Quick Starting Guidance, with advice to use additional contraceptive precautions for 7 days and to take a follow-up pregnancy test (if required) (see Table 2).**



### 12.1 Starting the etonogestrel implant at the beginning of a natural menstrual cycle

In line with manufacturer instructions,<sup>5</sup> it is established practice that the ENG-IMP can be inserted on days 1–5 of a natural menstrual cycle without the need for additional contraceptive precautions (see [Table 2](#)).

**Table 2: Starting the etonogestrel implant: no recent hormonal contraception**

Current situation		Last UPSI	PT now?	Consider EC?	Insert implant now?	Additional contraceptive precaution required?	Follow-up
No recent contraception (or expired Cu-IUD)  Check that LMP was a typical bleed at expected time (or consider PT)	Days 1–5 of natural cycle	N/A	No	No	Yes	No	None
	After day 5 of natural cycle or amenorrhoeic	Before start of LMP	No	No	Yes	Condoms for 7 days	None
		Since start of LMP <b>AND</b> ≥21 days ago	Yes	No	Yes, if PT negative	Condoms for 7 days	None
		Since start of LMP <b>AND</b> <21 days ago	Yes	Yes	Yes*, if PT negative	Condoms for 7 days	PT 21 days after UPSI
Cu-IUD in situ  Check that LMP was a typical bleed at expected time (or consider PT)	Days 1–5 of natural cycle	N/A	No	No	Yes	No	None
	After day 5	≥7 days ago	No	No	Yes	Condoms for 7 days <b>OR</b> retain IUD for 7 days	None
		<7 days ago	No	No	Yes	Retain IUD for 7 days after last UPSI <b>AND</b> condoms for 7 days	None
After childbirth	<Day 21	N/A	No	No	Yes	No	None
After childbirth (if LAM does not apply)	≥Day 21	After day 21 <b>AND</b> ≥21 days ago	Yes	No	Yes, if PT negative	Condoms for 7 days	None
		After day 21 <b>AND</b> <21 days ago	Yes	Yes	Yes*, if PT negative	Condoms for 7 days	PT 21 days after UPSI
After childbirth (if LAM applies)	Up to 6 months after delivery	N/A	No	No	Yes	No	None
After miscarriage, ectopic or abortion	Days 1–5	N/A	No	No	Yes	No	None
	After day 5	After day 5 <b>AND</b> ≥21 days ago	Yes	No	Yes, if PT negative	Condoms for 7 days	None
		After day 5 <b>AND</b> <21 days ago	Yes	Yes	Yes*, if PT negative	Condoms for 7 days	PT 21 days after UPSI

\*Unless ulipristal acetate oral emergency contraception is given (see [Section 7.2.2](#)).

Cu-IUD, copper intrauterine device; EC, emergency contraception; IUD, intrauterine device; LAM, lactational amenorrhoea method; LMP, last menstrual period; N/A, not applicable; PT, pregnancy test; UPSI, unprotected sexual intercourse.

## 12.2 Starting the etonogestrel implant after day 5 of a natural menstrual cycle

After day 5 of the natural menstrual cycle, the ENG-IMP can be quick started if a pregnancy test is negative (or it is certain that there has been no UPSI), even if very early pregnancy cannot be absolutely excluded because of UPSI in the last 21 days. Additional contraceptive precautions (eg, condom use) should be advised for the first 7 days of ENG-IMP use and a follow-up pregnancy test taken if appropriate. From the very limited available evidence there is no indication that use of the ENG-IMP in very early pregnancy is associated with adverse pregnancy outcomes. See FSRH Clinical Guideline [Quick Starting Contraception](#)<sup>48</sup> and also [Table 2](#).

For guidance when quick starting the ENG-IMP after oral EC see [Section 12.7](#).

## 12.3 Starting the etonogestrel implant after childbirth

The ENG-IMP can be inserted at any time after childbirth including immediately after delivery.<sup>49</sup> Contraception is required from day 21 after childbirth. If the ENG-IMP is inserted by day 21 after delivery it will be effective immediately with no requirement for additional contraception. If the ENG-IMP is quick started on day 21 or later, unless the criteria for lactational amenorrhoea are met, risk of existing pregnancy should be assessed prior to insertion and additional contraception (eg, condom use) is required for 7 days after insertion. See FSRH Clinical Guideline [Contraception After Pregnancy](#)<sup>49</sup> and also [Table 2](#).

## 12.4 Starting the etonogestrel implant after abortion

The ENG-IMP can be safely started at any time after medical or surgical abortion.<sup>49</sup> The evidence indicates that the ENG-IMP can be inserted at the time of mifepristone administration without affecting the effectiveness of medical abortion.<sup>49</sup> If the ENG-IMP is initiated at the time of abortion or within 5 days after abortion it will be effective immediately with no requirement for additional contraception. If quick started thereafter, risk of existing pregnancy should be assessed prior to insertion and additional contraception (eg, condom use) is required for 7 days after insertion. See FSRH Clinical Guideline [Contraception After Pregnancy](#)<sup>49</sup> and also [Table 2](#).

## 12.5 Switching to the etonogestrel implant from another contraceptive method

Evidence is lacking for maintenance of contraceptive effect when switching from other hormonal contraception to the ENG-IMP. Established FSRH guidance is given in [Table 3](#). This may be more cautious than advice given in the SPC for Nexplanon.<sup>5</sup> For switching from a Cu-IUD see [Table 2](#).



**Table 3: Switching to the etonogestrel implant from other hormonal contraception**

Current situation		Last UPSI	PT now?	Consider EC?	Insert implant now?	Additional contraceptive protection required?	Follow-up
Correctly taken CHC	Days 1–2 of HFI	N/A	No	No	Yes	None	None
	Days 3–7 of HFI	Before HFI	No	No	Yes	Condoms for 7 days <b>OR</b> restart CHC for 7 days	None
		Since start of HFI	No	No	Yes	Restart CHC for 7 days	None
	Week 1	Before HFI	No	No	Yes	Condoms for 7 days <b>OR</b> continue CHC until taken for 7 days after HFI	None
		Since start of HFI	No	No	Yes	Continue CHC until taken for 7 days after HFI	None
	Weeks 2–3 (and later weeks of continuous CHC use)	N/A	No	No	Yes	None	None
Incorrectly taken CHC	≥21 days ago	Yes	No	Yes, if PT negative	Condoms for 7 days	None	
	<21 days ago	Yes	Yes	Yes*, if PT negative	Condoms for 7 days	PT 21 days after UPSI	
DMPA (≤14 weeks since last injection)	N/A	No	No	Yes	None	None	
DMPA (>14 weeks since last injection)	Before 14 weeks	No	No	Yes	Condoms for 7 days	None	
	After 14 weeks <b>AND</b> ≥21 days ago	Yes	No	Yes, if PT negative	Condoms for 7 days	None	
	After 14 weeks <b>AND</b> <21 days ago	Yes	Yes	Yes*, if PT negative	Condoms for 7 days	PT 21 days after UPSI	
Correctly taken POP	Traditional POP	N/A	No	No	Yes	Condoms for 7 days <b>OR</b> continue POP for 7 days	None
	Desogestrel POP	N/A	No	No	Yes	None	None

Current situation		Last UPSI	PT now?	Consider EC?	Insert implant now?	Additional contraceptive protection required?	Follow-up
Incorrectly taken POP		≥21 days ago	Yes	No	Yes, if PT negative	Condoms for 7 days	None
		<21 days ago	Yes	Yes	Yes*, if PT negative	Condoms for 7 days	PT 21 days after UPSI
LNG-IUS (in date)		≥7 days ago	No	No	Yes	Condoms for 7 days <b>OR</b> retain IUS for 7 days	None
		<7 days ago	No	No	Yes	Retain IUS for 7 days <b>AND</b> condoms for 7 days	None
52 mg LNG-IUS (expired)	In situ 6–7 years	≥7 days ago	Yes	No	Yes, if PT negative	Condoms for 7 days <b>OR</b> retain IUS for 7 days)	Consider PT 21 days after UPSI
		<7 days ago	Yes	No	Yes, if PT negative	Retain IUS for 7 days <b>AND</b> condoms for 7 days	Consider PT 21 days after UPSI
	In situ >7 years	≥21 days ago	Yes	No	Yes, if PT negative	Condoms for 7 days	None
		<21 days ago	Yes	Yes	Yes, if PT negative	Condoms for 7 days (consider retaining IUS if UPSI ≤7 days ago)	PT 21 days after UPSI
Other LNG-IUS (expired)		≥21 days ago	Yes	No	Yes, if PT negative	Condoms for 7 days	None
		<21 days ago	Yes	Yes	Yes, if PT negative	Condoms for 7 days (consider retaining IUS if UPSI ≤7 days ago)	PT 21 days after UPSI

\*Unless ulipristal acetate oral emergency contraception is given (see [Section 7.2.2](#)).  
 CHC, combined hormonal contraception; DMPA, depot medroxyprogesterone acetate; EC, emergency contraception; HFI, hormone-free interval; LNG-IUS, levonorgestrel-releasing intrauterine system; N/A, not appropriate; POP, progestogen-only pill; PT, pregnancy test; UPSI, unprotected sexual intercourse.



### 12.6 Replacing the etonogestrel implant

Established FSRH guidance is given in [Table 4](#).

**Table 4: Replacing the etonogestrel implant**

Current situation		Last UPSI	PT now?	Consider EC?	Insert implant now?	Additional contraceptive protection required?	Follow-up
IMP (in situ ≤3 years)		N/A	No	No	Yes	No	None
IMP (expired)	In situ 3–4 years	≥21 days ago	Yes	No	Yes, if PT negative	Condoms for 7 days	None
		<21 days ago	Yes	No	Yes, if PT negative	Condoms for 7 days	Consider PT 21 days after UPSI
	In situ >4 years	≥21 days ago	Yes	No	Yes, if PT negative	Condoms for 7 days	None
		<21 days ago	Yes	Yes	Yes*, if PT negative	Condoms for 7 days	PT 21 days after UPSI

\*Unless ulipristal acetate oral emergency contraception is given (see [Section 7.2.2](#)).

EC, emergency contraception; IMP, progestogen-only implant; N/A, not appropriate; PT, pregnancy test; UPSI, unprotected sexual intercourse.

### 12.7 Starting the etonogestrel implant after oral emergency contraception

The ENG-IMP can be inserted immediately after LNG-EC. Additional contraception (eg, condom use) is required for 7 days after insertion and a pregnancy test should be taken 21 days after the last UPSI.

Insertion of the ENG-IMP should be delayed for 5 days after UPA-EC to avoid affecting the effectiveness of the UPA-EC. Additional non-hormonal contraception (eg, condom use) is required until the implant is inserted and then for a further 7 days. A pregnancy test is required 21 days after the last UPSI. See FSRH Clinical Guideline [Emergency Contraception](#)<sup>46</sup> and also [Table 5](#).

**Table 5: Starting the etonogestrel implant: after emergency contraception**

At time of emergency contraception			
EC type	Insert implant now?	Additional precautions?	Follow-up
Levonorgestrel oral emergency contraception (LNG-EC)	Yes	Condoms for 7 days	PT 21 days after last UPSI
Ulipristal acetate oral emergency contraception (UPA-EC)	No. Delay insertion for 5 days after UPA-EC	Condoms until implant inserted and for 7 days after implant inserted	PT 21 days after last UPSI
Copper intrauterine device (Cu-IUD)	Cu-IUD is effective for long term contraception	Retain Cu-IUD until PT 21 days after Cu-IUD insertion	

EC, emergency contraception; PT, pregnancy test; UPSI, unprotected sexual intercourse.




## 13 Checklist prior to etonogestrel implant insertion

The HCP inserting the ENG-IMP should ensure that (as a minimum) the following criteria are met prior to insertion:

- 1 Individual assessed as medically eligible
- 2 Checked no interacting drugs or herbal remedies
- 3 Checked no allergies to implant content or local anaesthetic
- 4 Checked suitable time to insert and requirement for additional contraception/follow-up pregnancy testing
- 5 Individual advised about:
  - ▶ Contraceptive effectiveness
  - ▶ Duration of use
  - ▶ Interaction with medicines/herbal remedies
  - ▶ Potential bleeding patterns
  - ▶ Other potential side effects
  - ▶ Insertion procedure and associated risks including local reaction/haematoma, deep insertion, intravascular insertion, migration and neurovascular damage
  - ▶ Removal procedure.

## 14 Nexplanon insertion

### *Clinical recommendations*

- 
**Nexplanon should only be inserted and removed by HCPs trained in these techniques.**
- 
**Nexplanon must be inserted subdermally in the inner upper arm, avoiding the sulcus between biceps and triceps. In line with manufacturer instructions, the point of insertion should be identified by measuring 8–10 cm proximally from the medial epicondyle along the sulcal line and then 3–5 cm posteriorly (over triceps), perpendicular to the sulcal line.**
- 
**An existing, in-date ENG-IMP located at another site in the arm should not be replaced on the basis of its position alone.**

See [Section 12](#) for recommendations as to when the ENG-IMP can be inserted.

Nexplanon is designed to be inserted just under the skin of the medial upper arm. **It is crucial that care is taken to ensure subdermal insertion.** Deeper insertion must be avoided to minimise risk of damage to underlying neurovascular structures or intravascular insertion and to facilitate removal. The Nexplanon insertion device should not be relied upon alone to ensure that insertion is subdermal.

To facilitate correct, safe, subdermal implant insertion it is established guidance, endorsed by the GDG for this guideline, that:

- ▶ Nexplanon should only be inserted (and removed) by a trained HCP who has kept their skills up to date.<sup>5,120,121</sup>
- ▶ Nexplanon should usually be inserted into the non-dominant arm to avoid neurovascular damage to dominant arm/hand function that could be associated with accidental incorrect deep implant insertion.<sup>5</sup> There is no requirement to change arm after any given number of implant insertions.



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- ▶ The sulcus between biceps and triceps should be avoided to reduce risk of neurovascular damage and intravascular insertion. However, major nerves and blood vessels are not confined to the sulcus and location of major neurovascular structures is variable.<sup>5,122</sup>
- ▶ Care must be taken to ensure superficial subdermal insertion.

### 14.1 What is the safest insertion site?

Robust clinical data do not exist to inform which Nexplanon insertion site is, in clinical practice, associated with lowest risk of accidental deep insertion, difficult removal, neurovascular injury and intravascular insertion.

#### *The evidence*

A recent manufacturer-funded study<sup>122</sup> involving dissection of cadaveric arms was carried out to identify the insertion site at which there were fewest underlying neurovascular structures and thus least theoretical likelihood of neurovascular damage or intravenous insertion.

Dissection of the whole medial upper arm demonstrated smaller, less prominent neurovascular structures posterior to the sulcal line than anterior to it. On that basis the assumption was made that neurovascular injury is less likely with insertion posterior to the sulcal line. (The sulcal line is defined as the groove between the brachialis/biceps anteriorly and the triceps posteriorly.)

Multiple dissection windows were opened over triceps in 40 female cadaveric arms to identify underlying neurovascular structures in the subcutaneous tissue and deep fascia. With the arm abducted to 90°, the elbow flexed and the hand behind the head, no neurovascular structures were identified in an area 8–10 cm proximal to the medial epicondyle along the sulcal line and 3–5 cm posterior to the sulcal line. In contrast, significant neurovascular structures were present in dissection windows closer to the medial epicondyle and to the sulcal line. It was noted that flexing the elbow moved the ulnar nerve anteriorly, towards the sulcus and away from the implant insertion site, thus potentially reducing risk of injury.

#### *GDG conclusions*

On the basis of this evidence and to align guidance with that of the manufacturer, the GDG makes the following recommendations about insertion site:

- ▶ During insertion, the individual should lie on their back with their arm abducted to 90°, the elbow flexed and the hand behind the head.
- ▶ To identify the insertion site, the HCP should:
  - ▶ Ask the individual to tense the biceps and the triceps muscles to allow palpation of the sulcus (the muscles can then be relaxed).
  - ▶ Start at the medial epicondyle and measure 8–10 cm proximally along the sulcal line.
  - ▶ From this point, measure 3–5 cm posteriorly, perpendicular to the sulcal line, to identify the insertion site (over triceps muscle).
  - ▶ Pierce the skin with the implant introducer at this point and advance the introduction needle proximally just under the skin, parallel to the sulcal line.

See diagrams included in the Nexplanon package insert, diagrams in the SPC for Nexplanon<sup>5</sup> and video (insertion and removal) online at [www.nexplanonvideos.eu](http://www.nexplanonvideos.eu).<sup>123</sup>

- ▶ After insertion, the presence of the implant under the skin should be confirmed by palpation of both ends. If the implant cannot be palpated it may not have been inserted, or could have been inserted too deeply. Check the insertion device and to ensure that the implant has been deployed, check the surrounding clinical area for the implant and see [Section 19](#) (Management of impalpable implants) for further guidance.

### 14.2 Insertion site in existing users

An individual who has an *expired* ENG-IMP in situ at another site should have that implant removed and the new implant inserted at the new recommended site. If the expired implant is already in the new recommended position, it is established practice that the new implant can be inserted through the removal incision and advanced along a fresh adjacent track. There is not, however, study evidence to inform whether outcomes are any different with this approach than if the new implant is inserted close by through intact skin.

### 14.3 Nexplanon insertion procedure

There is little published evaluation of specific Nexplanon insertion and removal techniques; both practice and expert opinion vary. Procedures described in this guideline are based on the opinion and experience of the GDG and are intended as a guide to good practice, but are not evidence-based.

See [Appendix 2 \(Suggested Nexplanon insertion procedure\)](#).

### 14.4 Advice after etonogestrel implant insertion

After ENG-IMP insertion, users should be provided with the following information:

- ▶ Any requirement for additional contraceptive precautions and follow-up pregnancy testing
- ▶ Instructions for dressing removal, wound care and removal of paper sutures
- ▶ Likelihood of initial discomfort and bruising
- ▶ Signs of local infection and how to access review if infection is suspected
- ▶ How to feel for the implant after removal of the wound dressing (the implant should always be palpable – all users should be advised to seek review if at any time they cannot feel their implant)
- ▶ How to access review of adverse effects and implant removal services
- ▶ When to attend for replacement.

The GDG recommends that *routine* follow-up by a HCP is not required during the 3 years of licensed use of an ENG-IMP.

## 15 Etonogestrel implant removal

### *Clinical recommendations*



**The ENG-IMP can be removed at any time until 3 years after insertion without requirement for abstinence or additional contraception prior to removal.**

### 15.1 When can the etonogestrel implant be removed?

The ENG-IMP should generally be removed if it has been in situ for the 3 years of licensed use. The ENG-IMP can be removed at the user's request at any time within 3 years after insertion without the need for abstinence or use of additional contraception prior to removal. If the individual does not wish to become pregnant, alternative contraception is required as soon as the implant has been removed.



### 15.2 Switching from the etonogestrel implant to another method of contraception

See **Table 6** and **Table 7** for guidance when switching from the ENG-IMP to another method of contraception.

In general, the ENG-IMP should be removed when it is no longer effective for contraception. This includes implants that are deeply sited or impalpable (these cases should be referred to specialist deep implant removal services). If an individual does not wish to have their ENG-IMP removed after 3 years the GDG recommends that they should be made aware that:

- ▶ The implant is likely to continue to have an effect on fertility for a considerable time.
- ▶ Limited evidence suggests the risk of pregnancy in the fourth year of use of an ENG-IMP is likely to be very low.
- ▶ Contraceptive effectiveness after 4 years of use of the ENG-IMP is unknown.
- ▶ Studies have not assessed whether indefinite retention of an expired ENG-IMP is associated with any adverse effect.
- ▶ There is inadequate evidence to inform whether there is any risk associated with presence of an expired ENG-IMP during pregnancy.

**Table 6: Switching from the etonogestrel implant to a hormonal method of contraception**

Situation		Starting CHC/POP/ ENG-IMP	Starting DMPA	Starting LNG-IUS
Removal of ENG-IMP in situ for ≤3 years		Start immediately No additional precautions	Start immediately No additional precautions	Insert immediately No additional precautions
Removal of ENG-IMP in situ for >3 but ≤4 years	PT negative <b>AND all UPSI ≥21 days ago</b>	Start immediately Condoms for 7 days (2 days POP)	Start immediately Condoms for 7 days	Insert immediately (PT <b>MUST</b> be negative) Condoms for 7 days
	PT negative <b>but UPSI within the last 21 days</b>	Start immediately Condoms for 7 days (2 days POP) PT 21 days after last UPSI	Start immediately Condoms for 7 days PT 21 days after last UPSI	Insert immediately* (PT <b>MUST</b> be negative) Condoms for 7 days PT 21 days after last UPSI
Removal of ENG-IMP in situ for >4 years	PT negative <b>AND all UPSI ≥21 days ago</b>	Start immediately Condoms for 7 days (2 days POP)	Start immediately Condoms for 7 days	Insert immediately (PT <b>MUST</b> be negative) Condoms for 7 days
	PT negative <b>but UPSI within the last 21 days</b>	Consider EC Start immediately (or after 5 days if UPA-EC given) Condoms until 7 days after starting new method (2 days for POP) PT 21 days after last UPSI	Consider EC Consider bridging with CHC/POP/ENG-IMP. If bridging unacceptable or unsuitable, start DMPA immediately (or after 5 days if UPA-EC given) Condoms for 7 days after DMPA given PT 21 days after last UPSI	Consider EC Delay insertion until pregnancy excluded by negative PT 21 days after last UPSI and consider bridging with CHC/POP/ENG-IMP (or DMPA if other methods unacceptable or unsuitable)

CHC, combined hormonal contraception; DMPA, depot medroxyprogesterone acetate; EC, emergency contraception; ENG-IMP, etonogestrel implant; LNG-IUS, levonorgestrel-releasing intrauterine system; POP, progestogen-only pill; PT, pregnancy test; UPA-EC, ulipristal acetate emergency contraception; UPSI, unprotected sexual intercourse.

\*This is a change to guidance, based on the fact that risk of pregnancy in the fourth year of use of ENG-IMP is likely to be very low and to compare favourably with use of CHC, POP and DMPA.

**Table 7: Switching from the etonogestrel implant to a non-hormonal method of contraception**

Situation		Starting Cu-IUD	Starting condoms
Removal of ENG-IMP in situ for ≤3 years		Insert immediately No additional precautions	Start immediately
Removal of ENG-IMP in situ for >3 but ≤4 years	PT negative <b>AND all UPSI ≥21 days ago</b>	Insert immediately (PT <b>MUST</b> be negative) No additional precautions	Start immediately
	PT negative <b>but UPSI within the last 21 days</b>	Insert immediately (PT <b>MUST</b> be negative) No additional precautions Consider PT 21 days after last UPSI	Start immediately Consider PT 21 days after last UPSI
Removal of ENG-IMP in situ for >4 years	PT negative <b>AND all UPSI ≥21 days ago</b>	Insert immediately (PT <b>MUST</b> be negative)	Start immediately
	PT negative <b>but UPSI within the last 21 days</b>	If all UPSI either ≥21 days ago or <5 days ago, insert immediately  If UPSI between 5 and 21 days ago, delay insertion until pregnancy excluded by negative PT 21 days after last UPSI  Consider oral EC  Consider bridging with CHC/POP/ENG-IMP (or DMPA if other methods unsuitable or unacceptable)	Start immediately Consider EC PT 21 days after last UPSI

CHC, combined hormonal contraception; Cu-IUD, copper intrauterine device; DMPA, depot medroxyprogesterone acetate; EC, emergency contraception; ENG-IMP, etonogestrel implant; POP, progestogen-only pill; PT, pregnancy test; UPSI, unprotected sexual intercourse.

After discussion, some individuals may make an informed decision to leave their ENG-IMP in situ indefinitely.

An ENG-IMP that is in the upper arm but is not in the position recommended by current guidance should *not* be removed solely because of its position.

**15.3 Standard etonogestrel implant removal procedure**

ENG-IMPs should only be removed by HCPs who have undergone formal training in ENG-IMP removal technique. It is noted that there is little published evaluation of specific Nexplanon insertion and removal techniques and that practice and opinion vary. Procedures described in this guideline are based on the opinion and experience of the GDG and are intended as a guide to good practice, but are not evidence-based.

See [Appendix 3 \(Suggested standard Nexplanon removal procedure\)](#).

**15.4 Advice after etonogestrel implant removal**

After etonogestrel implant removal, users should be provided with the following information:

**FSRH**

- ▶ Potential fertility from time of implant removal
- ▶ Any requirement for additional contraceptive precautions and follow-up pregnancy testing
- ▶ Options for (and access to) ongoing contraception unless a further subdermal implant has been inserted
- ▶ Wound care
- ▶ Likelihood of initial discomfort and bruising
- ▶ Signs of local infection and how to access review if infection is suspected
- ▶ When to remove any paper sutures.

The GDG recommends that routine follow-up by a HCP is not required after ENG-IMP removal or replacement.

## 16 Local anaesthesia for implant insertion and removal procedures

### 16.1 Lidocaine 1%

Lidocaine 1% is the accepted standard local anaesthetic for implant insertion and removal. It may be used with or without adrenaline 1:200 000 (adrenaline may reduce local bleeding). The syringe plunger should be drawn back prior to the injection to reduce risk of accidental intravenous administration. The skin should be infiltrated at the point of insertion; some clinicians choose also (in line with manufacturer guidance) to infiltrate along the insertion track, although there are no pain receptors in the subdermal layer. A maximum of 2–3 ml of 1% lidocaine is required.

### 16.2 Ethyl chloride spray

Ethyl chloride spray is an inexpensive vapocoolant that by cooling the skin and reducing impulses in local sensory nerves produces a local anaesthetic effect of rapid onset but short duration of action. The GDG considers that ethyl chloride spray is a good alternative to lidocaine for implant insertion procedures where the skin is not affected by conditions such as eczema or broken prior to the procedure. Care must be taken to follow manufacturer instructions to avoid over-cooling of the skin. Ethyl chloride spray may be of particular benefit for individuals who wish to avoid needles and those with lidocaine allergy. The insertion procedure needs to be performed quickly after application as the anaesthetic effect is of short duration (about 60 seconds). This makes ethyl chloride less suitable for implant removal procedures, but its use may be considered by individual HCPs.

#### *The evidence*

A 2016 Cochrane review<sup>124</sup> of RCTs that compared ethyl chloride spray and similar vapocoolants to placebo or no anaesthesia at the time of venous cannulation concluded that ethyl chloride application itself was associated with mild discomfort, but that it reduced the pain associated with the procedure. No serious adverse events were reported.

A small study<sup>125</sup> of use of ethyl chloride spray for ENG-IMP insertion reported that staff found use of ethyl chloride spray straightforward and that anaesthesia was adequate, without reported adverse side effects. The authors reported a projected cost saving compared with use of lidocaine. Larger studies would be required to ascertain whether the vapocoolant effect and the necessarily rapid insertion procedure have any impact on correct insertion.

## 17 Implant insertion and removal in anticoagulated individuals, those with inherited bleeding disorders and people with low platelet count

Both ENG-IMP insertion and standard ENG-IMP removal are minor procedures with minimal risk of significant bleeding (similar to that associated with minor dermatological procedures, dental extraction and cardiac pacemaker implantation).<sup>126,127</sup> Local haemostasis is likely to be achieved by application of wound site pressure. The risk of significant bleeding associated with these procedures in individuals using warfarin (with a stable international normalised ratio (INR)), direct-acting oral anticoagulants, low molecular weight heparin or antiplatelet drugs is likely to be low. In contrast, there is a risk of thrombosis if anticoagulants are stopped, which could in some cases have life-threatening consequences.

Warfarin,<sup>126</sup> direct oral anticoagulants,<sup>126,128</sup> low molecular weight heparin and antiplatelet drugs<sup>129</sup> should generally not be stopped for ENG-IMP insertion or standard removal. For individuals using direct oral anticoagulants or low molecular weight heparin, procedures should be scheduled to coincide with the lowest anticoagulant effect; for example, if the dose is taken daily in the evening, insertion in the afternoon would carry a lower bleeding risk than insertion in the morning. Non-steroidal anti-inflammatory drugs for pain relief should be avoided in the periprocedure period to avoid increased risk of bleeding.

Expert opinion suggests that a platelet count  $>50 \times 10^9/L$  is adequate for standard ENG-IMP insertion and removal procedures.

For individuals with inherited bleeding and platelet disorders and platelet count  $<50 \times 10^9/L$ , management of bleeding associated with implant insertion and removal procedures should be discussed with the haematologist on an individual basis.

See FSRH CEU Statement [Management of women taking anticoagulants or antiplatelet medications who request intrauterine contraception or subdermal implants](#).<sup>130</sup>

## 18 Complications of implant insertion and removal

Problems associated with ENG-IMP insertion or removal are uncommon and serious complications are rare.

### *The evidence*

A manufacturer-sponsored prospective cohort study (2011–2017) followed up 7364 Nexplanon insertions and 5159 removal procedures undertaken in the USA by 428 HCPs who had undergone insertion and removal training.<sup>131</sup>

**Insertion-related events.** In this study, 0.9% (95% CI 0.7%–1.1%) of insertions were reported to be deep, 0.4% (95% CI 0.2%–0.5%) were partial and there was one non-insertion (recognised at the time). Amongst the 65 deep insertions, two were located within muscle and 56 were adjacent to the deep fascia. There were no cases of intravascular insertion or distant migration, but the authors noted that the study was underpowered to detect rare events. Complications of insertion significant enough to require review were uncommon: 2.4% (95% CI 2.0%–2.8%) of participants reported “severe pain” in the implant arm at any time during follow-up; 2.8% (95% CI 2.4%–3.2%) reported pins and needles/



numbness in the arm, hand or fingers and 1% (95% CI 0.8%-1.3%) reported altered strength or movement.

**Removal-related events.** In this study, adverse removal-related events were rare. Multiple removal attempts were required in 0.3% (95% CI 0.2%-0.5%) of cases. Implants for removal were “too deep” in 0.25% of cases and had migrated locally in 0.14%. Almost half the participants were followed up 6 months or more after implant removal. Of these participants, 0.7% reported sensory disturbance in the hand or arm, 0.3% reported severe pain and 0.23% reported motor disturbance.

## 18.1 Implant migration

### Key information

- D** Cases of local migration of the ENG-IMP have been reported.
- D** Rare cases of intravascular insertion of the ENG-IMP and subsequent distant vascular migration have occurred.

### Clinical recommendations

- ✓ Individuals considering use of the ENG-IMP should be advised that intravascular insertion and distant migration are rare complications of the Nexplanon insertion procedure.
- ✓ ENG-IMP users should be advised to feel for the implant in their arm once the insertion wound has healed to check that it is in situ. If they cannot feel their implant at any time, users should have its presence confirmed by an HCP.
- ✓ HCPs should consider the possibility of implant migration if the implant is not palpable near to the insertion site.

### The evidence

**Local and non-vascular migration.** Evidence from an observational study that followed up 100 Implanon insertions (over biceps) suggests that if inserted correctly, migration of the implant from the insertion site was typically less than 2 cm.<sup>132</sup> There are, however, case reports of greater local migration.

Literature review identifies a small number of case reports of local migration of ENG-IMP 6–12 cm from their insertion site towards the axilla.<sup>133–139</sup> In addition, Kang *et al*<sup>140</sup> reported 11 cases of ENG-IMP migration to the axilla, one to the chest wall, two to the region of the clavicle/“neck line” and one to the shoulder region. These cases (from various countries) had been reported to the United States Food and Drug Administration (FDA) adverse event reporting system and had not been reported elsewhere in the literature.

Evidence level 4

Evidence level 4

Evidence level 4

**Distant vascular migration.** Rare cases have been reported of intravascular ENG-IMP insertion with subsequent distant vascular migration (usually to the pulmonary vasculature). Data held by the manufacturer suggest that worldwide there is one case of intravascular migration for every 1.3 million implants sold.<sup>120</sup> Other estimates differ, however. A survey<sup>141</sup> of French physicians identified 12 cases of Nexplanon migration to the pulmonary vasculature between January 2012 and July 2017. In the same period, French databases recorded insertion of 1.2 million Nexplanon implants. This suggests a rate of Nexplanon migration to the pulmonary vasculature of 1 in 100 000. There may be additional unrecognised or unreported intravascular insertions. It is noted that (unlike in the UK) in France there is no requirement for formal training in Nexplanon insertion. International case reports<sup>142–158</sup> describe intravascular migration of 17 ENG-IMP (both Implanon and Nexplanon) to the pulmonary vasculature after presumed insertion into veins in the upper arm. Kang *et al*<sup>140</sup> reported nine and Ohannessian *et al*<sup>141</sup> reported seven additional cases of implant migration to the pulmonary vasculature.

In some cases subjects reported significant local haematoma at the time of insertion, or later cough, chest pain or dyspnoea; others were asymptomatic. After establishing the absence of the implants from both arms, Nexplanon implants were located using X-ray and/or computed tomography (CT) scan. Many of the implants were retrieved from the pulmonary vasculature endovascularly; a few required thoracoscopy, and some individuals opted to leave the devices in situ.

One case of distal embolisation of an implant inserted into the brachial artery is reported, with initial profuse bleeding at the time of insertion and symptomatic distal arterial occlusion a few days later.<sup>159</sup>

### GDG conclusion

The GDG recommends that individuals considering ENG-IMP insertion should be made aware that intravascular insertion and distant migration are rare complications of the insertion procedure. Users should be advised to feel for their implant once the insertion wound has healed to check that it is in situ and to seek review by an HCP if they cannot feel the implant. It is noted that while some individuals with intravascular insertion reported associated symptoms including excessive bruising or haematoma at the insertion site, dyspnoea and cough, others were asymptomatic.

For management of non-palpable implants see **Section 19**. Cases of implant migration should be managed by specialist sexual and reproductive healthcare (SRH) services according to local protocols. All cases should be reported to the manufacturer and to the Medicines and Healthcare products Regulatory Agency (MHRA) so that accurate data can be collected.

## 18.2 Local reaction

Implant site pain during ENG-IMP use was reported by around 3%-5% of users, and local haematoma by about 2% of users in manufacturer-funded observational studies.<sup>2,28,85</sup>

Case studies<sup>160–167</sup> have described a small number of individual cases of local erythema, swelling, itch and pain, sometimes with purulent discharge, fractured implant or eruption of the implant through the skin. Some cases occurred soon after insertion, others after a significant interval and recurrence





with subsequent implants has been described. Authors variously attribute these local reactions to infection or allergy (possibly, it has been suggested, to barium). Variable response to treatment with antibiotics and/or antihistamine has been reported. Personal correspondence from specialist implant removers describes similar cases, many requiring removal of the implant to achieve resolution, despite use of antibiotics.<sup>168</sup>

There is no clear evidence-based approach to such cases. The GDG suggests that early intervention with antibiotics/incision and drainage is appropriate if infection is suspected and that removal should be considered, certainly if the implant has erupted through the skin.

### 18.3 Nerve damage

Case studies describe cases of neuropathy (most affecting the ulnar nerve) associated with ENG-IMP insertion<sup>169–173</sup> and injury to the median, cutaneous and ulnar nerves associated with ENG-IMP removal; in some cases, lasting loss of sensory and motor function is reported.<sup>174–182</sup> Robust data to inform incidence do not exist, as cases are not reliably reported and recorded.

### 18.4 Intramuscular insertion

Case studies describe individual cases of intramuscular insertion of ENG-IMP and removal of ENG-IMP from muscle.<sup>183–186</sup> Robust data to inform incidence do not exist, as cases are not reliably reported and recorded.

## 19 Impalpable and deeply sited etonogestrel implants

### *Clinical recommendations*



**No attempt should be made to remove an impalpable ENG-IMP that has not been localised.**



**If an ENG-IMP is impalpable, additional contraceptive precautions should be advised and investigation to locate the implant should be decided in consultation with local specialist services.**



**Removal of an ENG-IMP that is deeply sited in the arm should only be undertaken by a specialist trained in complex implant removal techniques.**

### 19.1 Initial management of impalpable implants

No attempt should be made to remove an impalpable implant that has not been localised. After checking that the ENG-IMP cannot be felt in the other arm, a pregnancy test should be taken, and advice given to use additional contraception until the presence of the implant is confirmed. Further investigation should be decided in consultation with local specialist SRH services according to their protocol. Initial investigation may include localisation of the implant by X-ray of the arm (note that Implanon is not radio-opaque) or by ultrasound using a high-frequency linear array transducer (10 MHz or greater).

### 19.2 Etonogestrel implants that have been identified deeply sited in the arm

**Contraceptive effectiveness.** Studies have not specifically considered the contraceptive effectiveness of an ENG-IMP that is in the arm, but sited more deeply than subdermal. In practice,

however, it is generally considered that a user may rely on a deeply sited ENG-IMP (that has been confirmed to be present) for contraception for 3 years after insertion.

Referral should be made to specialist services for removal after 3 years of use, or at the request of the user. Some individuals may opt to leave a deeply sited implant in situ indefinitely to avoid risk associated with removal (see [Section 15.2](#)). It is noted that a retained implant is likely to continue to have an effect on fertility for a considerable (but unknown) time after expiry.

**Removal.** To minimise risk of neurovascular damage, removal of an ENG-IMP that is impalpable or difficult to palpate should only be attempted after it has been localised in the arm, and then only by a practitioner trained and experienced in complex implant removal techniques, usually with ultrasound guidance<sup>187–193</sup> (fluoroscopic guidance has also been described<sup>184,187</sup>). Various techniques for removal of deeply sited implants are described in the literature,<sup>184,187,189,194–197</sup> there is no clear evidence as to which technique is safest or most effective; choice of method will often depend on implant location. Description of such specialist techniques is beyond the scope of this guideline.

### 19.3 Etonogestrel implants that are not identified in the arm

If, after appropriate imaging, the ENG-IMP is not identified in the arm, further investigation by specialist services may include serum ENG assay and imaging of the chest – chest X-ray/CT/CT pulmonary angiography according to local protocol.<sup>142–157</sup> Case studies report both percutaneous and endovascular retrieval of implants from the pulmonary vasculature as well as implants left in situ.<sup>142–157</sup>

## 20 Broken implants

Case studies have reported instances of ENG-IMPs (both Implanon and Nexplanon) that became bent or broken into two or more pieces whilst in situ.<sup>164,198–206</sup> In some cases, the patient was aware of blunt trauma to the arm, or of a hypersensitivity reaction at the implant site, but often there was no history of trauma or local reaction. In some cases, a change of bleeding pattern was noted around the time of implant breakage. No published evidence is identified to inform the *in vivo* contraceptive effectiveness of a bent or broken ENG-IMP. Cases of contraceptive failure associated with broken implants have been reported.<sup>14</sup>

In a statement on behalf of the manufacturer (MSD) in 2012,<sup>207</sup> Dr Hans Rekers stated:

“With a broken implant, the surface area of the skin [of the implant] will still be the same, as will the core content. The only difference is that instead of two ends there will now be four. The additional release surface for etonogestrel of two extra circles with a diameter of 2 mm is 6.28 mm<sup>2</sup>. This is small compared with the total release surface of an intact implant: 257 mm<sup>2</sup>.

During early development of Implanon, implants were deliberately damaged (bent and carved with a razor) to investigate their etonogestrel release rate *in vitro*. The *in vitro* release rate of the damaged implants increased only slightly compared to the *in vitro* release rate of undamaged implants (data on file, MSD, Oss, The Netherlands). The contraceptive efficacy will therefore not be affected by implant breakage. The decision whether or not to remove and replace a broken or bent Implanon or Nexplanon must be based on clinical judgment and discussion with the patient.”



The GDG recommends that users with a damaged ENG-IMP in situ should be informed that on the basis of laboratory studies, the manufacturer recommends that contraceptive effectiveness is not affected. Removal and replacement can, however, be offered, based on clinical judgement and patient preference.

### 20.1 Removal of broken etonogestrel implants

There is no agreed standard technique for removal of a broken ENG-IMP. The GDG suggests that removal through an incision over the site of breakage of an implant that is broken into two pieces may allow removal by a 'pop-up' technique from each end through a single incision. However, clinical judgement is required in individual cases. After removal, the implant should be checked and measured to ensure that the entire 4 cm device has been removed.

If an implant is damaged it is recommended that the problem is reported to the manufacturer and the [MHRA Yellow Card scheme](#).<sup>208</sup>

## 21 Cost-effectiveness of the etonogestrel implant

### Key information

**D**

**Evidence suggests that the ENG-IMP is highly cost-effective for services compared to use of no contraception or oral contraception.**

Costs associated with the ENG-IMP include not only that of the device itself, but also those costs associated with insertion, removal and management of implant-associated problems. To assess cost-effectiveness, these are weighed against costs associated with unplanned pregnancy and provision of other contraceptive methods. Non-contraceptive benefits may also be taken into account. Cost-effectiveness is dependent on duration of continued use.

### The evidence

Studies have modelled the cost-effectiveness of the ENG-IMP compared to other contraceptive methods and to no contraception, using estimated costs associated with method provision, management of method-related problems, method discontinuation and unplanned pregnancy and often using estimates from other observational studies for typical use contraceptive failure rate and method continuation. Such models, in UK and US settings, indicate that the ENG-IMP is highly cost-effective compared with use of no contraception and that it becomes cost-effective compared with oral contraception within 2–3 years of continued use.<sup>209–213</sup>

Evidence level 2-

A retrospective review<sup>214</sup> of 36 months of records for 493 ENG-IMP users and 493 users of oral contraception compared cost-effectiveness for the methods based on outcomes (eg, discontinuation, unplanned pregnancy) in real-life clinical practice in the UK in 2003–2006. In this cohort as a whole, the ENG-IMP was found to be more cost-effective than oral contraception even within the first 12 months of use.

Discontinuation is noted to be a major driver of cost-effectiveness of LARC.<sup>209</sup> Reported continuation rates vary widely between studies, which reflect diverse healthcare settings and different populations across different time periods. These do not necessarily reflect continuation rates for LARC in the

current UK setting. Thus cost-effectiveness of the ENG-IMP in the current UK setting relative to other effective methods of contraception is difficult to estimate accurately.

## 22 Other progestogen-only implants

The ENG-IMP is the only progestogen-only implant currently available in the UK. In other parts of the world, two-rod LNG implants (Jadelle<sup>215</sup> and Sino-implant (II)<sup>216</sup> with 5- and 4-year contraceptive licences, respectively) are widely used. The older, six-rod LNG Norplant<sup>217</sup> was licensed for contraception for 5 years. It is suggested that individuals requesting removal of such devices are referred to specialist services as recommended removal techniques differ from that for Nexplanon.

## Recommendations for future research

- ▶ Effectiveness of the ENG-IMP during a year of extended use
- ▶ Effectiveness of ENG-IMP in women with severe obesity
- ▶ Effect of ENG-IMP on BMD and fracture risk
- ▶ Effectiveness of addition of a desogestrel POP to manage problematic bleeding
- ▶ Risk of neurovascular damage and deep insertion associated with the new manufacturer-recommended insertion site

## Considerations for implementation of this guideline

The FSRH CEU produces a range of resources (summaries, webinars, lectures) to facilitate dissemination of guideline content and raise awareness of any changes to recommended practice. Changes in FSRH guidance are highlighted in FSRH emails to its membership and via social media platforms and are incorporated into FSRH training and educational materials. The FSRH CEU supports and facilitates national audit relevant to the key auditable standards for each FSRH guideline.

For this guideline there is a resource requirement associated with change of insertion site. HCPs that have been trained in Nexplanon insertion will be required to update their training to ensure that they identify the recommended insertion site and carry out the insertion procedure correctly. The change to FSRH guidance reflects a change in guidance from the manufacturer intended to improve safety. The manufacturer has produced audiovisual training resources to support retraining, and FSRH training and training materials will align with the manufacturer resources and this guidance.

## Useful links

- ▶ Audiovisual resources from Merck Sharp & Dohme B.V. on the insertion and removal of IMPLANON NXT<sup>®</sup>, 68 mg etonogestrel, implant for subdermal use. Available online [here](#).
- ▶ Contraceptive implant leaflets for patients from the Family Planning Association (FPA): the sexual health company. Available online [here](#).

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## Appendix 1: FSRH clinical guideline development process

### Who has developed the guideline?

This guideline is produced by the Clinical Effectiveness Unit (CEU) with support from the Clinical Effectiveness Committee (CEC) of the Faculty of Sexual & Reproductive Healthcare (FSRH). The FSRH is a registered charitable organisation which funds the development of its own clinical guidelines. NHS Lothian is contracted to host the CEU in the Chalmers Centre and to provide the CEU's services using ring-fenced funding from the FSRH. No other external funding is received. Chalmers Centre supports the CEU in terms of accommodation, facilities, education, training and clinical advice for the members' enquiry service. As an organisation, NHS Lothian has no editorial influence over CEU guidelines, although staff members may be invited to join the CEU's multidisciplinary guideline development groups (GDGs) in an individual professional capacity.

Development of the guideline was led by the secretariat (CEU staff) and involved the intended users of the guidelines (contraception providers) and patient/service user representatives as part of a multidisciplinary group. The scope of the guideline was informed by a scoping survey conducted among members of the FSRH and among service users from two sexual and reproductive health services (New Croft Centre, Newcastle upon Tyne Hospital NHS Foundation Trust and Chalmers Centre, Edinburgh NHS Lothian) across the UK. The first draft of the guideline was produced based on the final scope of the guideline agreed by the GDG. The first draft of the guideline (version 0.1) was reviewed by the GDG and a revised draft guideline (version 0.2) was produced in response to comments received, after which it was sent to international and UK-based external independent reviewers suggested by the GDG at the face-to-face meeting. A further revision generated a version of the draft guideline (version 0.3) which was placed on the FSRH website for public consultation between 15 June and 13 July 2020. The revised draft guideline (version 0.4) was sent to the GDG for final comments and to reach consensus on the recommendations (details of this process are given later).

Below is the list of contributors involved in the development of this clinical guideline.

### Guideline development group (GDG)

#### Secretariat

▶ Dr Sarah Hardman	Co-Director, Clinical Effectiveness Unit
▶ Dr Chelsea Morroni	Deputy Director, Clinical Effectiveness Unit
▶ Dr Zhong Eric Chen	Researcher, Clinical Effectiveness Unit
▶ Mrs Valerie Warner Findlay	Researcher, Clinical Effectiveness Unit

#### Multidisciplinary group

▶ Dr Savita Brito-Mutunayagam	Specialist Registrar in Community SRH, Honorary Research Fellow (University of Aberdeen)
▶ Dr Rachel D'Souza	Consultant in SRH (Margaret Pyke Centre, London)

▶ Dr Cindy Farmer	Associate Specialist Doctor in SRH (Unity Sexual Health Services, Bristol), Chair of General Training Committee, FSRH
▶ Dr Katherine Gilmore	Specialist Registrar in Community SRH (Newcastle upon Tyne)
▶ Dr Debbie Hallott	General Practitioner (New Southgate Surgery, Wakefield)
▶ Ms Claire Nicol	Advance Nurse Practitioner (Chalmers Centre, Edinburgh)
▶ Dr Farah Paruk	General Practitioner (Leighton Road Surgery, London), Chair of Clinical Effectiveness Committee, FSRH
▶ Dr Katherine Weaver	Associate Specialist in SRH (Chalmers Centre, Edinburgh)
▶ Mrs Michelle Kivlin	Patient Representative
▶ Ms Eilidh MacIver	Patient Representative

### Independent reviewers

▶ Clinical Associate Professor Deborah Bateson	Medical Director Family Planning (New South Wales, Australia)
▶ Dr Katie Boog	Consultant in Community SRH (NHS Fife)
▶ Professor Alison Edelman	Professor of Obstetrics and Gynecology (Oregon Health & Science University)
▶ Professor Oskari Heikinheimo	Professor, Department of Obstetrics and Gynecology (University of Helsinki)
▶ Associate Professor Raymond Li	Associate Professor in Obstetrics and Gynaecology, The University of Hong Kong) and Honorary Medical Consultant (The Family Planning Association of Hong Kong)

### Declaration of interests

None of the individuals involved had competing interests that prevented their active participation in the development of this guideline.

▶ Clinical Associate Professor Deborah Bateson	I have provided independent clinical education on Implanon NXT at sessions which have been sponsored by MSD. I am involved in an investigator-initiated clinical study on midwife-led postpartum implants which is funded in part by MSD.
▶ Dr Katie Boog	I have received payment from Consilient Healthcare to lecture at contraception training events where Consilient had no influence on the content of the talks.
▶ Professor Alison Edelman	I have received honoraria from Merck as a Trainer; no funds directly received since 2016. I have also received funding from Merck for an investigator-initiated project since December 2016 for which I am the Principal Investigator.





<p>▶ Dr Cindy Farmer</p>	<p>I have received honoraria from MSD to speak at the FSRH Current Choices lunchtime symposium. I am clinical lead in the development of the FSRH complex implant removal qualification.</p>
<p>▶ Professor Oskari Heikinheimo</p>	<p>I have served occasionally on advisory boards for Bayer AG, Exelgyn SAS, Gedeon Richter, Sandoz A/S and Vifor Pharma, and have designed and lectured at educational events for these companies.</p>

**Patient involvement**

Service users from two sexual and reproductive health services (New Croft Centre, Newcastle upon Tyne Hospital NHS Foundation Trust and Chalmers Centre, Edinburgh NHS Lothian) across the UK were involved in providing feedback on the scope of the guideline.

Two patient representatives were involved consistently throughout the development process. They provided valuable feedback on multiple drafts of the guideline; their input informed and supported the content and the development of recommendations.

**Public consultation contributors**

We would like to thank the contributors who provided their valuable feedback during the public consultation.

**Guideline development methodology**

This FSRH guideline was developed in accordance with the standard methodology for developing FSRH clinical guidelines (outlined in the FSRH’s ‘Framework for Clinical Guideline Development’ which can be accessed [here](#)). The methodology used in the development of this guideline has been accredited by the National Institute for Health and Care Excellence (NICE).

**Systematic review of evidence**

A systematic review of the literature was conducted to identify evidence to answer the clinical questions formulated and agreed by the GDG. Searches were performed using relevant medical subject headings and free-text terms using the following databases: PubMed, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, the Cumulative Index to Nursing and Allied Health Literature (CINAHL) and POPLINE. Further, the National Guideline Clearinghouse (NGC) and Scottish Intercollegiate Guideline Network (SIGN) were also used to identify relevant guidelines produced by other organisations; these guidelines were checked to identify missing evidence. No language restrictions were applied to the searches.

**Search date.** The databases were initially searched up to 17 February 2019. The evidence identified up to this point was used to develop the first draft of the guideline. The searches were re-run up to 3 March 2020 to check additional evidence published since the initial search. Any evidence published after this date was not considered for inclusion.

**Search strategy.** The literature search was performed separately for the different subcategories covered in this clinical guideline.

Articles identified from the search were screened by title and abstract and full-text copies were obtained if the articles addressed the clinical questions relevant to the guideline. A full critical appraisal of each article was conducted. Studies that did not report relevant outcomes or were not relevant to the clinical questions were excluded.

### Synthesis of evidence and making clinical recommendations

The recommendations are graded (A, B, C, D and Good Practice Point) according to the level of evidence upon which they are based (see later). The highest level of evidence that may be available depends on the type of clinical question asked. The CEU adopts the comprehensive methodology developed by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) (<http://www.gradeworkinggroup.org/>) to assess the strength of the evidence collated and for generating recommendations from evidence.

### Considerations when making recommendations

FSRH clinical guidelines are produced primarily to recommend safe and appropriate clinical practice in relation to the provision of different contraceptive methods. Therefore, when formulating the recommendations, the GDG takes into consideration the health benefits, side effects and other risks associated with implementing the recommendations, based on the available evidence and expert opinion. Further, the GDG takes into consideration the different financial and organisational barriers that healthcare practitioners and services may face in the implementation of recommendations to ensure that the recommendations are realistic and achievable.

### Reaching consensus on the recommendations

When further revisions based on public consultation feedback have been made, members of the GDG were asked to complete a form to indicate whether they agree or disagree with the recommendations proposed. The consensus process is as follows:

- ▶ Consensus will be reached when 80% of the GDG members agree with the recommendation.
- ▶ Recommendations where consensus is not reached will be redrafted in the light of any feedback.
- ▶ The recommendation consensus form will be sent again for all recommendations. Consensus will be reached when 80% of the GDG members agree with the recommendation.
- ▶ If consensus is not reached on certain recommendations, these will be redrafted once more.
- ▶ If after one more round of consultation, consensus is still not reached, the recommendation will be taken to the CEC for final decision.
- ▶ Any group member who is not content with the decision can choose to have their disagreement noted within the guideline.

### Updating this guideline

Clinical guidelines are routinely due for update 5 years after publication. The decision as to whether update of a guideline is required will be based on the availability of new evidence published since its publication. Updates may also be triggered by the emergence of evidence expected to have an important impact on the recommendations. The final decision on whether to carry out a full or partial clinical guideline update is taken by the CEU in consultation with the CEC of the FSRH.

### Classification of evidence levels and grades of recommendations

The evidence used in this guideline was graded using the scheme below and the recommendations formulated in a similar fashion with a standardised grading scheme.



Classification of evidence levels			Grades of recommendations
<b>1++</b>	High-quality systematic reviews or meta-analysis of randomised controlled trials (RCTs) or RCTs with a very low risk of bias.	<b>A</b>	At least one systematic review, meta-analysis or RCT rated as 1++, and directly applicable to the target population; <i>or</i> A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results.
<b>1+</b>	Well-conducted systematic reviews or meta-analysis of RCTs or RCTs with a low risk of bias.		
<b>1-</b>	Systematic reviews or meta-analysis of RCTs or RCTs with a high risk of bias.		
<b>2++</b>	High-quality systematic reviews of case-control or cohort studies or high-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal.	<b>B</b>	A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results; <i>or</i> Extrapolated evidence from studies rated as 1++ or 1+.
<b>2+</b>	Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal.	<b>C</b>	A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; <i>or</i> Extrapolated evidence from studies rated as 2++.
<b>2-</b>	Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal.	<b>D</b>	Evidence level 3 or 4; <i>or</i> Extrapolated evidence from studies rated as 2+.
<b>3</b>	Non-analytical studies (eg, case report, case series).		
<b>4</b>	Expert opinions.	✓	Good Practice Points based on the clinical experience of the guideline development group.*

\*On the occasion when the GDG finds there is an important practical point that they wish to emphasise but for which there is not, nor is there likely to be, any research evidence. This will typically be where some aspect of treatment is regarded as such sound clinical practice that nobody is likely to question it. It must be emphasised that these are NOT an alternative to evidence-based recommendations, and should only be used where there is no alternative means of highlighting the issue.

**Appendix 2: Suggested Nexplanon insertion procedure**

**NOTE THAT THIS IS BASED ON THE OPINION AND EXPERIENCE OF THE GUIDELINE DEVELOPMENT GROUP AND IS INTENDED AS A GUIDE ONLY.**

- ▶ **NEXPLANON SHOULD ONLY BE INSERTED BY A HEALTHCARE PRACTITIONER WHO HAS UNDERTAKEN APPROPRIATE TRAINING IN THE PROCEDURE AND MAINTAINED UP-TO-DATE SKILLS.**

▶ **Resuscitation equipment**

Ensure resuscitation equipment is available as required by local protocol. There is a small risk of collapse due to vasovagal reaction or anaphylaxis.<sup>218</sup>

▶ **Positioning the patient**

- ▶ Lie the patient flat on their back.
- ▶ Identify the non-dominant arm.
- ▶ Place the patient's arm in the appropriate position:
  - ▶ Abduct the arm to 90°
  - ▶ Bend the arm at the elbow
  - ▶ Put the patient's hand under their head.

▶ **Identifying the insertion point**

See diagrams included in the Nexplanon package insert, diagrams in the SPC for Nexplanon<sup>5</sup> and video (insertion and removal) online at [www.nexplanonvideos.eu](http://www.nexplanonvideos.eu).<sup>163</sup>

- ▶ Identify the sulcal line (the groove between brachialis/biceps anteriorly and triceps posteriorly) by asking the individual to tense the muscles. Consider marking the sulcal line.
- ▶ Measure 8–10 cm along the sulcal line from the medial epicondyle. From this point measure 3–5 cm posteriorly over triceps, perpendicular to the sulcal line. Consider making a mark here to identify the insertion site. A mark may also be made on the sulcal line 5 cm proximal to the insertion site to guide the direction of insertion.
- ▶ **Put on gloves (non-sterile or sterile) and clean the skin at the insertion site using chlorhexidine and alcohol or similar, according to local policy.**<sup>219</sup> The GDG is unable to comment as to whether wipes or solution should be used.
  - ▶ A 'no-touch' technique should be used from this point on to minimise infection risk.
  - ▶ Ensure that the arm remains in the correct insertion position as described above; do not straighten the arm during insertion.
  - ▶ Avoid puncturing the skin through any ink mark to avoid tattooing.
- ▶ **Anaesthetise the insertion site using either lidocaine 1% or ethyl chloride spray**
  - ▶ **Lidocaine 1%** may be used with or without adrenaline 1:200 000 (adrenaline may reduce bleeding). Aspirate prior to injection to avoid accidental intravenous administration. Infiltrate the skin at the point of insertion; some clinicians choose (and the SPC recommends) also to infiltrate along the insertion track, although there are no pain receptors in the subdermal layer. A maximum of 2–3 ml of lidocaine 1% is required.
  - ▶ **Ethyl chloride spray.** Spray the insertion site (avoiding contact with the face) for approximately 5 seconds, until the skin looks visibly white. Insertion must then be immediate, within 45–60 seconds. It is important to avoid over-cooling of the skin.
- ▶ **Nexplanon insertion**

**NOTE THAT THE INSERTION DEVICE MUST NOT BE RELIED UPON TO ENSURE SUPERFICIAL INSERTION.**

  - ▶ Keep the skin taught using the non-inserting hand (avoid putting fingers in front of the needle tip).
  - ▶ Work at eye level to ensure adequate visualisation.
  - ▶ Grip the insertion device on the textured areas just above the needle.

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- ▶ **Puncture the skin at the insertion site with the insertion needle at <math><30^\circ</math> to skin surface.** To avoid tattooing, insertion should be immediately adjacent to any insertion site mark rather than through the ink mark.
- ▶ **Once the skin has been punctured, lower the applicator to a horizontal position** and retract the insertion device slightly until the bevel is just under the skin (this aims to aid superficial subdermal insertion).
- ▶ **Advance the insertion needle proximally in the subdermal layer, parallel to the sulcal line while lifting the skin with the inserter.**
  - ▶ View from the side at eye level so that the applicator does not obstruct your ability to watch the needle advancing under the skin.
  - ▶ Ensure the insertion needle is always parallel to the skin surface.
  - ▶ Do not touch the purple trigger until you have **fully** inserted the needle subdermally as this would retract the needle and prematurely release the implant from the applicator.
- ▶ **Once the full length of the insertion needle is under the skin, lift the applicator and observe from the side to ensure subdermal insertion.**
  - ▶ If at this stage the insertion needle appears too deep, withdraw the applicator with the implant still in place until the bevel is just visible, then reinsert subdermally.
- ▶ **Once subdermal positioning is confirmed, keep the applicator still and pull the purple trigger back fully.**
  - ▶ This releases the implant under the skin and withdraws the insertion needle into the plastic casing. Check the insertion device to ensure that the implant has been inserted before disposing of the insertion device in a sharps bin.
- ▶ **Post-insertion**
  - ▶ Apply local pressure until haemostasis is achieved.
  - ▶ The practitioner must palpate the implant in situ following insertion (palpate both ends).
  - ▶ Apply a sterile pressure dressing for 24–48 hours. Some practitioners also apply a sterile adhesive dressing to the insertion site, underneath the pressure dressing.
  - ▶ Advise patient about infection, bruising and wound care.
  - ▶ Advise patient to feel for implant on removal of the dressing (with clean hands).

### Appendix 3: Suggested standard Nexplanon removal procedure (palpable implants with ‘pop-up’ sign only)

**NOTE THAT THIS IS BASED ON THE OPINION AND EXPERIENCE OF THE GUIDELINE DEVELOPMENT GROUP AND IS INTENDED AS A GUIDE ONLY.**

- ▶ **NEXPLANON SHOULD ONLY BE REMOVED BY A HEALTHCARE PRACTITIONER WHO HAS UNDERTAKEN APPROPRIATE TRAINING IN THE PROCEDURE AND MAINTAINED UP-TO-DATE SKILLS.**
- ▶ **Resuscitation equipment**
  - ▶ Ensure that resuscitation equipment is available as required by local protocol. There is a small risk of collapse due to vasovagal reaction or anaphylaxis.<sup>218</sup>

▶ **Identify the implant by palpation**

- ▶ Palpate the full length of the implant if possible.
- ▶ Ensure that the distal end pops up to the skin surface when gentle pressure is applied at the proximal end.
- ▶ If the implant is impalpable, difficult to feel or likely to be difficult to remove, do not attempt removal and refer to a specialist service.

▶ **Positioning the patient**

- ▶ Lie the patient flat on their back.
- ▶ Place the arm in the appropriate position. This will vary according to implant site. For removals at the new recommended site:
  - ▶ Abduct the arm to 90°
  - ▶ Bend the arm at the elbow
  - ▶ Put the patient's hand under their head.

An alternative position may be used if this enables better access to the removal site.

▶ **Anaesthetise the removal site**

Lidocaine 1% may be used with or without adrenaline 1:200 000 (adrenaline may reduce bleeding). Aspirate prior to injection to avoid accidental intravenous administration.

- ▶ Identify the distal end of the implant and push up to the skin surface by gently pressing on the proximal end.
- ▶ Clean the skin at the removal site using chlorhexidine and alcohol or similar, according to local policy.<sup>219</sup> The GDG is unable to comment as to whether wipes or solution should be used.
- ▶ Inject a maximum total of 0.5–1 ml lidocaine 1% into the skin overlying the distal end of the implant (some clinicians inject some of this subdermally just under the distal tip).

▶ **Removal equipment**

- ▶ Lay sterile removal equipment on a sterile field.
- ▶ Put on sterile gloves.
- ▶ **From this point onwards, aseptic technique is required.**

▶ **Removal procedure**

Note that the removal attempt should be stopped if there is any indication of nerve pain.

- ▶ Clean the area around the removal site again with chlorhexidine and alcohol or similar, according to local policy.<sup>219</sup> The GDG is unable to comment as to whether wipes or solution should be used.
- ▶ Ensure adequate visualisation.
- ▶ Pop up distal end of implant to skin surface using gentle pressure at the proximal end.
- ▶ Using a scalpel make a **small** (2 mm) longitudinal incision directly over the distal tip of the implant, at the site where the local anaesthetic was injected.
- ▶ Push the implant gently from the proximal end using the index finger of the non-removing hand to direct the distal end towards the incision site ('pop-out' technique). Push until the tip is visible at the incision.
- ▶ If the implant is encapsulated, make a small, gentle cut across the tissue sheath over the end of the visible implant so that the implant can be pushed out of the sheath.
- ▶ Grasp the implant with gloved fingers and remove.
- ▶ If the implant cannot be grasped, forceps can be used to gently grasp the implant. Only use forceps if the implant is visible at the incision site.

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- ▶ **Ensure that the complete implant has been removed (4 cm).** Consider measuring the removed implant to confirm.
  
- ▶ **Post-removal**
  - ▶ Apply pressure until haemostasis is achieved.
  - ▶ Apply paper sutures to oppose skin edges.
  - ▶ Apply sterile pressure dressing for 48 hours (some clinicians also apply a sterile adhesive dressing under the pressure dressing).
  - ▶ Advise the patient about infection, bruising and wound care.

## Questions for continuing professional development

- 1 Which of the following is the primary mechanism of action of the etonogestrel implant (ENG-IMP)?
  - a) Prevention of fertilisation
  - b) Delay of implantation
  - c) Inhibition of ovulation
  - d) Foreign body effect
- 2 When considering potential drug interactions, which of the following is **TRUE**?
  - a) Individuals taking ulipristal acetate for emergency contraception (UPA-EC) should be advised to wait 5 days before insertion of the ENG-IMP
  - b) Individuals taking levonorgestrel for emergency contraception (LNG-EC) should be advised to wait 5 days before insertion of the ENG-IMP
  - c) Individuals using an enzyme-inducing drug should be informed that the contraceptive effectiveness of the ENG-IMP could be reduced during use of the drug and for up to 7 days after stopping it
  - d) Individuals receiving treatment for chlamydia should be informed that the contraceptive effectiveness of the ENG-IMP could be reduced during use of doxycycline and for up to 7 days after stopping it
- 3 When considering duration of use of the ENG-IMP, which of the following statements is **TRUE**?
  - a) The FSRH recommends that the ENG-IMP can routinely be used for contraception for 3 years in users weighing >100 kg
  - b) The FSRH recommends that the ENG-IMP can routinely be used for contraception for 4 years
  - c) The FSRH recommends that the ENG-IMP can routinely be used for contraception for 4 years unless the user weighs >100 kg
  - d) The FSRH recommends that the ENG-IMP has no contraceptive effect after 3 years of use
- 4 Which of the following is UKMEC3 for initiation of the ENG-IMP?
  - a) Past migraine with aura
  - b) Past stroke
  - c) Past venous thromboembolism (VTE)
  - d) Past breast cancer
- 5 Regarding risk of adverse events associated with the use of the ENG-IMP, which of the following statements is **FALSE**?
  - a) Available evidence suggests no increased risk of venous or arterial thromboembolic events
  - b) The evidence indicates that the absolute risk of ectopic pregnancy is extremely small
  - c) Evidence suggests a possible small increase in breast cancer risk
  - d) Available evidence excludes any effect on bone mineral density
- 6 When can the ENG-IMP be inserted *without* the need for 7 days of additional precautions?
  - a) On day 7 of a natural menstrual cycle
  - b) On day 7 after abortion or miscarriage
  - c) On day 28 after childbirth if not breastfeeding
  - d) On day 42 after childbirth if fulfils lactational amenorrhoea method (LAM) criteria
- 7 When switching from another method of contraception, when can the ENG-IMP be inserted without the need for additional precautions?
  - a) At 14 weeks after the last depot medroxyprogesterone acetate (DMPA) injection
  - b) Switching from a correctly-taken levonorgestrel progestogen-only pill (POP)
  - c) Switching from a correctly-taken combined oral contraceptive (COC) on day 7 of the hormone-free interval
  - d) If removing an intrauterine system (IUS) on the same day as insertion





- 8 Regarding the ENG-IMP and emergency contraception (EC), which of the following statements is **TRUE**?
- Individuals should be advised to abstain for 7 days prior to ENG-IMP removal
  - UPA-EC should be considered if there has been unprotected sexual intercourse (UPSI) in the 5 days prior to ENG-IMP removal
  - EC should be considered if the ENG-IMP is not palpable and there has been UPSI in the last 5 days
  - LNG-EC should be considered if there has been UPSI in the 48 hours prior to ENG-IMP removal
- 9 When removing an ENG-IMP that has been in situ for <3 years, in which situation are additional precautions required?
- Switching to DMPA if the individual is taking sodium valproate
  - Switching to the desogestrel POP if the individual was taking St John's Wort until 2 weeks ago
  - Switching to an IUS if the individual was taking a COC to control bleeding until a week ago
  - Switching to a COC if the individual is taking a desogestrel POP to control bleeding
- 10 When considering bleeding patterns during use of an ENG-IMP, which of the following statements is **TRUE**?
- If bleeding pattern is 'unfavourable' in the first month of use there is a 10% chance that it will improve
  - On average the number of days of bleeding/spotting is greater than with use of combined hormonal contraception
  - Unpredictable bleeding/spotting is common and bleeding pattern may change at any time
  - The number of days of bleeding/spotting reduces over time and most users are amenorrhoeic by 1 year

## Auditable outcomes

- ▶ 100% of users have had a drug history taken to identify any drug interactions that could affect contraceptive effectiveness of the ENG-IMP.
- ▶ 100% of individuals starting the ENG-IMP have been advised about likely bleeding patterns.
- ▶ 100% of individuals quick starting the ENG-IMP have been advised to use additional contraceptive precautions for 7 days.
- ▶ 100% of healthcare practitioners undertaking Nexplanon insertion and removal procedures have been appropriately trained and have up-to-date FSRH certification or have maintained local accreditation through agreed local pathways.
- ▶ 100% of Nexplanon implants have been inserted at the site recommended by the manufacturer (the point of insertion should be identified by measuring 8–10 cm proximally from the medial epicondyle along the sulcal line and then 3–5 cm posteriorly (over triceps), perpendicular to the sulcal line), except in exceptional, documented circumstances.

## Comments and feedback on published guideline

All comments on published guideline can be sent directly to the Clinical Effectiveness Unit (CEU) of the Faculty of Sexual & Reproductive Healthcare (FSRH) via the FSRH website ([www.fsrh.org](http://www.fsrh.org)). The CEU may not respond individually to all feedback. However, the CEU will review all comments and provide an anonymised summary of comments and responses, which are reviewed by the Clinical Effectiveness Committee and any necessary amendments made subsequently.

### Correction notice

Since this set of guideline were published online the following changes have been made:

**July 2023** – Table 2 and Table 3 updated; Section 10.3 Breast cancer updated to reflect newly published evidence.