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## Progestogen-only subdermal implants

## What are progestogen-only subdermal implants?

This is a long-acting reversible contraceptive (LARC).

### **Available devices**

#### **Nexplanon®**

Nexplanon® is the only contraceptive implant on the UK market. From October 2010, it replaced the bio-equivalent Implanon®. It offered an improved insertion device and added barium sulfate to enable location of lost devices on X-ray.

Nexplanon® is a 4 cm flexible rod containing 68 mg etonogestrel (a progestogen) which is released slowly into the systemic circulation following subdermal insertion in the upper arm. [1] It must be removed after three years when it can be replaced immediately.

Norplant®, which consists of six small rods, was previously available in the UK, along with Norplant-2® (also called Jadelle®), which is still used in some countries.

## Mechanism of action

The main mechanism of action of Nexplanon® is to inhibit ovulation. It also thickens the cervical mucus, inhibiting the passage of sperm to the uterus, and thins the endometrium, preventing implantation were an egg to be fertilised.

## How common are progestogen-only subdermal implants? (Epidemiology)

Statistics on contraceptive use in the UK are sparse. The use of LARCs as a primary method of contraception amongst women has been slowly increasing and in 2017/18 accounted for 41% of all women making contact with sexual and reproductive health services. <sup>[2]</sup> This compares to 18% in 2003–04. 16% of the women in contact with sexual and reproductive health services, using LARCs in England in 2017/18, have the implant. <sup>[2]</sup> This data does not capture the use of implants fitted elsewhere, for example in general practice, in hospital, or at the time of termination of pregnancy.

## **Patient selection**

Progestogen-only subdermal implants (POSDIs) such as Nexplanon® are suitable for: [3]

- Those who want a reliable but reversible form of contraception which does not require daily vigilance or action at the time of intercourse.
- Women who have contra-indications to oestrogen therapy (another alternative is the injectable progestogen-only contraception).
- Diabetes it is not a contra-indication to using Nexplanon®.
- Breast-feeding it is not a contra-indication to using Nexplanon®.
- Migraine (with or without aura) it is not an absolute contraindication to using Nexplanon<sup>®</sup>.
- Body mass index (BMI) >30 kg/m²- higher body weight is not a not contra-indication to using Nexplanon®, indeed it has many advantages over the combined oral contraceptive (COC) pill for women at increased risk of VTE due to BMI. Because blood levels of etonogestrel are lower in the third year of use in women with a BMI >35 kg/m², the SPC says that 'it cannot be excluded that the contraceptive effect in [heavier] women during the third year of use may be lower than for women of normal weight. HPCs may therefore consider earlier replacement of the implant in heavier women. '[1] However, there is no evidence to support this requirement and the Faculty of Sexual and Reproductive Healthcare (FSRH) says that early replacement on the grounds of weight or BMI is not recommended. [4]

All patients should be carefully counselled before insertion - supplemented by a suitable patient information leaflet. [5]

### Failure rate

This is very low; most studies show no failures. In those studies where pregnancies were reported, rates were around 0.4 per 100 users over three years. The FSRH guidance notes that some studies include pregnancies occurring within 14 days of implant removal, and that postmarketing data and case studies usually refer to pregnancies which were conceived before the implant was inserted, before it became effective, or where the effectiveness was reduced due to the use of enzyme-inducing drugs. The number of true failures is very small and the implant has the lowest typical failure rate of any contraceptive method. [3] [4]

## Contra-indications<sup>[6]</sup>

All of the following are a UKMEC 4 (absolute contraindication) or UKMEC 3 (risks generally outweigh the benefits).

- Pregnancy:
  - Exclude pregnancy before insertion; a history of recent normal menstruation or reliable use of another contraceptive is adequate.
  - If there is any doubt, suggest a urine pregnancy test preinsertion.
  - Quick-starting, where pregnancy cannot be reliably excluded, is discussed below under timing of insertion.
- Unexplained vaginal bleeding.
- Progesterone-dependent cancers or a past history of breast cancer.
- Severe (decompensated) cirrhosis, hepatocellular adenomaand hepatocellular carcinoma.
- Continuation of implant use after a diagnosis of ischaemia heart disease or stroke - initiation in those circumstances is a UKMEC 2 (benefits generally outweigh risks).

- Hypersensitivity to any components of Nexplanon®.
- Acute porphyria, is not mentioned in the UKMEC, but other resources suggest that hormonal contraception may be dangerous. It would be sensible to discuss with the patient's consultant, if in doubt.
- Liver enzyme-inducing drugs eg, anti-epileptic drugs: The Summary of Product Characteristics (SPC) states that hepatic enzyme inducers may lower the blood levels of etonogestrel, which may explain some observed failures.
  - Women on short-term treatment with these drugs are advised to use a barrier method whilst taking the drug and for 28 days afterwards. This is not recommended if the drug being taken is teratogenic.
  - Women on long-term treatment with liver enzyme inducers are advised instead to consider using an intrauterine contraceptive device (IUD) or depot medroxyprogesterone acetate (DMPA). [7]
- Antiretroviral drugs for HIV- the advice above should be followed for enzyme inducing drugs. If there is any doubt about interactions, the Liverpool drug interactions checker is a reliable source to check. [8]

# Benefits of progestogen-only subdermal implants [9]

- Safety and convenience, steady dosing without an initial peak dose to the liver (as with injectables) or fluctuating hormone levels as with the contraceptive progestogen-only pill (POP).
- Dysmenorrhoea and pain associated with ovulation but with no identifiable cause may be improved or resolved by methods – including the implant – which suppress ovulation. It can also be used as part of the management of endometriosis.
- No demonstrable effect on systolic or diastolic blood pressure.
- Studies of women using Norplant® show very low rates of ectopic pregnancy. There are no studies of the effect of Nexplanon® on rates of ectopic pregnancy but because it inhibits ovulation it is presumed that the rates are very low. It is therefore suitable for women who have a history of ectopic pregnancy.

- Dysmenorrhoea usually improves while using Nexplanon®.
- There is no evidence of delay in return to fertility on removal of Nexplanon®. Etonogestrel levels are undetectable four days following removal.
- There is no evidence of reduced bone mineral density with Nexplanon<sup>®</sup>, unlike the contraceptive injection.
- There is no evidence (as for other progestogen-only contraceptives)
  of increased VTE risk.

## Disadvantages of progestogen-only subdermal implants [9]

- Local adverse effects can occur (infection, expulsion or migration of the device).
- No protection is provided against sexually transmitted infections.
- Unlike many methods of contraception, women cannot stop using an implant without the involvement of a properly trained healthcare professional.
- Removal of Nexplanon® is usually a straightforward minor operation under local anaesthetic but discomfort is possible.
- Possible complications include difficulty finding the rod and broken implants. [10]
- Women may experience worsening of, improvement to or new onset of, acne as a result of using the implant.

As with other progestogen-only methods, a change in bleeding pattern (amenorrhoea, irregular bleeding, menorrhagia) is common and is the main reason for early removal of Nexplanon®:

- The FSRH gives the following figures on bleeding patterns: [4]
  - Amenorrhoea 22%
  - Infrequent bleeding 34%
  - Normal frequency bleeding 38%
  - Frequent bleeding 7%
  - Prolonged bleeding = 18%
- Bleeding may be unpredictable and can change during use of the implant.
- If there are no contra-indications, short-term cyclical oestrogens
   (either as a COC pill or as ethinylestradiol), mefenamic acid and
   mifepristone may be of use in treating irregular or heavy bleeding.
   These uses are unlicensed. Counselling prior to insertion is important
   in decreasing discontinuation rates.

## Side-effects of progestogen-only subdermal implants

- Acne may improve or worsen while using Nexplanon®.
- If pregnancy occurs during use of hormonal contraception there is no evidence of increased risk of congenital malformation, but it is established practice that the implant be removed if the woman is continuing with the pregnancy. If the pregnancy is terminated, the implant can be left to provide ongoing contraception, if wished.
- Nausea, vomiting, dizziness and mastalgia. Breast pain may be caused by Nexplanon<sup>®</sup>.
- Breast cancer incidence is slightly raised during and for up to 10 years after use of progestogen-only contraceptives. The relative increase is around 20 30%; for most young women, with a very low background risk, this will result in a very small absolute increase. There is limited evidence on women who have a larger background risk, for example where there is a strong family history or genetic predisposition to breast cancer. [11]

There is no evidence that Nexplanon® causes headaches, weight gain, increased blood pressure, increased risk of VTE or changes in lipids or glucose. There is also no evidence that it has a clinically significant adverse effect on bone mineral density. [9]

## Administration of progestogen-only subdermal implants

### **Pre-insertion counselling**

- Always take a full medical history (family, menstrual, contraceptive and sexual).
- Always give full counselling about risks and benefits of the implant:
  - Method of insertion and removal of device, including possible adverse effects; women should be advised to expect some discomfort and bruising at the site of insertion.
  - Duration of action.
  - Timing of removal.
  - Return to fertility after removal.
  - Possible adverse effects of progestogen-only contraception.
- Always complete a sexual health risk assessment and include discussion of protection against sexually transmitted diseases.

### Timing

• Day 1-5 is the usual timing for immediate effect, with a recommendation of additional contraception for seven days after insertion if doing so at any other time in the menstrual cycle. [4] However, implants may be inserted at any time in the menstrual cycle as long as the woman is 'reasonably certain' that she is not pregnant. This includes those switching from another hormonal method of contraception. Therefore, if a woman is using DMPA or the COC pill then the implant may be inserted at any time without additional precautions.

- When switching from a levonorgestrel intrauterine device (LNG-IUD), the implant can be inserted immediately if the LNG-IUD was used correctly (or if the clinician is reasonably certain that the woman is not pregnant). The LNG-IUD should be continued for at least seven days.
- When switching from a copper intrauterine contraceptive device (Cu-IUD), the implant may be inserted immediately if the Cu-IUD was used correctly (or if the clinician is reasonably certain that the woman is not pregnant). The Cu-IUD should be continued for at least seven days.
- If the patient is amenorrhoeic or if insertion occurs after day 5 of the menstrual cycle, extra, non-hormonal contraceptive precautions should be taken for seven days.
- After termination of pregnancy (TOP) in the first or second trimester, insertion may take place immediately. If implanted >5 days after abortion or miscarriage, additional contraception is required for seven days.
- After pregnancy, Nexplanon® should be inserted 21-28 days after delivery or TOP. It may be inserted immediately but this may lead to an increase in irregular or heavy bleeding. If insertion takes place after day 28, additional contraception should be used for seven days.
- If a pregnancy cannot be excluded, the implant may be quick started if the woman prefers not to delay using contraception. A follow-up pregnancy test is needed, no sooner than 21 days after the last unprotected sexual intercourse. If ulipristal emergency contraception has been used, the implant insertion must be delayed until at least 5 days after the ulipristal. [12]

#### Insertion

Although the insertion technique is straightforward, it is a minor surgical procedure which cannot be learned from any book. Practical training (model arm plus supervised live patient training) is essential.

#### Method

 After injection of local anaesthetic, Nexplanon® is inserted into the subdermal tissue of the upper arm (flexor surface).

- After insertion, both the health professional and the patient should examine the arm and be satisfied that the implant is in place, thus reducing the risk of insertion failures.
- To replace a previous Nexplanon®, the new one may be inserted through the same removal incision, with additional local anaesthetic and ensuring that the needle is inserted to its full length.
- Technically difficult insertions are unusual (<1 in 100).

#### Removal

- Removal is usually simple and contraceptive effect is lost immediately.
- Under local anaesthetic, digital pressure is applied to the proximal end of the device where it is felt under the skin. A 2 mm incision over the distal end then leads to delivery of the rod, which is grasped with mosquito forceps. Formal practical training in the procedure is essential (model arm and supervised live patients).
- Good training minimises removal difficulties, including discomfort.
- Difficult removals usually relate to too-deep insertion. This is particularly a risk in thin or muscular woman who lack much subcutaneous tissue. Removal can also be difficult if a significant amount of weight has been gained since insertion. The device can be localised on X-ray but ultrasound guidance is needed for removal in these cases. Removal of a deep/impalpable implant should not be attempted in primary care; referral should be made to a deep implant removal clinic.

#### Follow-up

Unless the woman experiences problems, no follow-up is required until removal is due three years after insertion.

### St John's wort

St John's wort is a liver enzyme inducer available without prescription from health food shops and pharmacies, and is often used for premenstrual syndrome, headaches and anxiety and low mood.

There have been concerns for some years that St John's wort reduced the effectiveness of hormonal contraception, although at first there was uncertainty as to whether the theoretical risk translated into unplanned pregnancies.

In March 2014 the Medicines and Healthcare products Agency (MHRA) issued guidance on St John's wort and hormonal contraception, stating categorically that St John's wort reduces the effectiveness of these contraceptives and increases the risk of unplanned pregnancy. This applies to all hormonal contraceptives except intrauterine devices, for which there are currently no data. MHRA stated that four reports of suspected interactions between St John's wort and contraceptive implants resulting in unplanned pregnancy had been received through the Yellow Card Scheme since 2000. [13]

There are warnings about these interactions and their consequences in the product information provided with all contraceptives and the authorised St John's wort products. Some unlicensed products on the UK market or available online do not include the appropriate warnings regarding possible interactions.

Advise women who are using combined and progestogen-only hormonal contraceptives that herbal products containing St John's wort can decrease the effect of this contraceptive cover. Therefore, women taking hormonal contraception for pregnancy prevention should not take herbal products that contain St John's wort.

#### Dr Mary Lowth is an author or the original author of this leaflet.

Dr Hazell has written and presented on contraception for a variety of organisations. Some of these educational events have been sponsored by Organon, the company who makes Nexplanon in the UK.

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