Implants

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Implants
ENG-releasing implant

All data presented in this session are about the
Etonogestrel (ENG)-releasing implant
The only implant available across Europe
Contents
ENG implant

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- Mechanism of action
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- Health benefits
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- Summary
To design a single rod that provides controlled release of ENG over 3 years requires high-tech knowledge. It was discovered that a co-polymer, ethylene-vinyl acetate (EVA), appeared to be suitable for holding a hormonal substance and releasing it in a controllable manner.

Crystals of ENG are suspended in a polymer matrix of EVA to form a core. The core is then encased in an EVA membrane. This composition allows sustained release of ENG from an implant with a smaller surface area compared with previous implants.
ENG is mainly bound to albumin, which is not affected by changes in estrogen concentrations. This explains the small variations in serum concentrations of ENG, as will be shown shortly. (LNG is mainly bound to SHBG, which is affected by estradiol.) The half-life of ENG is around 25 h. This is much lower than the 41.7 h observed with LNG. Sixty percent of ENG is excreted in the urine and 40% in the faeces.

With a bioavailability that remains constant and close to 100% and a clearance of around 7.5 l/h it is evident that there is no accumulation and that the decrease in serum levels is only caused by the slightly decreasing release rate from the rod over time.
The main mechanism of action of Implanon is ovulation inhibition. Should there be an ovulatory escape, the thickness of the cervical mucus provides additional contraceptive protection. Concentrations that inhibit ovulation are achieved within 8 h of insertion.
2. Implanon (package insert) Manufactured by: N.V. Organon, Oss, The Netherlands, a subsidiary of Merck & Co., Inc., Whitehouse Station, NJ 08889, USA.

Ref 1:
The analysis included 11 international studies and data collected during 9 years of marketing experience (1998–2007). Seven studies were non-comparative; the four other studies included the six-rod LNG implant system or an IUD as a comparator. All studies except one were of at least 2 years’ duration, and all had contraceptive efficacy as the objective.

The integrated efficacy analysis included 923 non-breastfeeding women who were exposed to the implant for 24,100 cycles. No in-treatment or pre-treatment pregnancies were reported. Fifty post-treatment pregnancies were reported, six of which occurred within 14 days of implant removal, indicating that fertility had quickly returned. Over a 9 year
marketing period an overall pregnancy rate of 0.049 per 100 implants sold (estimated Pearl Index 0.031 based on all pregnancies reported) was calculated. When only counting contraceptive method failures the pregnancy rate amounts to 0.010 per 100 implants sold (estimated Pearl Index 0.006).

Ref 4:
The ENG implant was used by 200 women for at least 5 years. No pregnancies occurred during the additional 2 years of follow-up in either the ENG or LNG implant group.
This integrated safety analysis included 11 international studies of the 68 mg ENG implant, 10 of which had a duration of at least 2 years. Assessments included reports of adverse events, reasons and rates of discontinuation, insertion/removal complications, and the condition of the implant site. Metabolic and coagulation parameters are briefly discussed to fully describe the clinical safety profile.

In total, 942 women were exposed to the ENG implant for 24,679 cycles over the course of 1–5 years. The overall discontinuation rate was 32.7%; the most frequently reported reasons for discontinuation were adverse events (13.9%), bleeding irregularities (10.4%) and planning pregnancy (4.1%). The most commonly reported drug-related adverse event was headache (15.3%); however, headache was reported in only 1.6% of women as a reason for discontinuation. Insertion and removal times for the implant were short and there were few complications, none of which were major. From earlier studies it is known that treatment with this implant has little effect on metabolic and coagulation parameters.
In this study of 942 women using the ENG implant for at least 2 years, 11.8% of women had weight gain related to implant use. Objective analysis of weight change from baseline to last measurement revealed that 31% of women experienced no weight change or some weight loss. Twenty-five percent of women reported a weight increase of 0.1–2.5 kg, 24% reported an increase of 2.6–5.0 kg, 9% reported an increase of 5.1–7.5 kg, and a further 11% reported a weight increase 7.5 kg.


**Points to cover when seeing users of ENG implants complaining of unscheduled vaginal bleeding**

1. What are the woman’s main concerns?
2. Ask about her bleeding pattern prior to having the ENG implant fitted.
3. Ask her to describe the number of days each month she bleeds plus the number of episodes.
4. Does the bleeding or pain occur during or after sex, or is it associated with abdominal pain or urinary symptoms?
5. When was the implant fitted? Is the implant palpable? Is there any risk of pregnancy?
6. Have any other drugs or medication been taken, e.g. antiepileptic drugs?
7. Does she smoke and, if so, how much?
8. Is she at risk of an STI? Is she in a new sexual relationship, aged <25 years, or has had more than one partner in the last year?
9. When was her last cervical screening test?

- Frequent bleeding and prolonged bleeding are considered to be uncomfortable bleeding patterns for the majority of women.
- If the patient is unsatisfied with the bleeding pattern after 3 months of use, try to motivate her to persevere with the implant, as there is a high probability of an improvement in bleeding pattern.
- In the meantime, try to treat troublesome, prolonged bleeding as appropriate.
- Bleeding pattern after 6 months: amenorrhoea 18%; infrequent bleeding 30%; frequent bleeding 8%; prolonged bleeding 12%.
Management of bleeding irregularity

- Counsel the patient before implant insertion
- Exclude any organic pathology and STIs
- Treatments to stop prolonged bleeding:
  - Mefenamic acid 500 mg twice daily for 5 days
  - Ibuprofen 500–800 mg 2–3 times daily for 5 days
  - Doxycycline twice daily for 5 days
  - Tranexamic acid 500 mg twice daily for 5 days
  - Norethisterone 5 mg 2–3 times daily for 21 days/2–3 cycles
  - Mifepristone (off-label)
  - Estradiol 2 mg for 7 days/ estradiol patch 50 µg/24h
  - Cyclic CHCs for 2–3 months (if no contraindications)

Ref 1:
Literature was identified through database searches, reference lists, organisations and individuals, covering the period until December 2006. Twenty-three randomised controlled trials enrolling 2674 participants were included. Seventy percent were determined to reflect low to moderate risk of bias.

- **Estrogen treatments** reduced the number of days of an ongoing bleeding episode in DMPA and Norplant users. However, treatment frequently led to study discontinuation due to gastrointestinal upset. Estrogen 50 μg patch for 7 days is another option based on clinical experience.

- **Combinations of oral ethinylestradiol and levonorgestrel** improved bleeding patterns in Norplant users, but method discontinuation rates were unchanged. One trial reported successful use of combined oral contraceptives in treating amenorrhoea among DMPA users.

- **Tranexamic acid, mifepristone combined with an estrogen, and doxycycline** were more effective than placebo in terminating an episode of bleeding in women using progestin-only contraceptives, according to three
small studies.

Norplant users, but not Implanon users, administered the anti-progestin mifepristone reported fewer days of bleeding than those given placebo. Mifepristone used monthly by new Norplant users reduced bleeding when compared with placebo.

A variety of NSAIDS have been evaluated for their ability to treat abnormal bleeding, with mixed results.

Norplant users receiving tamoxifen had less unacceptable bleeding after treatment and were more likely to continue using Norplant than those receiving placebo.

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Contraindications

A small number of women may not be able to use implants

- Breast cancer
- Acute VTE, LE
- Severe liver disease
- Breastfeeding < 6 weeks postpartum (not recommended)

Adapted from Ref 1
With Implanon, no back-up method is needed if it is initiated within the first 5 days of the menstrual cycle.

If Implanon is initiated >5 days after the start of menstruation, the woman should be advised to use a back-up contraceptive method, such as condoms, for the first 7 days following insertion.

A woman who is not breastfeeding may have an implant inserted immediately after delivery. If a woman who is not breastfeeding wants to start using implants more than 4 weeks after she has given birth, pregnancy must be ruled before insertion.

Ideally, women who are breastfeeding should not start using implants until 6 weeks postpartum, because of theoretical concern that hormones in breast milk may have an adverse effect on the newborn during the first 6 weeks after birth.
Implant: Summary

- Safe and highly effective
- Low-dose (caution with enzyme-inducing drugs)
- Can be used in women with contraindications against estrogen use
- Most important adverse events: bleeding irregularity, weight gain, acne (rare)
- Effect on mood not clear
- No negative effect on lactation
- Immediate return of fertility

- Because it is a one-rod system, **insertion and removal** of Implanon might be expected to be more rapid than with a multi-rod system such as Norplant. This was confirmed in comparative studies which showed that both insertion and removal of Implanon were about four times faster than for Norplant.
- In 633 women, the mean time for insertion was 1.1 min (range 0.3–5 min) and for removal 2.6 min (range 0.2–20 min).
If the implant can not be localised by physical examination:
1. Localise the implant using radiology: US, MRI, CT, RX (try to remove the implant under US control).
2. If it can not be found using an imaging technique, carry out a blood analysis to check the ENG level.
3. Send the patient to a specialised, experienced centre for removal of the implant.

Caution: The ulnar nerve is very close.