TOPIC : Implant

Implants

An advanced slide kit complementing the WHO training tool is available from: www.fptraining.org

Update January 2020

TOPIC : Implant

ENG-releasing implant

All data presented in this session are about the

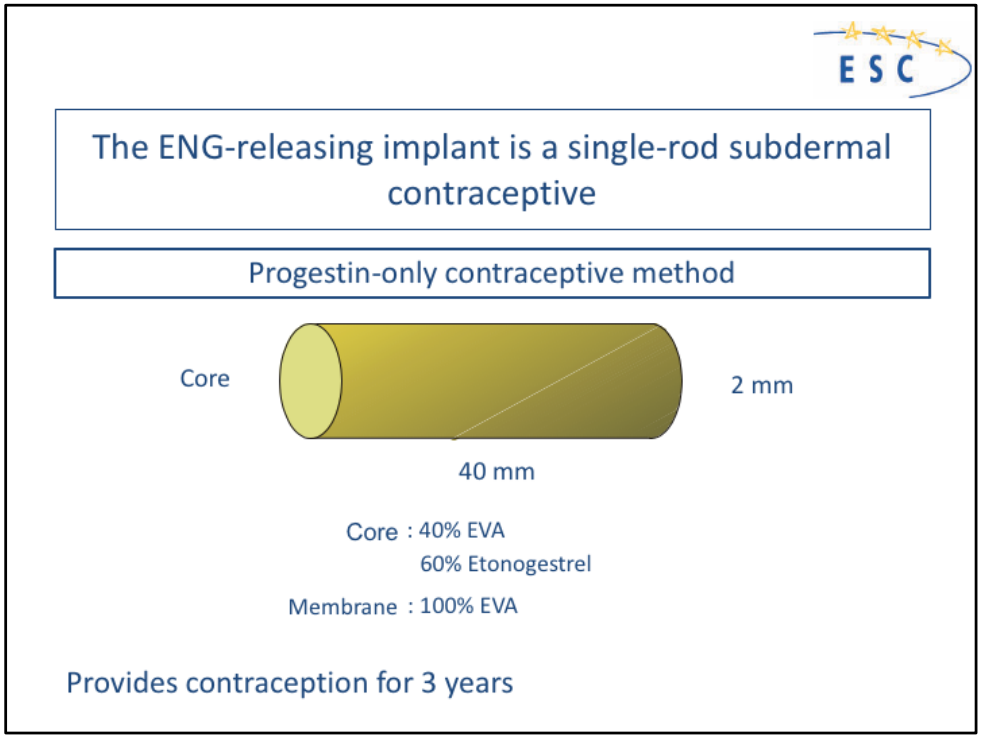
Etonogestrel (ENG)-releasing implant

The only implant available across Europe

TOPIC : Implant

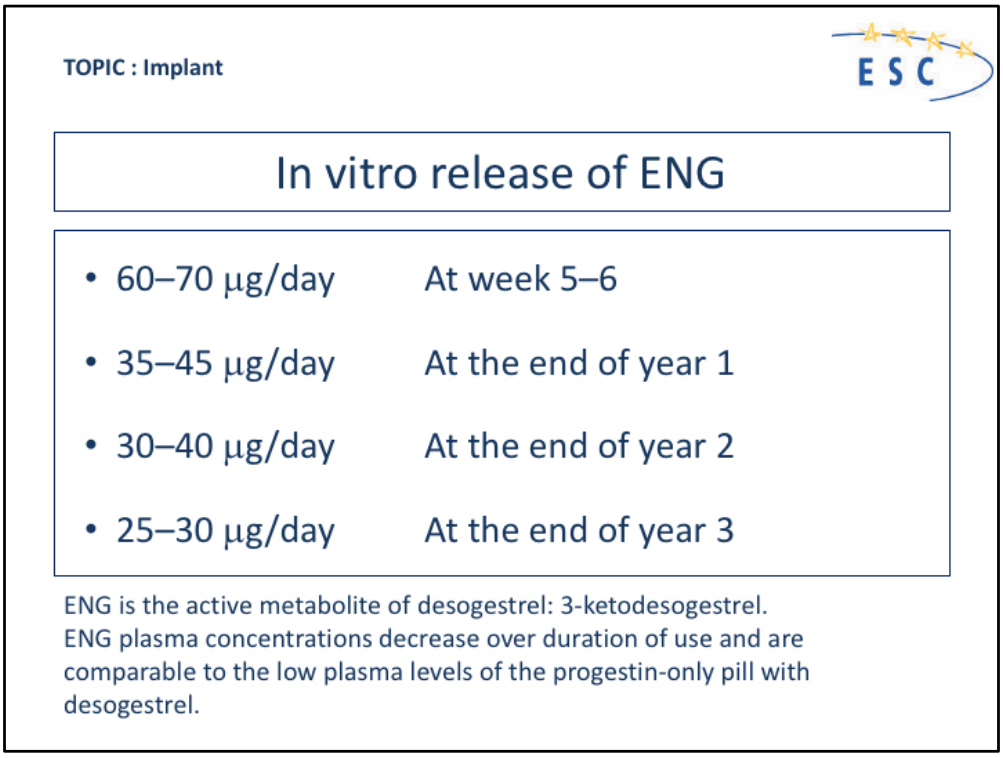
Contents

- General characteristics
- Mechanisms of action
- Contraceptive efficacy
- Insertion and removal, return of fertility
- Contraindications
- Adverse events
- Bleeding pattern and treatment
- Discontinuation
- Summary



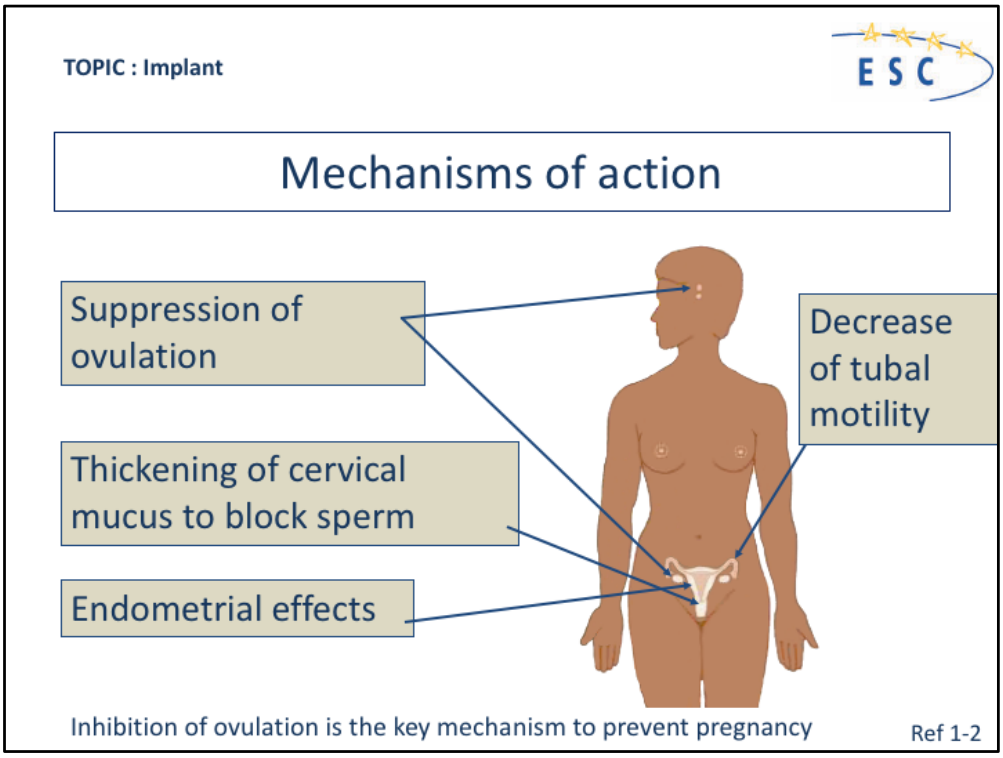
To design a single rod that provides controlled release of ENG over 3 years requires high-tech knowledge. It was discovered that a co-polymer, ethylene-vinyl acetate (EVA), appeared to be suitable for holding a hormonal substance and releasing it in a controllable manner.

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.



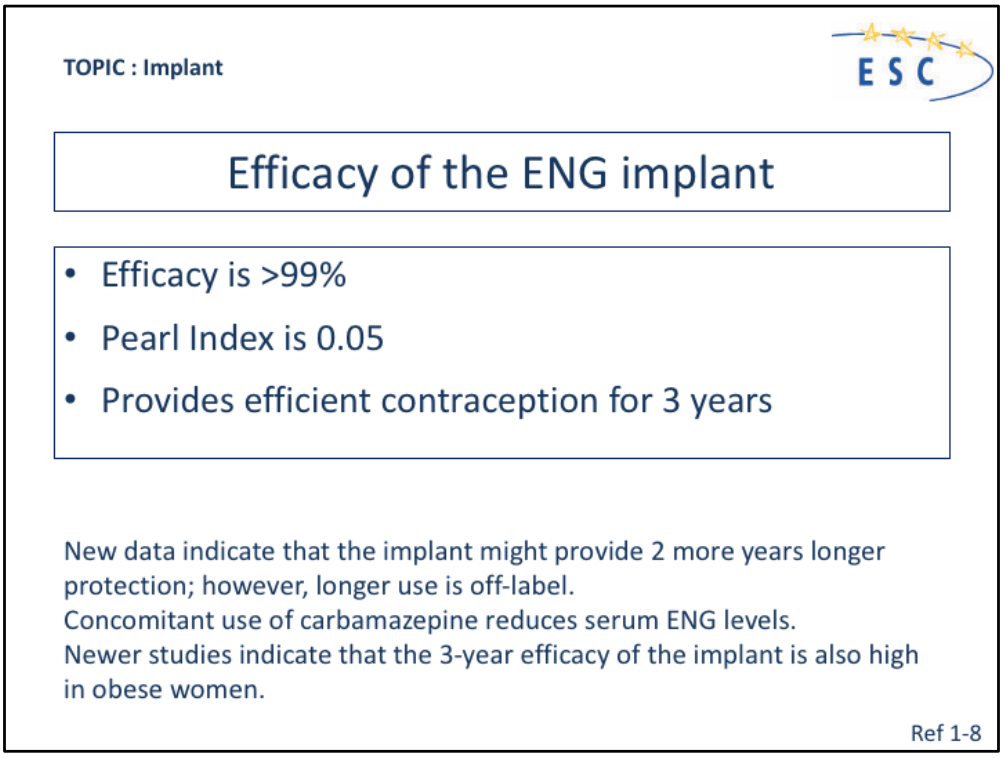
ENG is mainly bound to albumin, which is not affected by changes in estrogen concentrations. This explains the small variations in serum concentrations of ENG, as will be shown shortly. (LNG is mainly bound to SHBG, which is affected by estradiol.) The half-life of ENG is around 25 h. This is much lower 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.



1. Implanon (package insert) Manufactured by: N.V. Organon, Oss, The Netherlands, a subsidiary of Merck & Co., Inc., Whitehouse Station,NJ 08889, USA.
2. Mäkäräinen L et al. Ovarian function during the use of a single contraceptive implant: Implanon compared with Norplant. Fertil Steril 1998; 69: 714–21.

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.



1. Graesslin O et al. The contraceptive efficacy of Implanon: a review of clinical trials and marketing experience. Eur J Contracept Reprod Health Care 2008; 13 (suppl 1): 4–12.
2. Implanon (package insert) Manufactured by: N.V. Organon, Oss, The Netherlands, a subsidiary of Merck & Co., Inc., Whitehouse Station,NJ 08889, USA.
3. Mansour D et al. The effects of Implanon on menstrual bleeding patterns. Eur J Contracept Reprod Health Care 2008; 13 (suppl 1): 13–28.
4. Ali M et al. Extended use up to 5 years of the etonogestrel-releasing subdermal contraceptive implant: comparison to levonorgestrel-releasing subdermal implant. Hum Reprod 2016; 31: 2491–8.
5. McNicholas C et al. Prolonged Use of the Etonogestrel Implant and Levonorgestrel Intrauterine Device - Two Years Beyond FDA-Approved Duration. Am J Obstet Gynecol 2017; 216(6): 586.e1–586.e6.
6. Lazorwitz A et al. The effect of carbamazepine on etonogestrel concentrations in contraceptive implant users. Contraception 2017; 95(6): 571-577.
7. Morrell KM et al. Relationship between etonogestrel level and BMI in women using the contraceptive implant for more than 1 year. Contraception 2016; 93(3): 263-5.
8. Ciangura C et al. Etonorgestrel concentrations in morbidly obese women following Roux-en-Y gastric bypass surgery: three case reports. Contraception 2011;

84(6):649-51.

** In the official label the implant is licensed*

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).

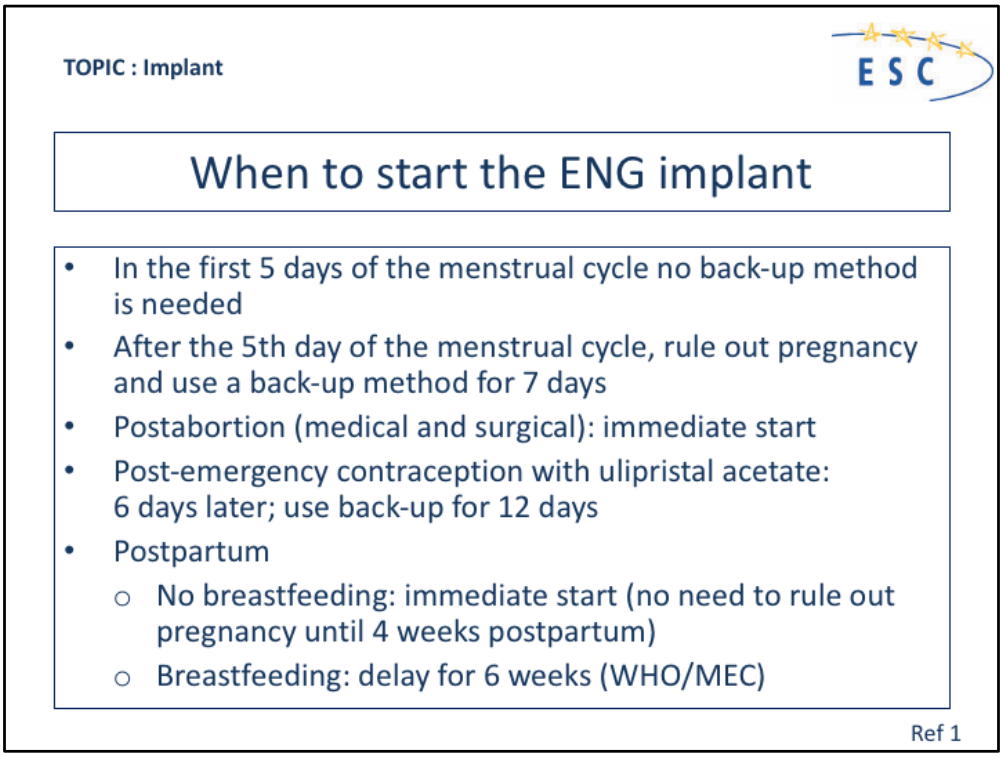
Ref 4:
The ENG implant was used by 200 women for at least 5 years. No pregnancies occurred during the additional 2 years of follow-up in either the ENG or LNG implant group.

Ref 5. There have been no documented pregnancies in implant users during the two years of post-expiration follow up. Calculated failure rates in the fourth and fifth years for the implant are calculated as 0 (one-sided %97.5 confidence interval (CI) 0–1.48) per 100 woman years at four years and 0 (one-sided %97.5 CI 0–2.65) per 100 women years at five years. Serum etonogestrel evaluation demonstrates median levels remain above the ovulation threshold of 90pg/ml for women of in all BMI classes.

Ref 6. Carbamazepine use significantly reduces serum etonogestrel concentrations in women using an etonogestrel contraceptive implant, with the majority of participants having etonogestrel concentrations below the threshold for ovulatory suppression. Our findings suggest that treatment with carbamazepine might increase the risk of pregnancy in etonogestrel implant users.

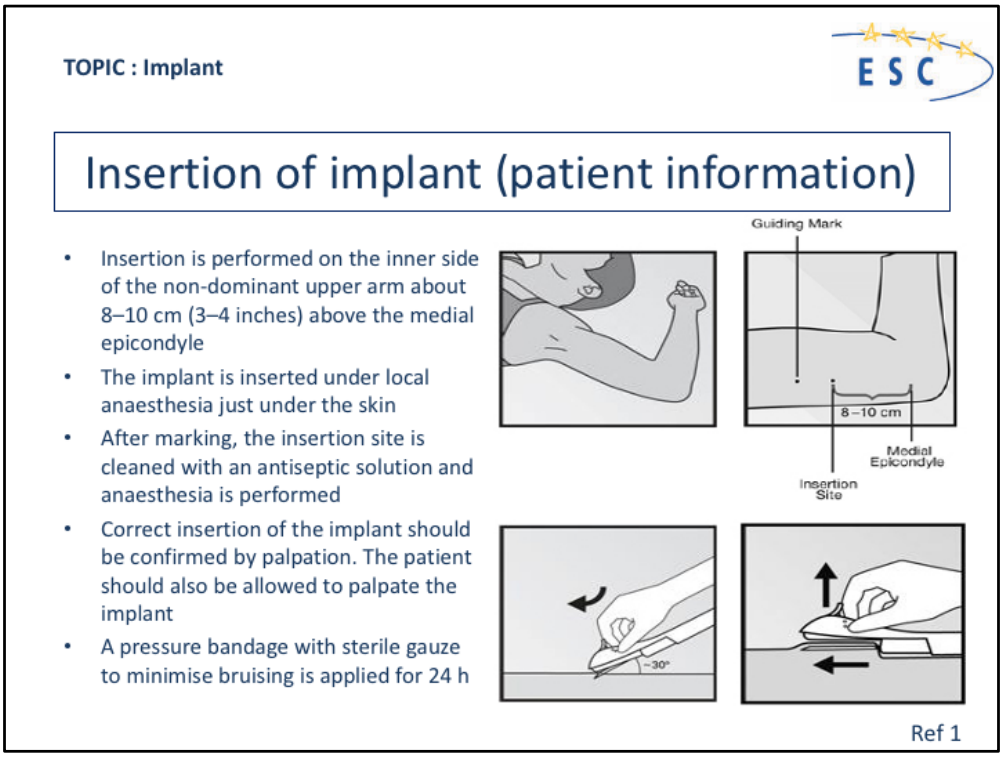
Ref 7. The results of this study further support that ENG levels independent of

BMI through 3 years of implant use and are thus reassuring that ENG implants will be effective for women of all BMIs.



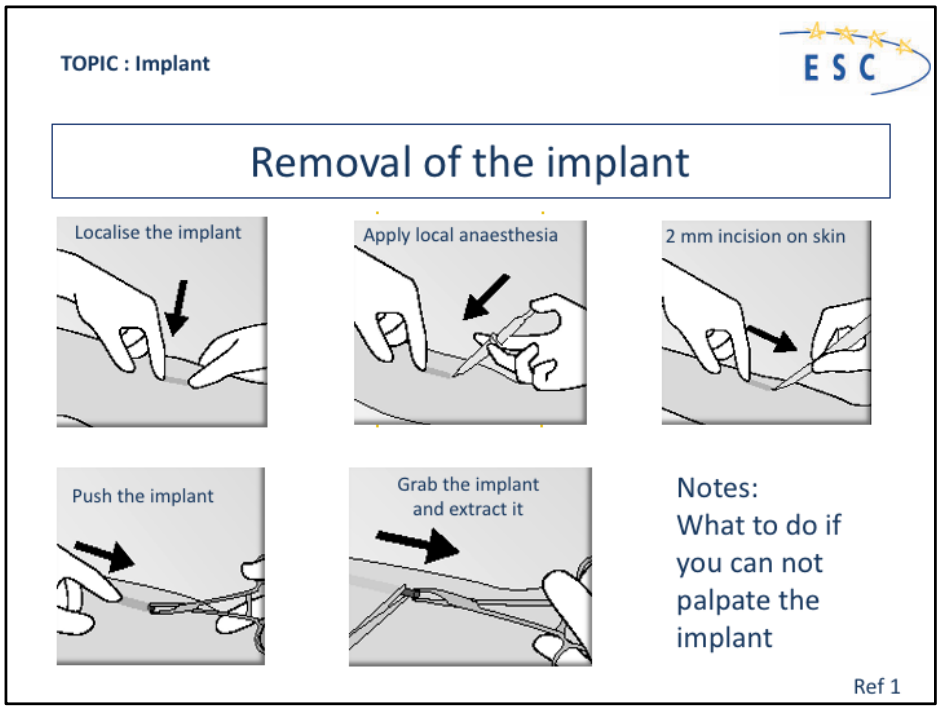
1. *World Health Organization. Selected practice recommendations for contraceptive use. 3rd ed. Geneva: WHO, 2016.*

- 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.



1. *Mascarenhas L et al. Insertion and removal of Implanon. Contraception 1998; 58 (6 suppl): 79–83S.*

- 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).



1. Kang S et al. Etonogestrel implant migration to the vasculature, chest wall, and distant body sites: cases from a pharmacovigilance database. Contraception 2017; 96(6): 439-445.

In the US Food and Drug Administration Adverse Event Reporting System (FAERS) database, we identified 38 cases of pronounced etonogestrel implant migration. Migration locations included the lung/pulmonary artery (n=9), chest wall (n=1), vasculature at locations other than the lung/pulmonary artery (n=14) and extravascular migrations (n=14) to other body sites (e.g., the axilla and clavicle/neck line/shoulder). A key determinant in the risk for etonogestrel contraceptive implant migration appears to be improper insertion technique.

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.

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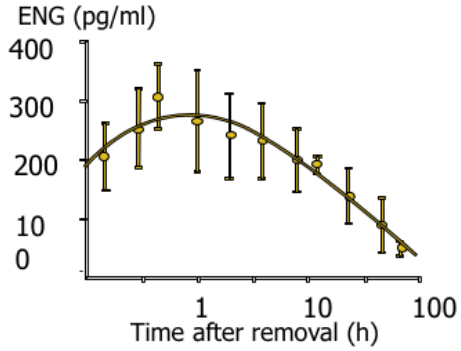
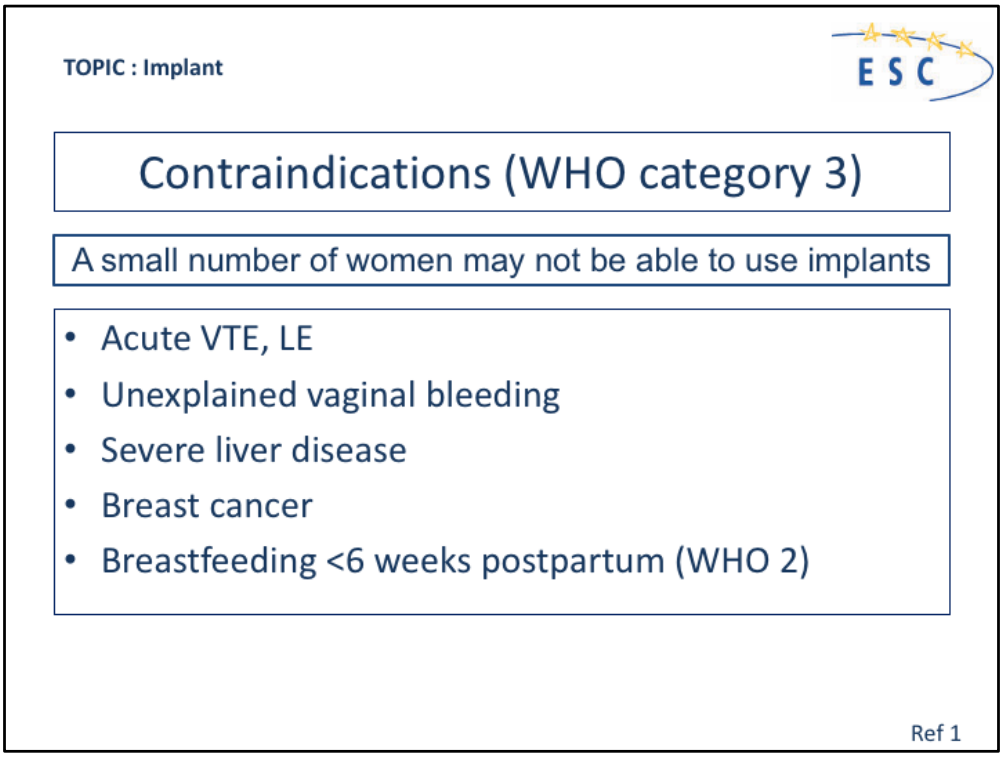
Return to fertility
Decrease of ENG levels after removal



Fertility returns within few days after removal

Ref 1

1. *Davies GC et al. Release characteristics, ovarian activity and menstrual bleeding pattern with a single contraceptive implant releasing 3-ketodesogestrel. Contraception 1993; 47: 251–61.*



1. *World Health Organization. Medical eligibility criteria for contraceptive use. Fifth edition, 2015 . Geneva: WHO.*

In contrast with progestin-only injectables, the advantages of progestin implants generally outweigh the theoretical or proven risks (WHO category 2) in conditions such as breastfeeding before 6 weeks postpartum, multiple risk factors for arterial cardiovascular disease (such as older age, smoking, diabetes, hypertension and known dyslipidaemias), untreated severe hypertension (≥160/≥100 mmHg), and complicated diabetes.
According to the WHO MEC, progestin implants are not generally recommended for women with category 3 conditions. In these situations, the risks of using this method usually outweigh the advantages. Category 3 conditions include: acute blood clot in deep veins of legs or lungs, unexplained vaginal bleeding, severe liver disease and most liver tumours, and current breast cancer (WHO 4).

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Adverse events recorded in clinical trials

Adverse events (WHO definition)	Incidence (%)	Reason for discontinuation (%)
Headache	15.3	1.6
Weight gain	11.8	2.3
Acne	11.4	1.3
Breast tenderness	10.2	<1
Mood variations	5.7	2.3
Abdominal pain	5.2	<1

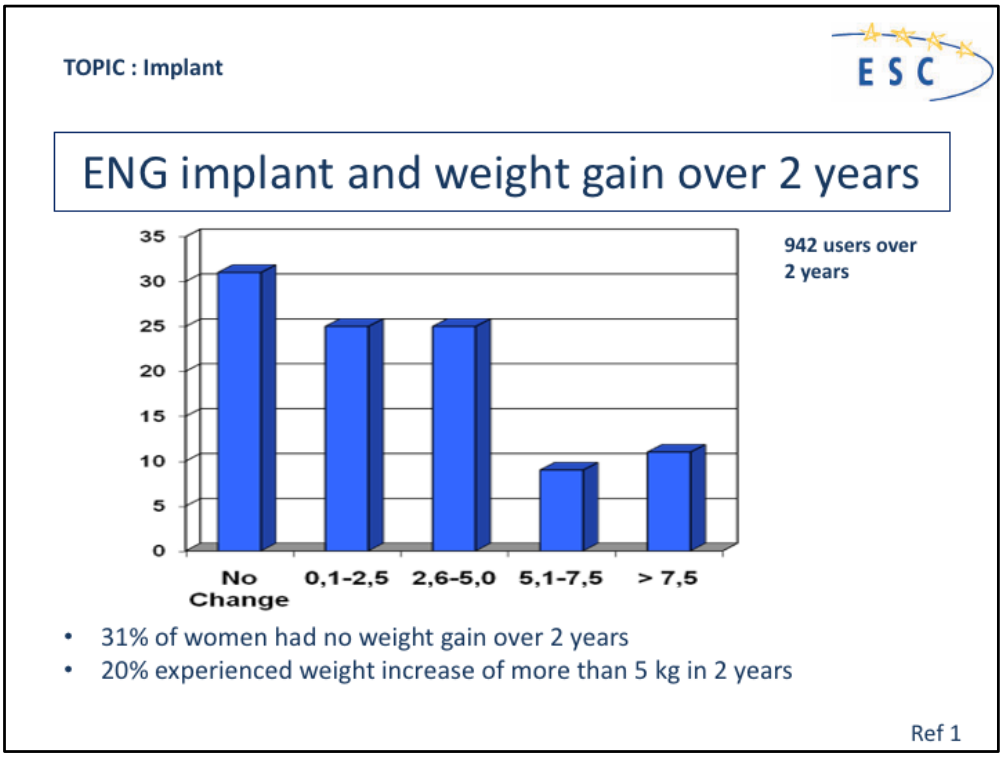
Bleeding irregularity was reported separately during this study

Ref 1

1. *Blumenthal PD et al. Tolerability and clinical safety of Implanon. Eur J Contracept Reprod Health Care 2008; 13 (suppl 1): 29–36.*

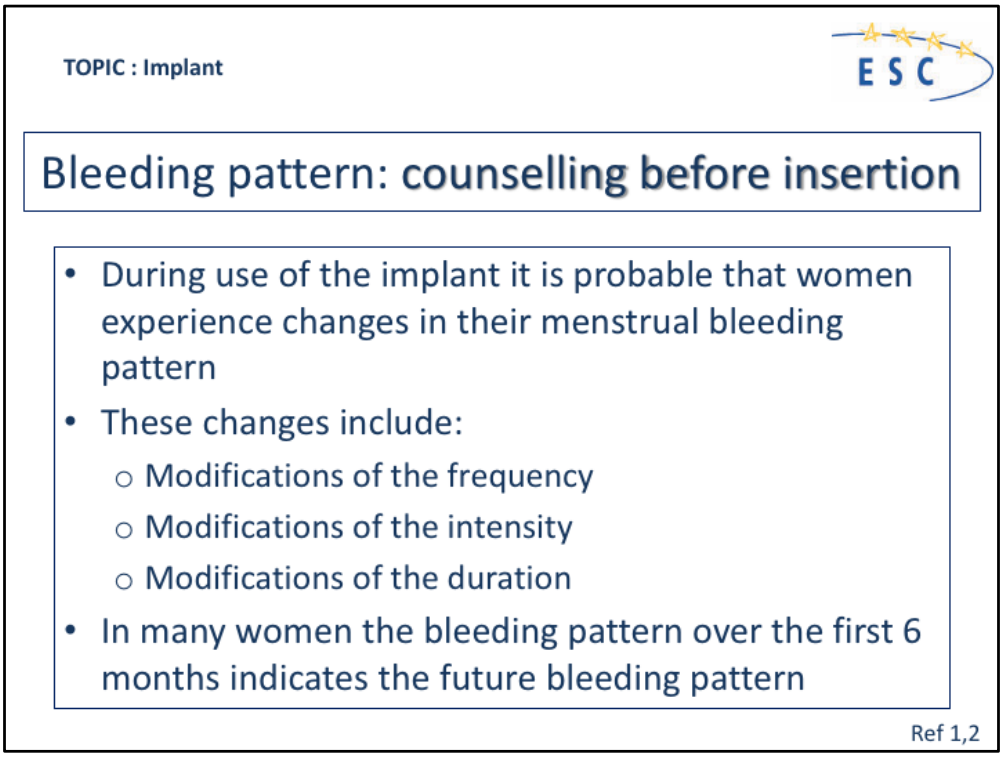
This integrated safety analysis included 11 international studies of the 68 mg ENG implant, 10 of which had a duration of at least 2 years. Assessments included reports of adverse events, reasons and rates of discontinuation, insertion/removal complications, and the condition of the implant site. Metabolic 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.



1. *Blumenthal PD et al. Tolerability and clinical safety of Implanon. Eur J Contracept Reprod Health Care 2008; 13 (suppl 1): 29–36.*

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.

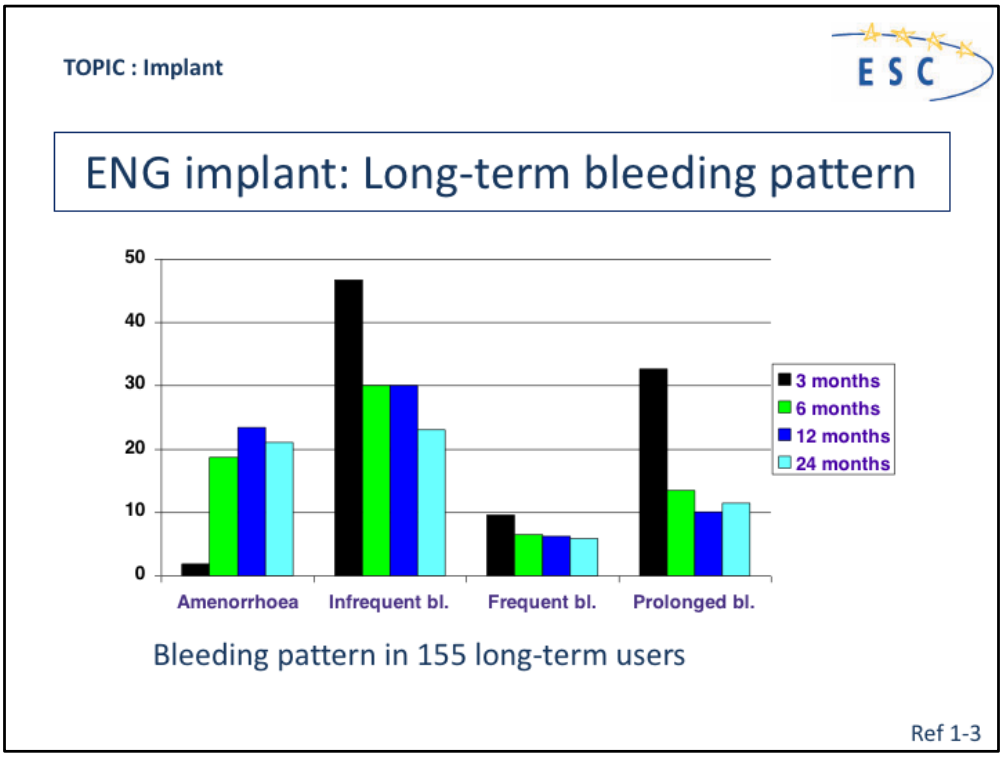


1. *Mansour D et al. The management of unacceptable bleeding patterns in etonogestrel-releasing contraceptive implant users. Contraception 2011; 83: 202–10.*
2. *Mansour D et al. Can initial vaginal bleeding patterns in etonogestrel implant users predict subsequent bleeding in the first 2 years of use? Contraception 2019; 100(4): 264-268.*

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

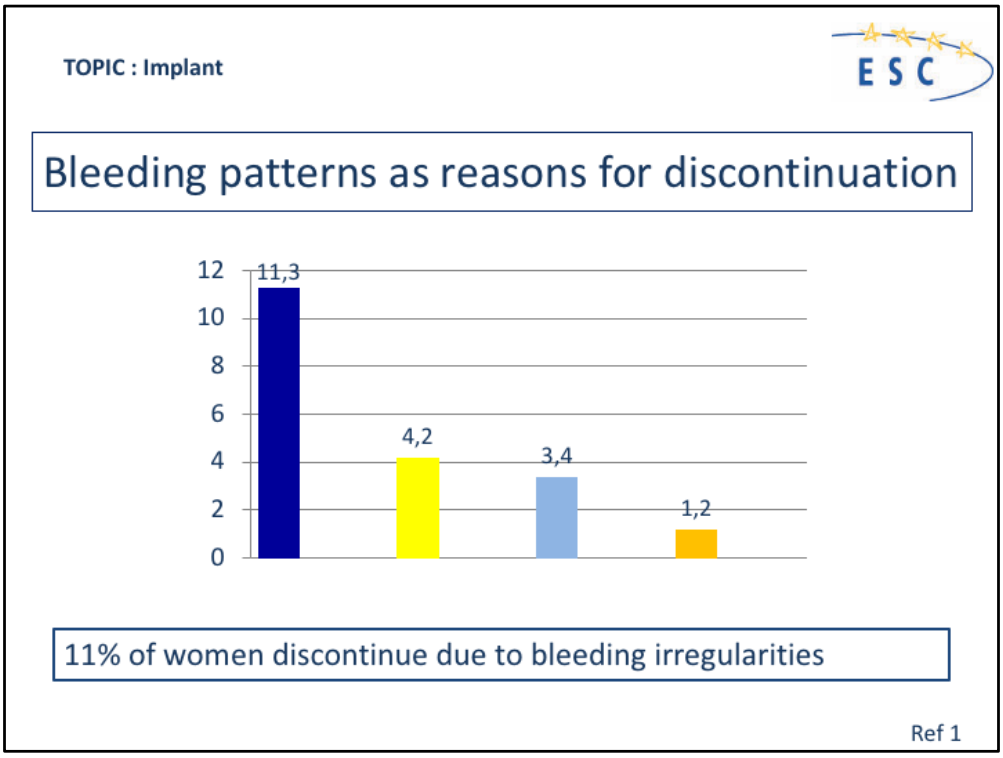
1. What are the woman's main concerns?
2. Ask about her bleeding pattern prior to having the ENG implant fitted.
3. Ask her to describe the number of days each month she bleeds plus the number of episodes.
4. Does the bleeding or pain occur during or after sex, or is it associated with abdominal pain 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?

Ref 2. Implant users with favorable bleeding in the first reference period are likely to continue with favorable bleeding over the next 2 years. Initial bleeding patterns predict overall continuation rates in years 1 and 2. Implications Statement: When evaluating vaginal bleeding in any 90-day reference period over 2 years of etonogestrel implant use, approximately 80% of women with favorable and 40% with unfavorable bleeding patterns will have favorable bleeding in the next reference periods. These findings can facilitate counseling regarding bleeding for women using the etonogestrel implant.

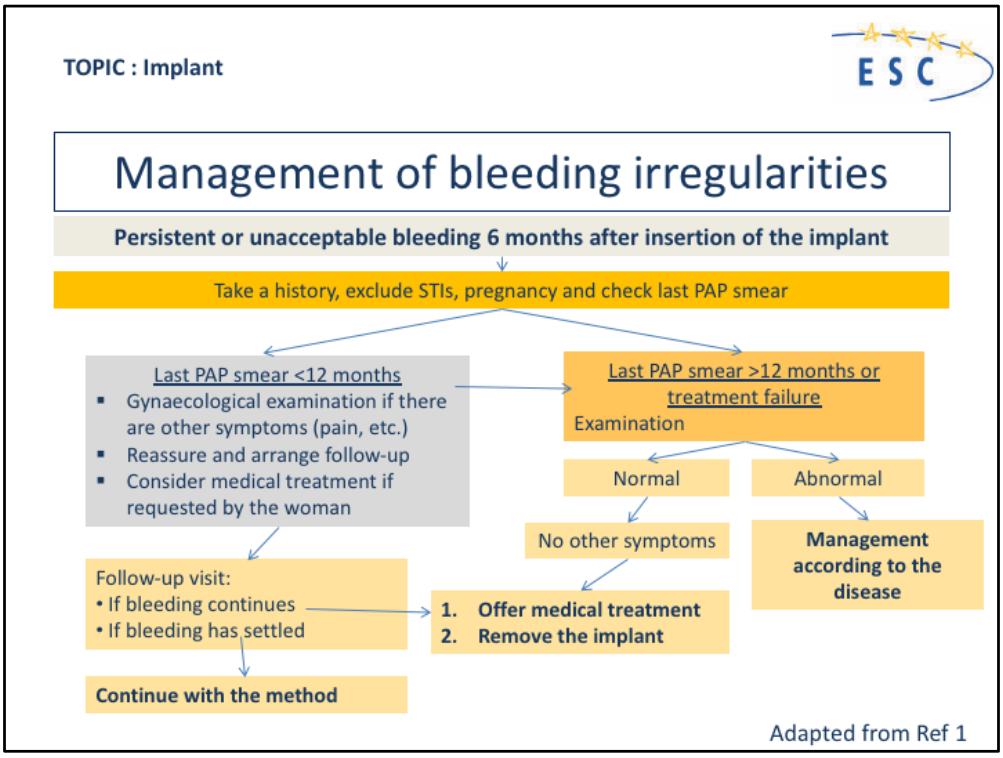


1. *Affandi B et al. An integrated analysis of vaginal bleeding patterns in clinical trials of Implanon. Contraception 1998; 58 (6 suppl): 99–107S.*
2. *Merki-Feld GS et al. A survey on Swiss women's preferred menstrual/withdrawal bleeding pattern over different phases of reproductive life and with use of hormonal contraception. Eur J Contracept Reprod Health Care 2014; 19: 266–75.*

- 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%.



1. *Mansour D et al. The effects of Implanon on menstrual bleeding patterns. Eur J Contracept Reprod Health Care 2008; 13 (suppl 1): 13–28.*



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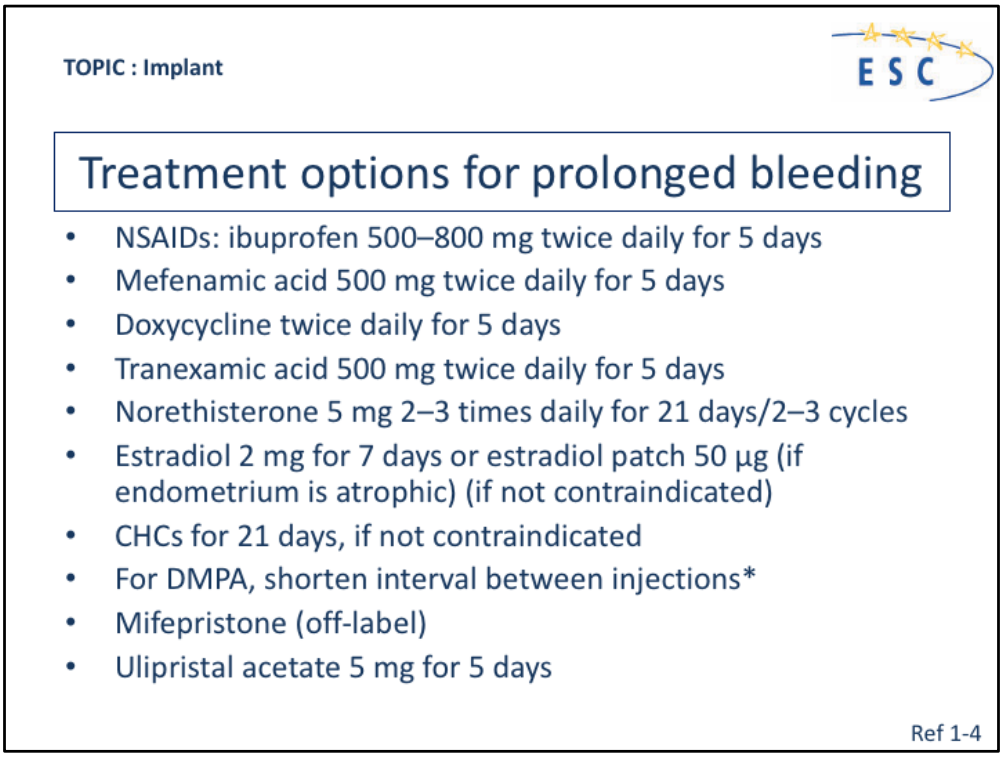


1. *Zigler RE et al. Unscheduled vaginal bleeding with progestin-only contraceptive use. Am J Obstet Gynecol 2016; Dec 14 [Epub ahead of print].*
2. *Mansour D et al. The management of unacceptable bleeding patterns in etonogestrel-releasing contraceptive implant users. Contraception 2011; 83: 202–10.*
3. *Abdel-Aleem H et al. Treatment of vaginal bleeding irregularities induced by progestin only contraceptives. Cochrane Database Syst Rev 2013; CD003449.*
4. *Zigler RE et al. Ulipristal Acetate for Unscheduled Bleeding in Etonogestrel Implant Users: A Randomized Controlled Trial. Obstet Gynecol 2018; 132(4): 888–894.*

* Clinical experience.

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 50 µg patch

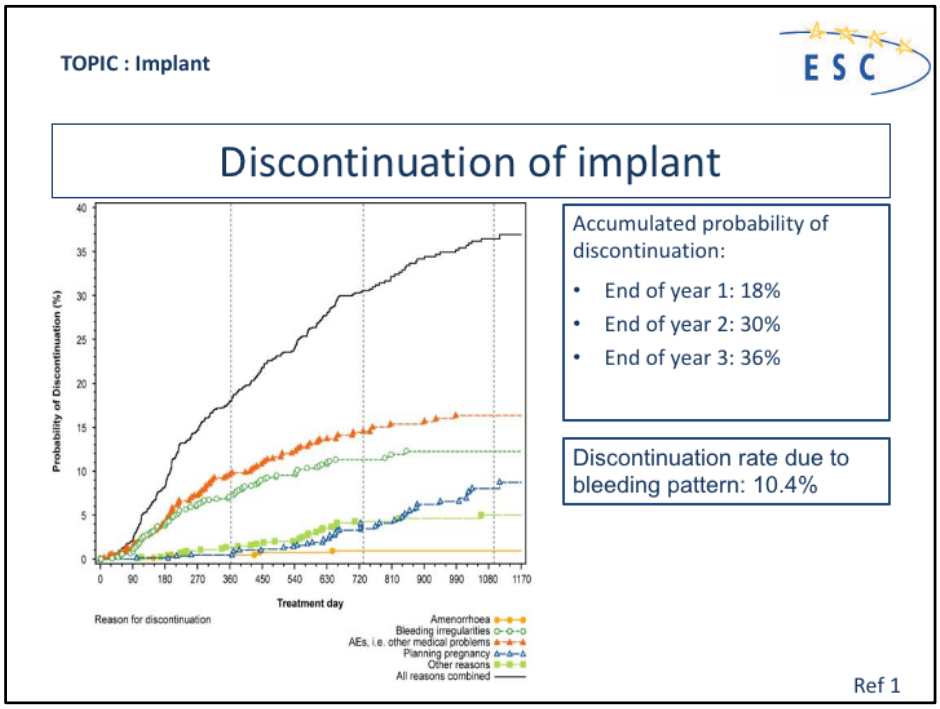
for 7 days is another option based on clinical experience.

- **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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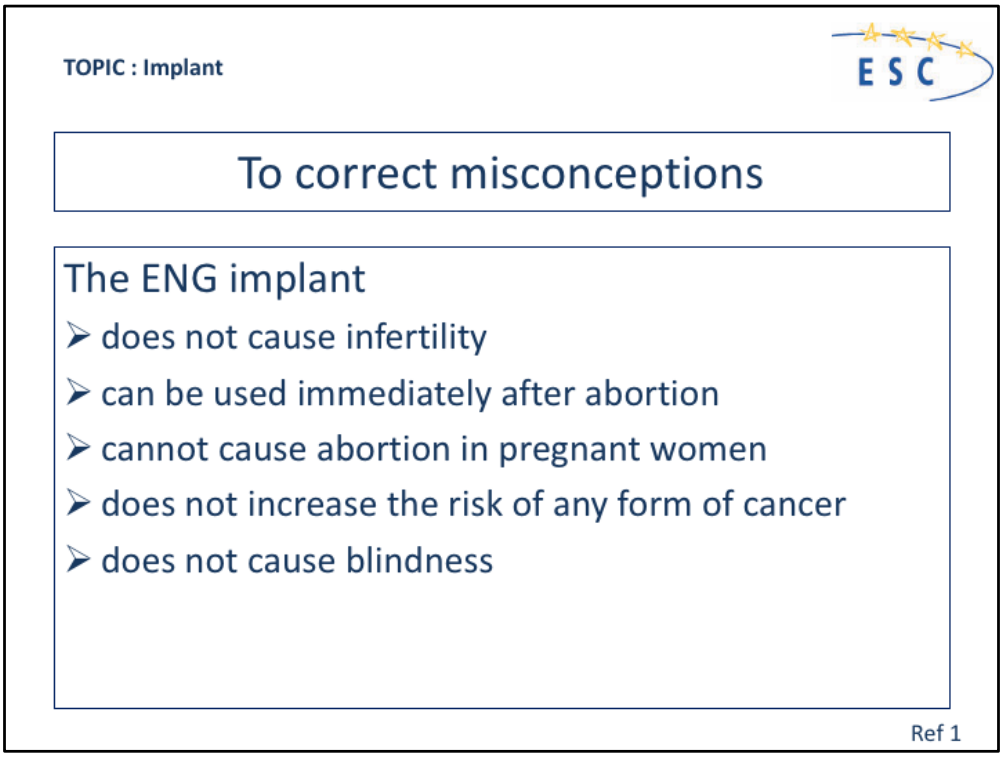

1. *World Health Organization. Training Resource Package for Family Planning. Contraceptive Implants. Geneva: WHO.*

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Summary ENG implant

- 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