
The Contraceptive Implant

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Abstract: Contraceptive implants provide long-acting, highly effective reversible contraception. Currently, the only subdermal implant available to women in the United States is the single rod etonogestrel implant, Implanon (N.V. Organon, Oss, the Netherlands) approved by the Food and Drug Administration in July 2006. Implanon is currently approved for 3 years of use, provides excellent efficacy throughout its use, and is easy to insert and remove. Similar to other progestin-only contraceptives, Implanon can cause irregular vaginal bleeding. Implanon has been shown to be safe to use during lactation, may improve dysmenorrhea, and does not significantly affect bone mineral density, lipid profile, or liver enzymes.

Key words: contraception, Implanon, progestin-only, ENG implant

The Contraceptive Implant

Contraceptive implants provide long-acting, highly effective reversible contraception. All subdermal implants for clinical use in humans use progestins. These methods offer an excellent contraceptive option for women who have contraindications to combined hormonal methods and an option for any woman who desires long-term protection against pregnancy that is rapidly reversible.

Background

Clinical research on subdermal implant contraception has been carried out since the late 1960s. Norplant System (Schering, Berlin) is a levonor-

gestrel (LNG) implant, which first received approval in Finland in 1983. Although it had been extensively used in Finland and in parts of Southeast Asia, it did not receive approval from the United States Food and Drug Administration (FDA) until 1990. Norplant System consists of 6 silicone polymer capsules containing a total of 216 mg of LNG and is FDA approved for 5 years of use, although evidence exists for effectiveness through 7 years.¹ One long-term study, the Norplant Postmarketing Surveillance Study (NPMS), enrolled 16,000 women in 8 different countries for a 5-year controlled cohort study to compare safety and contraception efficacy of Norplant System, intrauterine device (IUD), and sterilization. Follow-up was completed by 95% of women. Over 39,000 women-years of observation were completed for Norplant System users. Efficacy rates reported using a Pearl index were 0.27 per 100 women-years for Norplant System, compared with 0.88 per 100 women-years for copper IUD users and 0.17 per 100 women-years for sterilization.² In a multinational trial of 1210 women who were offered Norplant System for 7 years, the mean duration of use was 4.16 years but 22.6% of women continued use for the entire 7 years.³ At 5 years, the cumulative pregnancy rate was 1.1/100 women-years. The cumulative rate increased to 1.9/100 women-years at the completion of 7 years, giving women aged 18 to 33 a similar median pregnancy rate as expected with tubal sterilization³ and providing evidence for the effectiveness of the Norplant System for up to 7 years.¹

Despite this excellent efficacy profile, experience with the millions of worldwide Norplant System users prompted manufacturers to develop advances in implant technology, namely reducing the number of implants to 1 or 2 instead

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of 6 to facilitate easier insertion and removal. A 2-rod LNG implant was developed in the 1980s and is currently available in European countries marketed under the name Norplant II or Jadelle (Schering, Berlin). This 2-rod system was approved by the FDA in 1996 but has never been marketed in the United States. Jadelle contains a total of 150 mg of LNG in two 4-cm rods. Similar efficacy rates are seen with this implant as with the original 6-rod system.^{1,4} Other implants are available and undergoing research in countries outside of the United States. Nestorone^{5,6} containing implants are marketed in Brazil on a limited basis and Uniplant^{7,8} implants are still under investigation. None of these methods are expected to be available in the United States in the near future.

Although Norplant System entered the US market with initial enthusiasm, by the mid-1990s the implant was surrounded by controversy secondary to allegations of misuse including coercion directed against low-income women. Wyeth-Ayerst, the manufacturer of Norplant System was also dealing with lawsuits alleging significant side effects and claims of complicated and painful removals.⁹ Ironically, none of these claims were substantiated and all class action lawsuits were decertified. In 2000, Wyeth-Ayerst advised physicians to stop insertions secondary to lower than expected hormone release rates noted from a single manufacturing lot.¹ Although further testing revealed that this lower rate was not problematic for efficacy, US distribution was officially halted in 2002.

In July, 2006 the FDA-approved Implanon (N.V. Organon, Oss, The Netherlands), also referred to as the etonogestrel (ENG) implant. This single rod subdermal implant is currently the only implant available to women in the United States, and will be the further focus of this review. The ENG implant has been extensively used in Australia, Indonesia, the Netherlands, and more than 30 other countries. Implanon is currently approved for 3 years of use, provides excellent efficacy throughout its use, and is easy to insert and remove. Additionally, Implanon can be used during lactation^{10,11} and may improve dysmenorrhea.¹² However, similar to other progestin-only contraceptives, Implanon can cause side effects such as irregular vaginal bleeding.¹³

Description and Pharmacology

The ENG implant is a single rod implant that releases the gonane progestin ENG, also known as 3-ketodeosgestrel, the biologically active



FIGURE 1. Implanon in palm.¹⁶

metabolite of desogestrel.¹⁴ ENG is the same progestin used in the contraceptive vaginal ring. This new implant measures 4-cm long and 2 mm in diameter and has a core made from a non-biodegradable solid composed of ethylene vinyl acetate impregnated with 68 mg of ENG¹⁵ (Fig. 1). The ethylene vinyl acetate copolymer of Implanon allows controlled release of hormone over 3 years of use.¹⁷ Each implant is provided in a disposable sterile inserter for subdermal application (Fig. 2).

After ENG implant insertion, serum levels of ENG rapidly rise to a mean serum concentration of 265.9 ± 80.9 pg/mL by 8 hours,¹⁸ a level that exceeds the 90 pg/mL needed to prevent ovulation.¹⁹ Maximum serum concentrations are usually seen by day 4 after implant insertion, with a variation from day 1 to day 13. ENG levels decrease slightly to a mean serum concentration of 196 pg/mL at 1 year of use^{15,18,20} and 156 pg/mL by 3 years.^{14,15} After removal, serum levels are undetectable (less than 20 pg/mL) by 1 week in the majority of users, with most women demonstrating ovulation within 6 weeks of implant removal.¹⁸ Serum ENG levels showed less individual variation over time compared with LNG levels detected in Norplant System users.¹⁸ Potential explanations include differences in the release mechanism or that ENG is chiefly bound to albumin which is not affected by varying physiologic endogenous estradiol concentration, whereas LNG is mainly bound to sex hormone binding globulin.¹⁷

Estradiol (E2) levels initially decrease to early follicular-phase range after insertion of the ENG implant.²¹ This initial decrease is followed by a gradual rise in E2 levels. Given the ENG implants ability to suppress ovulation, that is, the LH surge, a situation of anovulation with normal endogenous E2 synthesis occurs with use.

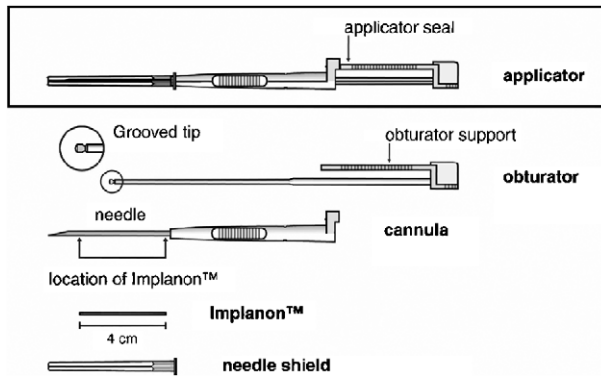


FIGURE 2. Implanon with applicator and parts.¹⁵

Wenzl et al¹⁷ examined the bioavailability and accumulation of drug in 8 healthy women aged 18 to 40, weighing between 80% and 130% of ideal body weight [body mass index (BMI) ranging from 19.6 to 27.5]. The study demonstrated that the ENG implant has an absorption rate of approximately 60 $\mu\text{g}/\text{d}$ after 3 months, which decreases to 30 $\mu\text{g}/\text{d}$ at 2 years. The elimination half-life was approximately 25 hours compared with over 41 hours for Norplant System. One subject with a BMI of 27.5 demonstrated an increased elimination half-life of 40 hours. This result is most likely secondary to ENG's lipophilic nature.

Mechanism of Action

The ENG implant was specifically designed to provide contraceptive efficacy by inhibiting ovulation.¹⁴ Makarainen et al¹⁸ reported data from 32 women randomized to either receive Norplant System or Implanon. All women had confirmed ovulation before the start of the study and weighed between 80% and 120% of ideal body weight, with a mean body weight of 60 ± 6.7 kg. Subjects received the ENG implant between day 1 and 5 of menses or Norplant System between day 1 and day 7 of menses. Women were scheduled to complete 36 months of observation; 7 women in the ENG implant group and 3 women in the Norplant System group completed the full time course. Researchers evaluated evidence for ovulation using progesterone concentrations ≥ 16 nmol/L with ultrasound confirmation of ovulation if possible. Progesterone concentrations were elevated above the 16 nmol/L threshold for the first time after 30 months in 2 ENG implant users and

again after 33 months. In 1 subject, confirmation of ovulation was demonstrated with ultrasound at both time periods, but for the other subject ovulation was only demonstrated with ultrasound at month 30. The first progesterone concentration above 16 was seen at 12 months in 1 Norplant user, although ovulation was not confirmed via ultrasound. The first confirmed ovulation was seen in a Norplant System user at 18 months. Further, in both groups estradiol levels decreased to early follicular range after implant insertion. During treatment, no subjects had continuously low or high estradiol levels.

Davies et al²² demonstrated a similar effect on ovulation suppression in an assessment of 15 women during a 1-year period. Women with a mean age of 32 years had leached ENG implants inserted on day 1 to day 5 of their menstrual cycle. The implants were partially leached of hormone to assure a release rate of 40 $\mu\text{g}/\text{d}$. No luteal activity was demonstrated with either ultrasound evaluation or serum hormone levels. Additionally, 6 weeks after implant insertion, cervical mucus assessment demonstrated a significant thickening based on a mean Insler value that had fallen significantly from 13, preinsertion, to 3.5 ($P = 0.0001$). Although these studies used small numbers of ENG implant users, the results combined with the knowledge that ENG levels remain above the ovulation-inhibiting levels for the full 3 years of use, suggests that ovulation inhibition is the ENG implant's primary mechanism of action.

Efficacy

Several large trials have demonstrated the efficacy of the ENG implant. A review of ENG

implant studies published in 1998 found no pregnancies among 1716 women who used the implant between 2 and 5 years [Pearl index 0.0 (95% confidence interval (CI) 0.00, 0.09)].²¹ Subsequent studies have confirmed this high efficacy level for the implant. An American open-label single treatment study of 330 women followed ENG implant users for 2 years. All women were sexually active, between the ages of 18 and 40, and weighed between 80% and 130% of their ideal body weight.²³ About one fourth of the originally enrolled women had a BMI greater than 26. Four hundred and seventy-four women-years of ENG implant use were observed, with 68% of subjects continuing the implant for 1 year and 51% completing 2 years. No pregnancies occurred while the ENG implant was in place. Importantly, of 46 subjects who chose not to use any contraception after having the implant removed, almost 24% became pregnant between 1 and 18.5 weeks after removal; thus, supporting the pharmacologic data that demonstrate the lack of ENG accumulation in the body.¹⁷

A multicenter efficacy trial performed in Europe and South America²⁴ examined ENG implant use in 635 women with a mean age of 29 years. The 436 women (68.6%) who completed 2 years were asked if they were willing to extend ENG implant use for an additional year. Approximately one third ($n = 147$) agreed and completed the third year of use. Although this study population included women who were between 80% and 130% of ideal body weight, only 9.0% of women followed for 2 years were over 75 kg at the start of the study and only 3.4% of women followed for 3 years weighed more than 75 kg at the start of the study. Overall, total exposure to the ENG implant was for 1200 women-years, which is equivalent to 15,653 28-day cycles of use. Similar to other ENG implant studies, no pregnancies were recorded in this trial yielding a Pearl index of 0.0 (95% CI, 0.0-0.2). Thus, this study provides clinical data to support excellent contraceptive efficacy of the product through 3 years of use.

A multicenter Mexican study followed a total of 417 women during 3 years of ENG implant use with 256 women (61.4%) completing the full 3-year use.²⁵ Overall, this study enrolled women with a mean weight of 59.4 ± 9.3 kg and a mean BMI of 24.9 ± 3.9 , with 19.4% of subjects categorized as overweight (BMI > 25) and 8.9% categorized as obese (BMI > 30). Once again, no pregnancies were recorded in this study,

which corresponded to 958.5 women-years of observation.

Of course data from controlled clinical trials can differ from what is seen after a new contraceptive is brought onto the market. One large body of postmarketing data comes from Australia during a 3-year time period after the ENG implant was first introduced to that country. A total of 218 confirmed pregnancies during ENG implant use were reported.²⁶ Of the cases reported, 21% of patients were found to have been pregnant before the time of implant insertion and 39% of pregnancies were due to "noninsertion." Although the study reports that some physicians recognized their noninsertions, the series did not include the number of providers who recognized or failed to recognize these events. For the total number of confirmed pregnancies, 21% of cases had insufficient data to detect the reason for failure and the remaining 19% of pregnancies were due to method failure. Thus, this data set gives a failure rate of 1.07 per 1000 insertions. It is important to understand the reasons for method failure. Of the 43 women who experienced a contraceptive failure, 8 were determined to be secondary to interactions with other medications, carbamazepine being the most notable. Interestingly, one of the failures was in a woman who had a reported weight gain of over 10 kg between the time of insertion and pregnancy, thus highlighting the fact that there is limited data about ENG implant efficacy in overweight and obese women. Furthermore, this information emphasizes the importance of having proper training in inserting the implant so the clinician can better recognize instances of noninsertion. Lastly, although no specific studies have been carried out to examine the ENG implant's interactions with hepatic enzyme inducing medication, the package insert instructs women to use an additional contraceptive method during and for at least 7 days after stopping such drugs. Until further research is performed in this particular area, the ENG implant should not be considered first-line contraception for women chronically on these types of medications.

The results of the above studies demonstrate the ENG implant's excellent efficacy. Even when accounting for the failures noted in the Australian postmarketing surveillance, the implant continues to have one of the highest efficacies of any method available. Of course, the trials discussed above were all open-label studies and did not directly compare the ENG implants efficacy with any other methods. A Chinese

study randomized 200 women to directly compare the ENG implant with the 6 capsule LNG implant over a period of 4 years.²⁷ Of 153 women who completed the full trial, no pregnancies were reported in either group. These data further support the ENG implant's effectiveness and suggests that further research may demonstrate that the device has acceptable efficacy for greater than 3 years of use.

Safety and Side Effect Profile

BLEEDING PATTERNS

Similar to other continuous progestin-only contraceptives, irregular and unpredictable bleeding patterns are reported with ENG implant use. A review of noncomparative trials and open randomized trials of the ENG implant demonstrates that bleeding patterns were similar through out the various trials. The following bleeding patterns were reported for 1716 ENG implant users. Amenorrhea increased from low levels early in the studies to between 30% and 40% at 12 months. Infrequent bleeding occurred in about 50% of subjects at 3 months and decreased to 30% after 6 months. Prolonged bleeding, although high during the first 3 months of use, decreased to 10% to 20% after 3 months of use.¹³ Unfortunately, although bleeding patterns were similar between the studies no consistent bleeding pattern can be demonstrated for any individual woman.

A retrospective Swiss study was performed at 12 centers to assess acceptability and side effect profile of the ENG implant.²⁸ A total of 1183 women had the ENG implant inserted, of which 991 (84%) completed 1 follow-up visit. Mean time from insertion to first follow-up was 224 days. Normal bleeding patterns were reported by only 11% of women. Infrequent bleeding was seen in 28% of women, where as prolonged bleeding was reported in 15% of women and metromenorrhagia was reported in 16% of women. Of women with 1 follow-up visit, 23.7% had the implant removed prematurely. The most frequently reported adverse event leading to removal was prolonged and frequent bleeding, comprising 45% of removals for side effects.

In a prospective US study of 330 women, 43 discontinued the ENG implant secondary to bleeding irregularities as their primary adverse event.²³ Episodes of prolonged and frequent bleeding was highest during the first 3 months of use (36% and 14%, respectively) and decreased

during the remainder of the study (14% and 7%, respectively). The number of subjects discontinuing implant use was highest during the first 8 months of use. This number is similar to results found for the above Swiss study in which the mean time from insertion to removal for those who chose to discontinue the product was 9.2 months.²⁸

Given the potential of prolonged and frequent bleeding to lead to discontinuation of the ENG implant, researchers have examined different regimens to improve bleeding profiles.²⁹⁻³¹ Earlier studies of Norplant System users demonstrated that providing combined oral contraceptive pills (COC) with 50 µg of ethinyl estradiol (EE)/250 µg LNG for 20 days shortened bleeding episodes to 2.6 days compared to 12.3 days with placebo. Oral doses of EE 50 µg also shortened bleeding episodes, but not to the same extent as seen with the COC.³¹ Despite reduction in bleeding duration, these high doses of estrogen are associated with side effects such as nausea.³⁰ Other data on Norplant System users demonstrated decreased duration of bleeding episodes without change in number of episodes with the administration of EE 30 µg/150 µg LNG for 21 days.²⁹ Currently, Weisberg et al³⁰ has the only study published that examined treatments for prolonged and frequent bleeding specifically in ENG implant users. This study randomized 179 women into 1 of 4 treatments. Subjects were women who had used the implant for greater than 3 months and experienced prolonged or frequent bleeding. An EE arm alone was excluded in this study because of the increased number of subjects needed for adequate power. Treatments were mifepristone 25 mg taken twice on day 1 followed by 4 days of placebo, mifepristone 25 mg twice on day 1 followed by 4 days EE 20 µg in the AM and placebo at night, doxycycline 100 mg twice a day for 5 days, or placebo twice a day for 5 days. Mifepristone was used because of prior data showing effect in Norplant System users³² and doxycycline was used secondary to its known anti-inflammatory properties. Mifepristone combined with EE and doxycycline both significantly reduced bleeding episodes [mean, 4.3 d (95% CI 3.5-5.3) and 4.8 d (95% CI 3.9-5.8), respectively].³⁰ Despite the results of this study, the limited availability of mifepristone in the United States decreases the utility of this study's results. Doxycycline may be considered as a method to decrease bleeding episodes in ENG implant users, keeping in mind the risk of side effects. For women without contraindications to

estrogen, data from Norplant System users suggest COC use as a method to decrease duration of bleeding episodes. Given the possibility of side effects with COCs containing EE 50 µg, a COC containing a lower EE doses is recommended.

ACNE

Clinical results regarding acne are mixed. In a 3-year study of 635 women, acne was the second most common (12.6%) nonbleeding adverse event associated with ENG implant use.¹² This number is consistent with the results of a Swiss retrospective study of ENG implant users in which 12% of side-effect removals were secondary to reports of acne.²⁸ Croxatto¹² also reported an opposing trend in women who reported having acne at baseline, with 78 out of 133 reporting improvements in this skin condition during ENG implant use.

Funk et al²³ had 315 subjects provide baseline and posttreatment acne information. About 26% of women had acne at baseline and 24% had acne after treatment. From the total population, 16% reported a decrease from baseline, 70% reported no change, and 14% reported increased acne. Of subjects with baseline acne, 61% reported decreased acne posttreatment and only 7% reported an increase in acne posttreatment. For those women without acne at baseline, 84% reported no change and 16% reported increase in this skin condition.

The opposing nature of these data, and the lack of control group, makes it difficult to provide patients with a clear expectation regarding the incidence or severity of acne while using the ENG implant. Patients should be counseled that there is no apparent trend with regard to acne incidence or improvement while using the ENG implant.

BONE MINERAL DENSITY

The role of hormonal contraception's influence on bone mineral density (BMD) has become an area of controversy since the FDA required an inclusion of a black box warning on the package insert for depot medroxyprogesterone acetate. Beerthuizen et al³³ reported on a comparative study of BMD in users of the ENG implant versus users of nonhormonal IUDs. Forty-four ENG users and 29 IUD users, aged 18 to 40 years, were followed for 2 years. BMD was measured through the use of dual energy x-ray absorptiometry at the lumbar spine, proximal femur, and distal radius. Estradiol levels were comparable between the groups at baseline and showed no correlation to baseline BMD. No clinically

significant difference was seen in BMD between the ENG implant users and the IUD users. No relationship was noted between estradiol levels and changes in BMD in this study.

Bahamondes et al³⁴ performed a trial of ENG implant and Norplant System users comparing BMD at the ulna and distal radius. At 18 months, both groups demonstrated a decrease in BMD at the midshaft of the ulna, but no difference at the distal radius. It should be noted that although the BMD was significantly decreased, the decrease never went outside of the limit of 1 standard deviation. Also, the study only looked at the BMD of the forearm, which is not the best site to use to predict fracture risk. Further, there are no long-term data, which show that this result has any clinical significance.

DYSMENORRHEA

Data regarding incidence of dysmenorrhea in ENG implant users suggests that use of the implant may improve this condition. Funk et al²³ showed that the percentage of subjects with dysmenorrhea decreased from a baseline of 59% to a posttreatment level of 21%. Of the total population, 48% reported decreased dysmenorrhea with ENG implant use, whereas 8% showed an increase in the condition. Of those women who reported a history of dysmenorrhea at baseline, 81% showed improvement with implant use. In a similar study, Croxatto¹² reported a 35% incidence of dysmenorrhea among subjects at baseline with 82% of these women reporting improvement in symptoms at the end of the study. When complying data from multiple ENG implant studies, differences in bleeding pattern during ENG implant use was not correlated to reported incidence or severity of dysmenorrhea.¹³

WEIGHT CHANGES

Weight changes attributed to the use of the ENG implant have been described in a number of clinical trials, although the percentage of women who ultimately have the implant removed for this reason is low. On the basis of results of the large American trial of the implant over a 2-year period, weight increase was reported in about 12% of subjects,²³ but only 3.3% of women withdrew because of this weight increase. The mean increase in BMI from baseline to last measurement was 0.7 kg/m² in this trial. Croxatto et al²⁴ reported that approximately 20% of women reported a greater than 10% increase in BMI over baseline at one or more measures. The mean increase in BMI over the study's 3-year

time period was 3.5%, but the mean change in BMI was only 0.8 kg/m², similar to the results from the American trial. Zheng et al²⁷ reported a change in body weight in 100 Chinese women using the ENG implant with a breakdown of 0.82, 1.15, 2.5, and 3.1 kg for years 1, 2, 3, and 4 of use. Importantly, no women withdrew from the study secondary to weight gain. In a retrospective Swiss study of implant users, 9% of 991 women at first visit (mean time of 272 d since implant insertion; range, 1 to 677 d) and 9% of 306 women at second visit (mean time of 347 d since implant insertion; range, 15 to 709 d) reported weight gain during implant use, but only 7% of women requesting implant removal reported the primary reason as weight gain.²⁸ Lastly, in a retrospective British study following ENG implant use in 324 women, of the 277 for whom information was available, 14 (5%) women who discontinued implant use with-in 1 year cited weight change as their primary reason.³⁵ Thus, the overall removal rates because of weight change seem to be in the 3% to 7% range in non-Asian populations.

OVARIAN CYSTS

Progestin-only contraceptive methods have been associated with ovarian cyst formation.³⁶ Hidalgo et al³⁷ performed a prospective study comparing ovarian cyst formation in 344 women using the ENG implant, Jadelle, or the copper IUD. One-year follow-up was available for 90% of ENG implant users, 84% of Jadelle users, and 75% of IUD users. Throughout the study, copper IUD users had an approximate 2% or less rate of ovarian cyst formation compared with 5% and 13% of ENG implant and Jadelle users, respectively, at 3 months and 27% and 15% of ENG implant and Jadelle users at 12 months, respectively. All ENG implant users and all but 1 Jadelle user were anovulatory based on progesterone levels. Notably the authors reported that the time to ovarian cyst resolution in ENG implant users ranged from 7 to 72 days. In conclusion, although ovarian cysts may be associated with ENG implant use, the majority of cysts will regress spontaneously and do not need additional treatment.

BREAST FEEDING

ENG implant use seems to be safe for breast-feeding women. Reinprayoon et al¹⁰ performed an open-label nonrandomized group comparison study of breast-feeding women using either the ENG implant or a copper IUD for contraception. A total of 80 women and infants parti-

cipated in this study and were initially followed for 4 months. The study found that there was no significant difference in total fat, protein, or lactose content in the breast milk of the 2 groups. Further, 24-hour milk production was not different between the 2 groups. Although infants' ENG dose was highest during the first month of implant use (19.86 ng/kg/d, equivalent to 1.7% of the maternal dose), the dose significantly decreased by months 2 and 4. Infant growth rate did not differ significantly during the first 4 months of use between the ENG implant group and the copper IUD group. As a secondary outcome of the study, the researcher continued to follow the breast-fed infants over a 3-year period to evaluate any differences in long-term outcomes.¹¹ A total of 81% of the ENG implant exposed infants and 86.8% of the copper IUD exposed infants completed the study. Over the 3-year period, there was no difference between the 2 group's growth rates or biparietal head circumferences. Even though the original study was not powered for this outcome, the results further support the initial conclusion of ENG implant safety for breast-feeding women. Clinicians should feel comfortable recommending this form of contraception to breast-feeding patients.

EFFECT ON LIPID PROFILE

Biswas et al³⁸ performed a randomized trial with 80 subjects receiving either the Norplant System or the ENG implant and followed subjects for 2 years. Overall, only 3 ENG implant users discontinued before the study's completion. For the ENG implant users, there was a significant decrease in serum total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol, which was similar for women receiving the Norplant System. A similar decrease in TC in 21% of subjects was noted in the American trial of the ENG implant,²³ but unlike the results from Biswas et al,³⁸ this trial also reported a decrease in triglycerides in 33% of women using the ENG implant. No significant change in the HDL/TC ratio was reported by Biswas et al,³⁸ but a significant decrease in the HDL/LDL ratio for ENG implant users was seen at 1 year with a return to preinsertion level at 2 years. Despite these results, the change in HDL was only 5.8% lower at 2 years compared with baseline and the HDL/LDL ratio was never within a range associated with increase risk of cardiovascular disease. Accordingly, the authors concluded that ENG implant use should not significantly increase the risk of cardiovascular disease.

Manufacturers of the implant recommend following cholesterol values in women with known elevated lipid profiles throughout the use of the implant.¹⁵

EFFECT ON LIVER FUNCTION

Biswas et al³⁹ reported the effects of the ENG implant on liver function tests using the same study design as described above. The authors reported a significant increase in mean total and unconjugated bilirubin in both Norplant System and ENG implant users, although levels never exceeded the normal range. The researchers did notice an initial significant increase in aspartate transaminase levels in ENG implant users at 6 months, but after a year of use levels decline toward baseline. An increase in total bilirubin was seen in a similar prospective randomized trial of 86 subjects randomized to either Norplant System or the ENG implant for 6 months of use.⁴⁰ Contrary to the above trials, Funk et al²³ reported no significant change in liver function parameters over a 2-year use of the ENG implant. Thus, even though results are mixed, clinicians should be aware that there may be mild changes in liver function tests during ENG implant use. Although these changes may not be clinically significant in healthy women, these changes may have serious consequences in women with preexisting liver disease.

Counseling

Given the number of contraceptive options available to women, it is essential that providers concentrate their efforts not only on helping women choose the best contraceptive method, but also focus on counseling that helps improve continuation. The best birth control method is one that is safest and most effective for that

individual woman.⁴¹ This approach places a strong value on medical considerations, but also includes consideration of a woman's lifestyle, preferences, and level of prevention desired. When discussing long-term, reversible contraception, physicians are obligated to present all suitable options to their patients (Table 1).

Before providing the ENG implant, providers should review the indications and contraindications for its use. Contraindications to ENG implant use listed on the package insert include known or suspected pregnancy, active venous thromboembolic disease, active liver disease, undiagnosed genital tract bleeding, known or suspected breast cancer, progesterone dependent tumors, or allergy to any of the implants components.¹⁵ Although the package insert lists venous thromboembolic disease as a contraindication to ENG implant use, there is no evidence to support this restriction. Also, as mentioned above, women chronically using hepatic enzyme inducing medications are not proper candidates for this type of contraception.

When explaining the ENG implant, the physician needs to address any concern and fears a woman may have about this method of contraception. In particular, women may have concerns about implant removal based on media coverage regarding the Norplant System. Also, side effects such as irregular bleeding should be discussed in advance with your patients, as an unexpected side effect may cause women to request early removal of the implant. The bottom line is that bleeding patterns are irregularly irregular. Clinicians should consider discussing plans for treatment of unsatisfactory bleeding patterns in advance of insertion in the hope that this may minimize discontinuation. Lastly, all women need to be reminded about safe sexual practices, as the implant does not provide

TABLE 1. Comparison of Long-acting, Reversible Contraceptives⁴²

| | Perfect Use Failure Rate (%) | Typical Use Failure Rate (%) | Return to Fertility | Hormonal Method | Long-term Effectiveness |
|-----------------------------------|------------------------------|------------------------------|------------------------|---------------------|-------------------------|
| DMPA (DepoProvera) | 0.3 | 3 | Approximate 6-mo delay | Yes, progestin only | At least 3 mo |
| Copper-T IUD (ParaGard T 380A) | 0.6 | 0.8 | Immediate | No | Up to 10 y |
| LNG-IUD (Mirena) | 0.1 | 0.1 | Immediate | Yes, progestin only | Up to 5 y |
| Single-Rod ENG Implant (Implanon) | 0.1 | 0.1 | 1-mo delay | Yes, progestin only | Up to 3 y |

DMPA indicates medroxyprogesterone acetate.

protection against sexually transmitted diseases.¹⁵ Patients who are good candidates for this form of contraception are those that desire long-term reversible birth control, have no contraindications to ENG implant use, accept implant insertion and removal, and are ready to accept a change in menstrual bleeding patterns.

Insertion and Removal

Proper insertion and removal techniques are essential for clinical efficacy and for the prevention of complications. Timing of insertion is dependent on the patient's prior use of contraception and the clinician's evaluation of the appropriateness for each individual. For women without preceding hormone use, the ENG implant should be inserted within 5 days from the start of menses. When switching from a COC, insertion should occur within 7 days of the last active pill. Patients switching from another progestin-only method can have the implant placed at anytime while on the progestin-only pill, at the time of IUD or implant removal, or on the due date of the next contraception injection. Implants may be inserted within 5 days of a first trimester abortion, within 6 weeks of a second trimester abortion, or within 6 weeks of childbirth.¹⁵ Additionally, a clinician may prescribe and insert the ENG implant at any time during a woman's menstrual cycle with recommendations adopted from the "quick start" guidelines for oral contraceptives.⁴³ Before insertion the patient needs a negative, high-sensitive urine pregnancy test. Additionally, emergency contraception should be provided if she has had unprotected intercourse within the last 120 hours. Patients should also be instructed to be abstinent or use a backup method of contraception or abstain for 1 week after insertion and perform a urine pregnancy test 3 to 4 weeks after ENG implant insertion.

The ENG implant is inserted with a single use, sterile applicator. Each implant is preloaded in the needle of the applicator, minimizing handling of the implant before insertion. The implant is typically inserted in the nondominate arm 6 to 8 cm above the elbow. It is essential that the clinician have proper training to decrease complications. It is critical that the physician verify proper placement of the implant after insertion through palpation of the patient's arm.⁴⁴ Results from a large American trial of 330 women demonstrated the mean time to ENG implant insertion was 0.5 minutes (range, 0.05 to 15 min).²³ Most other studies report insertion

times averaging 2 minutes or less.⁴⁴ However, none of these studies clearly stated who was doing the insertions or what level of training the inserter had. Also, the authors of the above studies did not account for a learning curve as the inserters gained more experience.

Low numbers of ENG implant site complications are reported in the literature. In 1 study of 330 American women, only 2.5% reported intermittent pain at the insertion site over a 2-year period.²³ In a large multicenter trial, Croxatto et al²⁴ reported a 1.3% complication rate with insertion with the author citing examples such as a visible implant tip and blood loss from injection site.

Follow-up after ENG implant insertion can be based on a physician's individual practice. A study of early Norplant System users found routine follow-up to be of no clinical benefit.⁴⁵

The package labeling indicates that the ENG implant needs to be removed at the end of 3 years of use.¹⁵ However, there are no known risks for leaving the implant in longer unless the patient desires pregnancy. Unless future data demonstrate otherwise, the patient can only rely on the ENG implant for contraception for 3 years. Before removal, the clinician needs to palpate the implant. Under sterile conditions, a 2 to 3-mm incision is made vertically over the implant. The rod is then removed using the "pop-out" technique previously described for Norplant System removal.⁴⁶ If inserted correctly, removal has been shown to be simple. The American trial published by Funk et al²³ had an average removal time of 3.5 minutes (range, 0.2 to 60 min) and reported difficulties in 2 of the 330 removals, including a implant that broke during removal necessitating a second attempt for complete removal. In a large multicenter study, removal difficulties were reported in 3% of case.²⁴ The most common reason for difficulty was secondary to implants being placed to deep. If the implant is unable to be palpated by the clinician before removal, imaging techniques may be necessary before proceeding. Case reports have used high frequency (10 MHz) ultrasound to detect the acoustic shadow associated with the implant⁴⁷ and magnetic resonance imaging as a second line modality if needed.⁴⁸

Conclusions

The ENG implant provides women with an additional highly effective non-user-dependent reversible contraceptive option. With greater contraceptive options available, we as providers may

be better able to match women's contraceptive needs and desires with the appropriate method. The primary advantage of the ENG implant over other types of contraception is the lack of contraceptive failure in women who have the implant inserted. The trade-off for women is irregularly irregular bleeding that occurs throughout the lifespan of use. Because of the high efficacy, we need to find ways to minimize bleeding issues to improve continuation rates.

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