Chapter 7
Implantable Contraception

Valerie French

Introduction

Contraceptive implants are progestin-based, highly effective, and rapidly reversible methods of contraception that require little of the user and have few side effects.

Over the past 35 years, they have been approved in more than 60 countries and used by millions of women worldwide [1]. Their high efficacy along with ease of use makes them a good contraceptive option for women of all ages who require progestin-only methods, desire highly effective contraception, as well who desire long-term protection. In most countries, two different contraceptive implants are available: the single rod etonogestrel implant and the two-rod levonorgestrel system. The pharmacological profile and physical effects of all the implantable contraceptives are similar. While the etonogestrel implant is the only form of implantable contraception available in the United States (and the focus of this chapter), clinicians may encounter other systems in use worldwide.

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History of Implantable Contraception

Norplant, a six-capsule implantable system containing 216 mg of levonorgestrel, was developed by the Population Council and first approved in 1983 in Finland, where it was manufactured. The United States' FDA approved the device in 1990, but the distributor withdrew it from the market in 2002. Over one million US women had chosen Norplant as their contraceptive. Norplant proved highly effective; over a 7-year duration of use, approximately 1% of users became pregnant [2]. Despite low rates of pregnancy and few serious side effects, limited supplies of the silastic components and unwarranted negative media coverage led to Norplant's withdrawal from distribution in 2002, leaving no implant alternative for American women [3]. Production of Norplant was discontinued worldwide in 2008.

The 15-year experience with Norplant instigated further development and improvements in implant design. A two-rod LNG system (Jadelle) was also developed by the Population Council and manufactured in Finland. It was approved in the United States in 1998, but never marketed. Jadelle is effective for 5 years and was first registered for this length of use in the year 2000. Sino-implant (II) is a two-rod implant system designed to imitate the performance of Jadelle. It is manufactured in China and is substantially less expensive to manufacture than Jadelle (US$8 compared with US$23) [4]. This levonorgestrel implant has the potential to improve access to contraceptive implants in resource-poor settings.

In 2006, the US Food and Drug Administration approved Implanon, a single-rod etonogestrel implant. Implanon's single rod provided great improvements over the previously available six-capsule Norplant system in time and ease of insertion [5, 6]. The etonogestrel implant inserter is preloaded and disposable. Since only one rod is implanted, there is no chance of moving previously placed capsules out of position with insertion of additional ones. It is not necessary, as it was with Norplant, to create channels under the skin with a local anesthetic, which made implants difficult to palpate right after insertion. In addition, ethylene vinyl acetate, the plastic from which Implanon is made, is less likely than Norplant's silastic to form a fibrous sheath that can prolong removals [7]. These differences simplify the insertion and removal technique for the etonogestrel implant. For patients, this simplicity means little discomfort at insertion or removal, an unobtrusive implant, and almost no scarring. For clinicians, it means simpler insertion and removal procedures of a predictably short duration. The etonogestrel implant has subsequently been modified and marketed as Nexplanon. In December 2012, Merck stopped supplying Implanon to its distributers, whose supply was exhausted in early 2013. Implanon is no longer available for purchase in the United States. Implanon and Nexplanon are bioequivalent, but Nexplanon is radio-opaque and is pre-loaded into a simpler inserter that helps ensure subdermal placement.

Candidates for Implantable Contraception

Contraceptive implants are a good choice for women of reproductive age who are sexually active and desire highly effective contraception.

Most women are candidates for implantable contraception; there are few medical disorders where the risk of the method exceeds the benefit (e.g., current breast cancer). For clinicians in the United States, the Centers for Disease Control and Prevention (CDC) has listed these conditions in the table, "United States Medical Eligibility Criteria (USMEC) for Contraceptive Use" [8]. Large epidemiologic studies have not identified an increased risk of stroke, myocardial infarction, or venous thromboembolism in users of progestin-only oral contraceptives [9–11], and none of these events occurred in any of the trials on which approval of the implants was based [11, 12]. Subsequently published data support this conclusion [13].

For this reason, the World Health Organization (WHO) and the CDC have indicated that progestin-only contraceptives represent a reasonable contraceptive choice for women with risk factors for, or a past history of, venous thromboembolic disease [8].

This recommendation differs from Nexplanon package labeling, which lists current or past thrombosis as a contraindication to use. Etonogestrel is the biologically active metabolite of the synthetic progestin desogestrel. Controversy remains as to whether desogestrel or its derivatives may be associated with an increased risk of venous thromboembolism compared with other progestins. Evidence of this increased risk comes from studies of oral contraceptives where desogestrel is administered in combination with ethinyl estradiol, rather than alone as in the implant [14]. A randomized controlled trial of maternal hemostasis during the 6-week postpartum period found no increase in coagulation factors for women using the etonogestrel implant when compared to women with no hormonal contraception, supporting the safety of the method in women at increased risk for thrombotic events [15].

Women with Chronic Medical Conditions

Implant contraceptives can be a good choice for women with chronic illnesses because there are no clinically significant metabolic changes associated with the sustained, low doses of progestin delivered by the implant.

Studies of liver function, blood coagulation, immunoglobulin levels, serum cortisol levels, and blood chemistries have failed to detect changes outside of normal ranges and the etonogestrel implant has not been found to have important clinical effects on the lipoprotein profile, carbohydrate metabolism, thyroid and adrenal function, liver function, or the clotting mechanism [16–19]. A literature review concluded that the etonogestrel implant does not appear to have clinically significant effects on lipid metabolism or liver function, although there may be small changes in laboratory values [20]. These findings suggest that implant contraceptives are safe for woman at risk for metabolic, cardiovascular, or thromboembolic disorders.

For women with diabetes whose disease is well controlled by insulin or diet, implant contraceptives are a safe option. Although progestins can affect carbohydrate metabolism, most effects are seen with high doses of androgenic progestins, not the low doses found in implants or with the less androgenic etonogestrel. Few studies have evaluated carbohydrate metabolism in women with the etonogestrel implant, although one prospective study found that there was no difference in fasting glucose, oral glucose tolerance test, and hemoglobin A1C levels at 12 months in women who use the etonogestrel implant [21].

Lactating Women

As progestin-only methods, the contraceptive implants are a safe option for breastfeeding women because they do not interfere with breast milk production. Studies show no effects on breast milk quality or quantity, and infants of mothers with implants grow normally [22, 23]. Implants also seem to be a good choice for immediate post-partum administration. A small study comparing immediate postpartum insertion of the etonogestrel implant to depot medroxyprogesterone acetate at 6 weeks showed no impact on continuation of exclusive breastfeeding at 12 weeks and normal infant weight gain [24]. The etonogestrel implant does not affect breastfeeding outcomes when placed in the immediate post-partum period (within 1–3 days of delivery) compared with delayed insertion (4–8 weeks) [25, 26]. Immediate placement has also been found to be cost-effective when compared with delayed insertion [27].

Adolescents

Adolescents are candidates for contraceptive implants. This method that does not require repeated adherence and offers a discrete method of highly effective contraception. Adolescents most frequently use methods with high failure rates, including condoms, withdrawal, and oral contraceptive pills [28]. Long-acting reversible contraception, including implants and intrauterine devices, has a high uptake among adolescents, with younger adolescents choosing the implant more commonly [29].

The etonogestrel implant is well accepted by postpartum adolescents as well [30]. Women under the age of 18 years have no medical contraindication to implantable contraception based on age alone and the American College of Obstetricians and Gynecologists recommends including implants when discussing contraception with adolescents [8, 31]. Recent studies indicate that use of implantable contraception has been increasing, particularly among adolescents [32].

Pharmacology

The Nexplanon implant is 40 mm × 2.0 mm and consists of one nonbiodegradable rod of 40% ethylene vinyl acetate and 60% etonogestrel (the 3-keto derivative of desogestrel), covered with a rate-controlling ethylene vinyl acetate membrane 0.06 mm thick. The rod contains 68 mg of etonogestrel that is slowly released over at least 3 years: initially at 60–70 mcg/day, decreasing to 35–45 mcg/day at the end of the first year, to 30–40 mcg/day at the end of the second year, and then to 25–30 mcg/day at the end of the third year (Fig. 7.1) [33]. The high initial rate of absorption is probably due to a significant amount of etonogestrel released from the uncovered ends of the implant. Peak serum concentrations (266 pg/mL) of etonogestrel are achieved within 1 day after insertion, suppressing ovulation, which requires only 90 or more pg/mL [34, 35].

Etonogestrel is approximately 32% bound to sex hormone binding globulin (SHBG) and 66% bound to albumin in blood. Like other contraceptive steroids, serum levels of etonogestrel are reduced in women taking liver enzyme-inducing drugs such as rifampicin, griseofulvin, phenytoin, and carbamazepine, but are

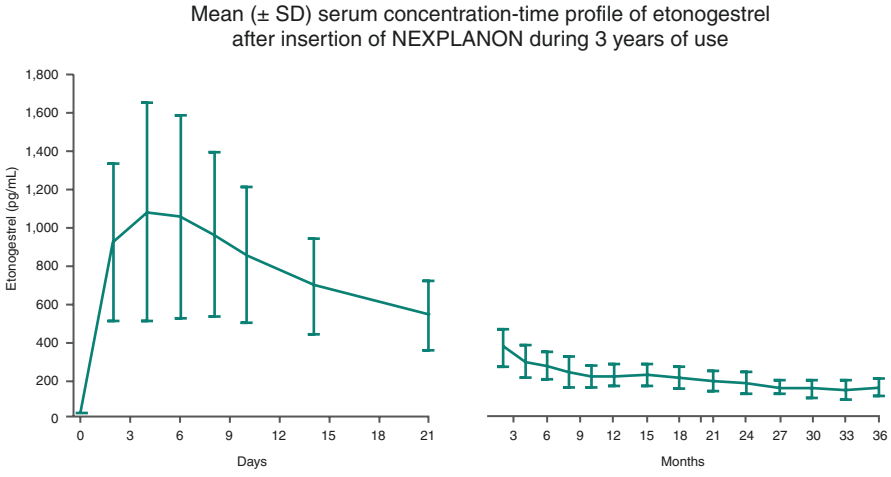

Fig. 7.1 Mean (±SD) serum concentration-time profile of etonogestrel after insertion of Nexplanon during 3 years of use

not affected by antibiotics. Steady release of etonogestrel into the circulation avoids first-pass effects on the liver. Bioavailability of etonogestrel remains nearly 100% throughout 2 years of use. The elimination half-life of etonogestrel is 25 hours. After implant removal, serum etonogestrel concentrations become undetectable within 1 week. Return of ovulation occurs in 94% of women within 3–6 weeks after method discontinuation [34, 35]. Unlike Implanon or the levonorgestrel implants, the Nexplanon rod is radio-opaque, so it can be detected by X-ray and does not require magnetic resonance imaging (MRI) for locating an non-palpable implant.

Mechanism of Action

Progestin diffuses from the implant into the surrounding tissues where it is absorbed by the circulatory system and distributed systemically, providing an initial level in the circulation that is lower than with oral or injected steroids. The release rate of the contraceptive implants is determined by total surface area and the density of the plastic (Silastic or EVA) in which the progestin is contained. Progestin-containing implants have two primary mechanisms of action: inhibition of ovulation and restriction of sperm penetration through cervical mucus [36]. Antiestrogenic actions of the progestins affect the cervical mucus, making it viscous, scanty, and impenetrable by sperm, thus inhibiting fertilization [37]. At high doses, progestins also inhibit gonadotropin secretion, thereby inhibiting follicular maturation and ovulation [38]. The etonogestrel implant inhibits ovulation for 3 years, accounting for almost all of its contraceptive effect [1]. Although progestins suppress endometrial activity making the endometrium unreceptive to implantation, this is not a contraceptively important effect since the major mechanisms of action prevent fertilization [34]. No signs of embryonic development have been found among implant users, indicating that progestin implants have no abortifacient properties.

Efficacy

General Population

The etonogestrel implant is among the most effective contraceptives available (Table 7.1), as good or better than sterilization procedures [38].

An analysis of 11 clinical trials in which 942 women enrolled for 2–4 years showed that the etonogestrel implant was well tolerated and effective: no pregnancies occurred while women were using this method of contraception [12]. Six pregnancies

Table 7.1 Percentage of women experiencing an unintended pregnancy during the first year of typical use and the first year of perfect use of contraception and the percentage continuing use at the end of the first year in the United States

	Percentage of women experiencing an unintended pregnancy within the first year of use		
	Typical use[b]	Perfect use[c]	Percentage of women continuing use at 1 year[a]
Method			
No method[d]	85	85	–
Spermicides[e]	28	18	42
Fertility awareness-based methods[f]	24	0.4–5	47
Withdrawal	22	4	46
Sponge			36
Parous women	24	20	
Nulliparous women	12	9	
Male condom[g]	21	5	41
Female condom[g]	18	2	43
Diaphragm[h]	12	6	57
Combined pill and progestin-only pill	9	0.3	67
Combined patch	9	0.3	67
Combined ring	9	0.3	67
DMPA	6	0.2	56
Copper IUD	0.8	0.6	78
Levonorgestrel IUD	0.2	0.2	80
Etonogestrel implant	0.05	0.05	84
Female sterilization	0.5	0.5	100
Male sterilization	0.15	0.1	100

Adapted from Trussell [5]

[a]Among couples attempting to avoid pregnancy, the percentage who continue to use a method for 1 year

[b]Among typical couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason

[c]Among couples who initiate use of a method (not necessarily for the first time) and who use it perfectly (both consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason

[d]The percentages becoming pregnant are based on data from populations where contraception is not used and from women who cease using contraception in order to become pregnant. Among such populations, about 89% become pregnant within 1 year. This estimate was lowered slightly (to 85%) to represent the percentage who would become pregnant within 1 year among women now relying on reversible methods of contraception if they abandoned contraception altogether

[e]Foams, creams, gels, vaginal suppositories, and vaginal film

[f]Includes the Ovulation, TwoDay, Standard Days, and Symptothermal methods

[g]Without spermicides

[h]With spermicidal cream or jelly

Table 7.2 Extended use data and number of events by year and cohort

	LNG implant	ETG implant	Copper IUD
Number of pregnancies in the first three years[a]	3	3	14
Extended 4-year data			
Number of women starting	522	390	416
Number of women completing	470	311	373
Woman-months of observation	6254	4606	4995
Number of pregnancies	0	0	1[b]
Extended 5-year data			
Number of women starting	470	311	373
Number of women completing	330	204	256
Woman-months of observation	4629	2454	3521
Number of pregnancies	0	0	2
Year 1–5 cumulative data			
Total woman-months of observation	30,325	22,044	24,134
Total number of pregnancies for 5 years of observation	3	3	17
Cumulative pregnancy rates[b] (Kaplan Meier Rates)	0.8 (0.2–2.3)	0.6 (0.2–1.8)	4.1 (2.5–6.5)

Table from: Ali et al. [39]
LNG levonorgestrel, *ETG* etonogestrel
[a]Number of pregnancies reported previously in Bahamondes et al. (2015) in the first 3 years [79]
[b]One additional pregnancy that occurred around 36 months was reported above. The Kaplan–Meier (K–M) method was used to estimate the overall cumulative pregnancy rates

have been reported during the first 14 days after implant removal. The manufacturer cites a Pearl Index of 0.38 pregnancies per 100 women-years of use, effectiveness similar to that of other long-acting methods of contraception. Post-marketing data indicate that the etonogestrel implant's efficacy at pregnancy prevention continues as long as 5 years (Table 7.2) [39, 40]. In the rare event of failure, pregnancy may be intrauterine or extrauterine [41]. Because compliance does not require frequent resupply or instruction in use as necessary with oral contraception, the actual or typical use effectiveness is very close to the theoretical (lowest expected) effectiveness.

Overweight and Obese Women

The etonogestrel implant is not contraindicated in obese women [8].

Although the effectiveness of the etonogestrel implant has not been adequately studied in women more than 130% of their ideal body weight (body mass index [BMI] greater than 30 kg/m^2), available data show no decrease in contraceptive

efficacy even though lower plasma etonogestrel concentration is seen in obese women [42, 43]. Etonogestrel concentrations do not decline below contraceptive levels as body weight increases, nor is there an increased risk of difficult insertions or removals with increasing BMI [due to superficial insertion] [44].

Drug Interactions Impacting Efficacy

Contraceptive efficacy may be decreased in women taking medications that affect the metabolism of etonogestrel [45]. Two case reports describe contraceptive failure in women on carbamazepine for epilepsy; both women had an etonogestrel implant in place for over 18 months [46, 47].

Contraceptive failures have been described for women living with human immunodeficiency virus (HIV) while using the etonogestrel implant and taking efavirenz-based antiretroviral therapy [48]. All implants appeared to be correctly positioned and there was no obvious reason for the contraceptive failures other than a possible decrease of etonogestrel efficacy related to administration of efavirenz, a hepatic enzyme-inducing antiretroviral medication. Pharmacokinetic studies of the etonogestrel implant in women on antiretroviral medications showed substantial decreases in the bioavailability of etonogestrel in women on efavirenz-based and nevirapine-based regimens, whereas women on a lopivanir-based regimen had increased bioavailability of etonogestrel. [49, 50]

Emerging evidence also suggests that efavirenz-based antiretroviral regimens affect levonorgestrel levels more profoundly, resulting in higher contraceptive failure rates [51, 52]. In one retrospective study of HIV-positive women with the levonorgestrel implant, one of the 221 women on nevirapine or lopinavir/ritonavir-based regimens became pregnant, whereas 15 of the 121 women on efavirenz became pregnant [52]. Neither nevirapine-based regimens nor tenofovir disoproxil fumarate-emtricitabine regimens have been shown to alter levonorgestrel levels [51, 53].

Although it is not currently possible to assess the magnitude of the risk of contraceptive failure in this setting, prospective users taking antiretrovirals should be informed that efavirenz use accelerates etonogestrel and levonorgestrel metabolism and greatly increases implant failure rates. From the available evidence on the etonogestrel implant in women taking efavirenz, it appears that the contraceptive failures occur later within the 3 years that the device is efficacious, possibly due to a more rapid depletion of etonogestrel levels.

The accelerated metabolism of progestin does not preclude use of implants, which remains highly effective for most women on antiretroviral and antiepileptic

Some experts have suggested replacing implants early or placing more than one implant for women on efavirenz due to the decreased levonorgestrel or etonogestrel levels, but these practices have not been studied.

drugs. Furthermore, HIV-positive women are typically advised to use condoms to protect against transmission of HIV and other sexually transmitted infections; thus, they typically have back-up contraceptive protection.

Counseling

Irregular Bleeding

Unscheduled bleeding is a common side effect, which may or may not decrease with continued use. Because implants allow for follicular development but not ovulation, endogenous estrogen production is nearly normal, and unlike the combined estrogen–progestin contraceptives, progestin is not regularly withdrawn to allow endometrial sloughing. Consequently, the endometrium sheds at unpredictable intervals and menstrual bleeding patterns can be highly variable among users of implant contraception. Changes include alterations in the interval between bleeding, the duration, and volume of menstrual flow, and spotting.

> In the analysis of 11 clinical trials, unscheduled bleeding was the primary reason for discontinuation, with a rate of 14.8 percent in the United States and Europe, but only 3.7 percent in Southeast Asia, Chile, and Russia [12]. United States users were more likely to discontinue because of prolonged or heavy bleeding than women from other countries (7.0 versus 4.3 percent). The mean number of bleeding and spotting days per 90-day reference period was 7.3 and 10.4 days, respectively. One-third of 90-day reference periods had fewer than three bleeding/spotting episodes; one-fifth had no bleeding/spotting (amenorrhea); 17 percent had a bleeding episode that lasted more than 14 days, and 6 percent had more than five bleeding/spotting episodes. The number of unscheduled bleeding days was highest in the first three months of use, decreased during the first year of use, and then plateaued for the second and third years of use. However, this decrease may have resulted from patients discontinuing as a result of a bleeding irregularity, leaving for analysis those less likely to experience bleeding. Although amenorrhea occurs in approximately 20% of women in the first year of use, the rates of amenorrhea actually decline with duration of use to 13% by year 3 [54].
>
> Women who experienced more days of bleeding were more likely to discontinue, especially if the bleeding was prolonged. For example, the mean number of bleeding/spotting days in women who discontinued and who continued implant use during a 90-day reference period was 45.2 and 16.5 days, respectively. Frequent or prolonged bleeding/spotting was reported in about 90 percent of women who discontinued the implant but in only 22 percent of those who continued its use [55].

Management of Irregular Bleeding

Treatment of unscheduled bleeding is not necessary, but since bleeding disturbances are the principal cause of discontinuation, several approaches to their treatment have been used. For women who have no contraindications to estrogen, prolonged bleeding may be treated with a short course of oral estrogen: conjugated estrogens,

1.25 mg, or estradiol, 2 mg, administered daily for 7 days [56]. An alternative approach is to administer an estrogen–progestin oral contraceptive for 1–3 months. One randomized controlled trial found that a 7-day course of tamoxifen 10 mg twice daily decreased the number of bleeding/spotting days that women experienced during breakthrough bleeding with the etonogestrel implant [57]. Another randomized controlled trial found that etonogestrel implant users who were treated with 7 days of daily ulipristal acetate 15 mg had a reduced number of bleedings days and higher satisfaction with their bleeding profile when compared to those treated with placebo [58]. Short courses of treatment with non-steroidal anti-inflammatory drugs (NSAIDs) for 5–7 days have also been recommended to manage irregular bleeding [59]. Clinicians have many tools to manage women who experience bleeding disturbances with the etonogestrel implant.

Other Side Effects

The most common adverse events besides unscheduled bleeding that were deemed possibly, probably, or definitely related to the etonogestrel implant included headache (16%), weight gain (12%), acne (12%), breast tenderness (10%), emotional lability (6%) and abdominal pain (5%) [12].

The etonogestrel implant does not induce bone loss. In contrast, depot medroxyprogesterone acetate (DMPA), another progestin-only contraceptive that reduces estrogen levels, can decrease bone mineral density.

A large epidemiologic study using registry data from Denmark did not find an increased risk of arterial events among 24,954 implant users compared with over 9 million nonusers of hormonal contraception [13]. For thrombotic stroke, there were three events among users, incidence 12/100,000 person years, RR 0.88, 95% CI 0.28–2.72; for myocardial infarction, there were three events among users, incidence 12/100,000 person years, RR 2.14, 95% CI 0.69–6.65.

Sexually Transmitted Infections

Sexually active women are exposed to the risk of pregnancy as well as to the risk of sexually transmitted infections (STIs), such as HIV, hepatitis B, human papillomavirus, *Chlamydia trachomatis*, syphilis, and gonorrhea whose sequelae may be life-threatening. Implantable contraceptives neither increase the risk of nor offer protection against STIs [60]. Women counseled about contraception should also be informed about the risks of STIs. They should be advised that use of condoms concomitantly with an effective method of pregnancy prevention is the best means of protection against unintended pregnancy and STIs. It seems likely that the etonogestrel implant, like oral contraceptive pills and DMPA, reduces the risk of pelvic upper tract infection (PID), probably because of progestin effects on cervical mucus.

Some evidence suggests that DMPA use increases the risk of human immunodeficiency virus (HIV) acquisition [61]. There is no evidence that other contraceptive progestins at lower doses, such as the etonogestrel implant, have similar effects.

Initiation

For healthy women, no physical examination or laboratory tests are indicated before insertion of an etonogestrel implant [59].

Although some medical conditions represent contraindications to hormone use [8], the low prevalence of these conditions in women of asymptomatic reproductive age does not warrant screening for these conditions by physical examination or laboratory testing for the safe initiation of implants [59].

The possibility of early pregnancy can generally be assessed by review of the woman's menstrual, sexual, and contraceptive history. The absence of pregnancy can be reasonably inferred if she meets any of the criteria in (Box 1). An appropriately timed pregnancy test (at least 2 weeks after the last episode of sex) can be obtained if the absence of pregnancy is uncertain.

There is no evidence that the etonogestrel implant or other hormonal contraceptives have caused abnormal fetal development. Most of the few pregnancies reported among etonogestrel implant users were present before insertion. The implant can be inserted at any time as long as the clinician is reasonably certain that the patient is not pregnant. Women who are postabortion (either medical or surgical) or postpartum (even if breastfeeding) can have the implant inserted immediately after termination of pregnancy or delivery [8].

Back-Up Contraception

Abstinence or back-up contraception is suggested for the first 7 days after insertion if the implant is inserted more than 5 days since the beginning of the patient's last menstrual period [59], although data to support this need are lacking [62]. This conservative approach is recommended because changes in cervical mucus occur rapidly and are probably complete within 36 hours of insertion. Options for back-up contraception include use of condoms or continued use of the woman's previous method of contraception. For women who are postpartum, not exclusively breastfeeding, and have not resumed menses, back-up contraception is suggested for those who are more than 3 weeks postpartum. For women who are postpartum,

exclusively breastfeeding, and have not resumed menses, back-up contraception is suggested for those who are more than 6 months postpartum. For women who are post-abortion, back-up contraception is suggested if the implant is not placed on the day of the abortion.

If the woman has been using an intrauterine device (IUD) and is switching to the implant, she may have residual sperm in her reproductive tract, which could result in fertilization and implantation if the IUD is removed. Options include the following:

- Advise the woman to retain the IUD for at least 7 days after the implant is inserted and then return for IUD removal.
- Advise the woman to abstain from sexual intercourse or use barrier contraception for 7 days before removing the IUD and switching to the implant. Back-up contraception is suggested if the implant is inserted more than 5 days since the beginning of the patient's last menstrual period.
- Advise the woman to use emergency contraception at the time of IUD removal and use back-up contraception if the implant is inserted more than 5 days since the beginning of the patient's last menstrual period.

Insertion

Insertion of Nexplanon is a brief office procedure performed under local anesthesia. A clinician who has been trained in the technique can do it in less than 1 minute [63]. The US Food and Drug Administration (FDA) and Nexplanon's maker, Merck, agreed that Implanon and Nexplanon would be distributed only to clinicians who have received 3 hours of training in patient selection, counseling, insertion, and removal. Questions regarding training can be answered at 1-877-467-5266. Merck is required to coordinate and provide instructors and materials for training, as well as to monitor clinician reporting of adverse events. This voluntary reporting system has not revealed any unexpected problems with insertion or removal of the etonogestrel implant [64]. In 2018, Merck updated the recommended insertion location to avoid the blood vessels and nerves that lie in the biceps groove.

Required Equipment for Etonogestrel Implant Insertion

- A 25-gauge needle (1.5 inches in length) attached to a 2–5 mL syringe
- 1% chloroprocaine or lidocaine without epinephrine
- Antiseptic solution (e.g., povidone iodine, chlorhexidine gluconate, isopropyl alcohol)
- An adhesive strip for closure of the puncture site
- Elastic pressure bandage (e.g., "Kerlex")

- Surgical gloves (need not be sterile)
- Sterile drape
- Sterile, preloaded Nexplanon applicator

Positioning the Patient

The patient is placed in a supine position with the full length of her arm exposed. The manufacturer suggests positioning the upper inner arm by bending the elbow to 90° and rotating the arm out. Some providers find the procedure is easier when the arm is extended, allowing full exposure of the crease between the biceps and triceps muscles. Adequate support under the arm should be provided to ensure comfort with, e.g., a pillow. In 2018, Merck updated the recommended insertion location to avoid the blood vessels and nerves that lie in the biceps groove. The insertion site overlies the triceps muscle about 8–10 cm from the medial epicondyle of the humerus and 3–5 cm posterior to the sulcus between the biceps and triceps muscles (Fig. 7.2). The optimum site depends upon an individual woman's anatomy, such as the length of the upper arm (avoid placing the end of the implant too near the axilla) and the area where the crease between the biceps and triceps muscles is clearest.

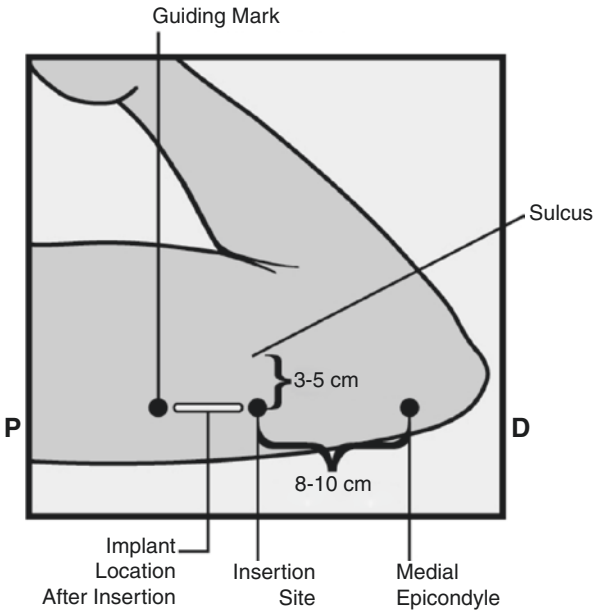

Fig. 7.2 The insertion site is overlying the triceps muscle about 8–10 cm from the medial epicondyle of the humerus and 3–5 cm posterior to the sulcus (groove) between the biceps and triceps muscles

To minimize the risk of infection, strict aseptic technique should be maintained throughout the procedure, e.g., do not touch the trocar containing the implant. A sterile drape is placed under the arm, and the insertion site on the arm is cleaned with an antiseptic such as povidone-iodine. Some clinicians mark the skin to help guide insertion. One mark is made where the rod will be inserted, and a second mark is made a few centimeters proximal to the first mark to serve as a direction guide during insertion. However, insertion directly through the marked skin should be avoided as it can result in "tattooing." Use of skin marks is at the clinician's discretion.

Anesthesia

Local anesthesia for the incision is obtained by raising a wheal of 1% chloroprocaine or lidocaine using a 1½ inch 25-gauge needle and injecting 1–3 ml under the skin along the track of the implant insertion needle. A burning sensation is common during injection of the local anesthetic. This effect can be eliminated for most patients by adding 1 meq of sodium bicarbonate to each 10 mL of anesthetic (however, this buffering shortens shelf life to 24 hours) [65]. Local anesthesia should be allowed a few minutes to take effect and the insertion site should be tested prior to beginning the procedure to ensure that the patient is comfortable.

Insert Implant

The operator should view the insertion site from the side, not from above the device. Most women feel no more than a pressure sensation during the insertion procedure. The sharp, beveled trocar easily penetrates the skin, making a separate scalpel incision unnecessary. Grasp the applicator above the needle cap on its textured surface between thumb and forefinger. Remove the clear plastic needle cover. Place the needle against the insertion site holding the applicator at an angle 30° to the skin (Fig. 7.3). While applying counter traction to the skin around the insertion site, puncture the skin with the needle tip. Lower the applicator so that it is parallel to the skin and advance the needle in the subdermal connective tissue while lifting the skin with the tip of the needle. Advance the needle to its full length. If the needle is not fully advanced under the skin, the implant will not be correctly inserted. Unlock the slider with downward finger pressure on the lever, then move the slider fully backward (distally) and withdraw the needle.

Verify Placement

Immediately after insertion, palpate the skin to verify correct placement of the rod; both ends should be palpable. Ask the patient to feel her implant, then place an adhesive closure on the insertion puncture and wrap the site with a pressure bandage

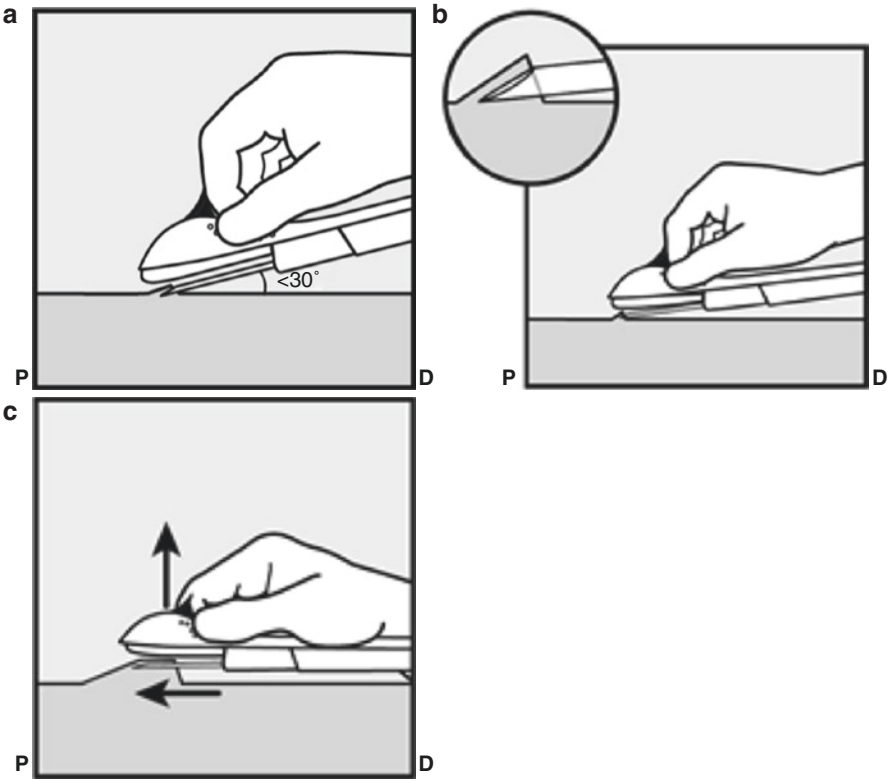

Fig. 7.3 (**a**–**c**) Grasp the applicator above the needle cap on its textured surface between the thumb and forefinger. Remove the clear plastic needle cover. Place the needle against the insertion site holding the applicator at a 30° angle to the skin

to minimize bruising. If you cannot feel the implant, check the applicator to make sure the implant is no longer in the applicator. The applicator obturator is purple, while the implant is white. If there is doubt about the presence of the implant, use sonography or an X-ray to determine its presence. Magnetic resonance imaging (MRI) is not required.

Post-Insertion Care and Follow-Up

Complete the Patient Chart Label for the patient's medical record and the User Card, which must be given to the patient. The woman may remove the pressure bandage in 24 hours and the small bandage in 3 days. Most women do not experience pain after insertion, but if it occurs, aspirin, acetaminophen, or nonsteroidal anti-inflammatory agents usually provide relief. The patient may be discharged

immediately after the procedure. A routine follow-up visit is not necessary [59]. She should call the provider if she develops pain, discharge, or swelling at the insertion site, fever, or other concerns. She should also contact her provider if she has a change in her health status that could affect safe and effective use of this method, or when she wants to switch contraception methods, remove the implant to attempt pregnancy, or replace the implant when efficacy wanes.

Complications of Insertion

Complications are rare, reported in 0.3–1% of insertions and 0.2–5.9% of removals [64, 66, 67]. Potential complications include infection, hematoma formation, local irritation or rash, expulsion, and allergic reactions. The implant may migrate a short distance (less than 2 cm) over time [68]. The incidence of complications is minimized by clinician training and experience, and the use of strict aseptic technique. Incorrect placement can result in nerve injury or neuropathy [69]. In very rare cases, improper placement can result in implant migration to the vasculature, chest wall, or distant body sites [70]. When placed by a trained clinician, complications of etonogestrel implant insertion are rare and clinical consequences did not result in serious injury [66].

Removal

The rod can be removed at any time but should be removed when efficacy begins to decline (3 years after insertion according to the package insert; 5 years according to WHO studies). The hormonal effects end promptly after removal; circulating levels of etonogestrel are undetectable in 1 week. Return of ovulation occurs in 94% of women within 3–6 weeks after method discontinuation [34, 35]. If the implant is not removed at 3 years, contraceptive effects persist for at least an additional 2 years [39, 40].

Implant removal is an office procedure requiring only local anesthesia. Equipment is the same as that listed above for insertion, except that the Nexplanon applicator is replaced by sterile mosquito forceps (curved and straight) and a #11 scalpel. For removing deeply inserted implants, modified (<2 mm diameter ring) vasectomy forceps can be useful. Removal takes about 4 minutes [44] for Implanon and 2 minutes for Nexplanon [71]. Fibrous tissue surrounding Nexplanon is rare (4%) but increases removal time [44, 71]. Clinicians can view an instructional video and practice removal on a model arm before attempting the procedure on a patient. A removal kit containing a model arm and a manual and compact disc illustrating basic technique is available at no charge from Merck (by calling 877-467-5266). The patient should read and sign an informed consent, which is filed in her medical record. The patient also should be given a copy.

Procedure

Position the patient and prepare the implant site as described above for rod insertion. Some clinicians prefer that the patient extend her arm for the insertion procedure but bend her arm for implant removal.

Palpate the distal tip of the rod (the end closest to the elbow). If it is not palpable, then removal should be postponed until the rod can be localized with sonography or X-ray imaging combined with a referral to a provider with experience in removing non-palpable contraceptive implants. Push down on the proximal end of the rod (the end closest to the axilla) and inject no more than 0.5 mL of buffered lidocaine with epinephrine into the dermis immediately under the elevated distal tip of the rod, raising a wheal about 5 mm in diameter. Too much anesthetic, especially if it is injected on top of the rod, makes it difficult to palpate the tip of the rod. Massage this area to disperse the anesthetic.

Use your fingers to again apply pressure on the proximal (axillary) end of the rod so that the distal (elbow) end pushes up against the skin. As the rod is pushed against the skin, the blade of a #11 scalpel is positioned so that the point is immediately available to incise the sheath without releasing pressure on the rod. It is best to keep the scalpel in one hand with thumb and index finger while manipulating the rod with the rest of the fingers of both hands. Pushing the rod against the incision with finger pressure is critical for success with this "Pop Out" technique because, if pressure is released, the rod will slip back into its sheath in the subdermal tissue.

Make a 2–3 mm longitudinal incision through the skin over the end of the rod. Deepen the incision until you feel a rubbery sensation against the point of the scalpel blade; this is the rod encased in its fibrous sheath. Nick the fibrous sheath covering the end of the rod with the tip of the scalpel blade. It may take several nicks in different directions to fully open the sheath.

The end of the rod will come into view as the sheath is opened. Continue to exert finger pressure on the proximal (axillary) end of the rod to push the distal (elbow) end through the incision until it can be grasped with fingers or forceps and pulled out. Confirm that all 40 mm of the rod have been removed. Close the incision with an adhesive strip (e.g., butterfly bandage) and cover with a pressure bandage to minimize bruising.

Difficult Removals

If the rod will not move toward the incision with finger pressure, it can be grasped with a hemostat or modified vasectomy forcep (filed down to a 2 mm diameter grasping ring), but the incision will usually have to be lengthened in order to admit the clamp. It may be necessary to inject more local anesthetic, and to dissect around the rod with a straight mosquito clamp. The disadvantage of instrument removal is that it can be more painful, cause more bleeding, require a larger incision, and increase the risk of breaking the rod.

Once a rod is damaged, it can fracture with further attempts to grasp it with clamps. To decrease this risk, the rod should be grasped by its end whenever possible and with as little traction as possible for exposure and removal.

If it is not possible to grasp and push up on the end of a deeply implanted rod to open the fibrous sheath, use a scalpel to cut longitudinally, not across, the fibrous sheath covering the rod. Rarely, removal of a cut or broken rod will require an additional incision at the proximal end of the rod so that the remaining piece can be extracted. When the rod must be grasped around its diameter [a mid-implant removal], rather than at the end, the vasectomy forceps are particularly useful.

Rods too deeply placed cannot be palpated under the skin but can be seen with imaging studies (Implanon can be identified with high-resolution sonography or magnetic resonance imaging [MRI]; Nexplanon can be identified with high-resolution sonography, plain X-ray, computed tomography, or MRI). Such "lost" rods should be located with a high frequency (10–15 megahertz) linear ultrasound transducer prior to attempting the removal [72–74]. Use a transverse orientation to identify an acoustic shadow (the rod itself is more difficult to see), measure the depth, and draw a line representing the rod location on the surface of the skin. After making an incision, a straight hemostat clamp is used to divide the subcutaneous tissue until the level of the implant, as determined by the pre-procedure ultrasound study. The modified vasectomy clamp grasps around the implant and brings it to the skin surface. A scalpel is used to clear any overlying fibrotic tissue to free the implant for removal (Videos 7.1, Part 1 and 7.1, Part 2). If the rod is very deep (>1.5–2 cm), sonography should be used during the removal procedure because movement of the patient's arm may change the location of skin marks in relation to the underlying implant.

Patients with "very" (>2 cm) deep (as determined sonographically) implants should be referred to an experienced gynecologist. The contraceptive specialist can then work with interventional radiologists to remove the implant under direct imaging and controlled conditions. A case series of implant removal with a hook-wire marker method used in breast tumor surgery has been proposed [75] as has use of ultrasound with a modified vasectomy clamp [76].

Removal of contraceptive implants is *never* an emergency; there is no evidence that their presence adversely affects pregnancies or other conditions. Therefore, we suggest waiting until removal can be performed by a surgeon with expertise in removal of difficult contraceptive implants. Consultation with an orthopedic or plastic surgeon without specific expertise managing this problem is rarely required and not advised.

Reinsertion

If the patient wants to continue to use implant contraception, a new rod can be inserted immediately. If the previous implant was correctly positioned, the new implant can be placed through the same incision that was used to remove the old

rod. If the previous implant was placed in the biceps groove, the new implant should be placed in the updated insertion site (over the triceps muscle about 8–10 cm from the medial epicondyle of the humerus and 3–5 cm posterior to the biceps groove). Alternatively, the new implant can be placed in the other arm.

Jadelle

Each Jadelle rod contains 75 mg of levonorgestrel for a total of 150 mg, 66 mg less than that in the six Norplant capsules [compared to 68 mg etonogestrel Nexplanon]. The thin, flexible Jadelle rods are wrapped in silastic tubing (the same material used by Norplant), 43 mm in length and 2.5 mm in diameter, thus slightly longer and thicker than Norplant [77]. Whereas the levonorgestrel in Norplant is packed into the capsules in crystal form, the core of the Jadelle rod is a mixture of levonorgestrel and an elastic polymer (dimethylsiloxane/methylvinylsiloxane). Long-term clinical trials indicate that the performance and side effects are similar to Norplant, but removal is faster [2, 78].

Because the release rates with the two levonorgestrel systems are comparable, it is reasonable to conclude that clinical studies with Norplant and Jadelle should yield similar results. While Norplant has been more extensively studied, clinicians can assume that the findings apply as well to Jadelle, except that Norplant was shown to be effective for 7 years and Jadelle for 5.

Summary

Implants offer women a highly effective, long-term, and easy-to-use method of contraception. They may be used in most women, including women with contraindications to estrogen, adolescents, women with chronic illnesses, and breastfeeding women. Implantable contraception is safe and cost-effective immediately post abortion and postpartum. Providers interested in placing and removing implants should undergo appropriate training, but all providers counseling women about contraception should be offered implantable contraception.

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