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Review Article

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Comparison Between Levonorgestrel and Etonogestrel Implants, the Two Silicone-Based Long-Acting Reversible Subdermal Contraceptives

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Abstract

Levonorgestrel (LNG) and etonogestrel (ENG) subdermal implants symbolize the most widely used long-acting reversible contraceptives (LARCs) among modern family planning methods and offer 3-5 years of protection against unintended pregnancies (UPs), by providing effective and user-friendly contraception. In this review, we have performed a comparative analysis of both types of implants with respect to their historical evolution, chemical and pharmaceutical differences, clinical performance, such as safety, efficacy, and acceptability, side effect profiles, global accessibility, cost-effectiveness, and overall satisfaction and implications for users' health, independence, and socioeconomic contribution. LNG implants (e.g., Jadelle, Sino-implant II) and ENG implants (Implanon, Nexplanon) show more than 99% of contraceptive efficacy for the intended duration with serum progestogen levels enduring above the threshold to suppress ovulation, needed for contraception. LNG implants offer 3-5 years of contraception, whereas ENG implants, although labeled for 3 years, demonstrate evidence of 5 years of pregnancy protection. Common side effects include weight gain, irregular menstruation, and frequent bleeding, with ENG usually accompanied by easier insertion and removal and a low rate of early discontinuation. LNG implants are more cost-effective and generally subsidized in low-income countries, whereas ENG implants prevail more in high-income regions due to their higher cost. These two reversible contraceptive implants boost user compliance, diminish unintentional gravidity, and have a positive influence on the women's lifestyle, freedom, and reproductive health. Therefore, both implants are highly effective, safe, and acceptable LARCs, with discrete benefits in length of duration, availability, and acceptability, and their wider range of contraception, mostly in low-resource regions, can significantly decrease the problem of UPs during women's empowerment and socioeconomic promotion.

Keywords: Levonorgestrel, Etonogestrel, Subdermal Implants, Long-Acting Reversible Contraceptives, Pharmacokinetics, Family Planning, Women's Health and Lifestyle

1. Introduction

Globally, over seven hundred million women of reproductive age use modern contraceptives, with a significant portion relying on long-acting reversible contraceptives (LARCs). LARCs are increasingly promoted because they offer 3-5 years of protection, depending on the method type, and require minimal user action once inserted, thereby reducing the risk of failure from missed doses or incorrect dosage regimens. They are also considered among the most effective reversible contraceptive methods. Additionally, LARCs play a crucial role in empowering women and complement efforts to improve access to education, employment, and socioeconomic development. Despite the rise in contraceptive use, particularly across South Asian and African countries, unintended or unplanned pregnancies (UPs) still occur. Contributing factors include the high costs of some methods, geographic and infrastructural barriers to service delivery, and

ongoing gaps in awareness and counseling. These challenges emphasize the need for policies that promote equitable access to affordable, effective contraceptives, especially LARCs, to lessen the global burden of Ups [1]. Implantable subdermal contraceptives consist of small, flexible, non-biodegradable rods resembling a matchstick. These are inserted into the upper arm and deliver a steady release of low-dose progestin, most commonly LNG and ENG. They are effective hormonal treatments used to manage menstrual issues and endometriosis. Both hormones simulate the activity of natural progesterone, which is incorporated into widely used contraceptive formulations, including emergency oral contraceptive pills (EOCPs), combined oral contraceptives (COCs), subdermal or subcutaneous injectables, silicone-based LARC subdermal implants, and intrauterine device systems (IUDs) [2]. Among the contraceptive options, LNG and ENG subdermal implants, the two most prominent methods, have emerged as consistent and long-term reversible contraceptives for preventing Ups that have converted the landscape of birth control due to safety, efficacy, tolerability, and acceptability profile. The demand for intrauterine devices (IUDs), LNG-releasing IUDs, and progestin implants has approximately doubled in recent years [1].

Among LNG-containing LARC implants, Jadelle (Bayer Oy, Finland), Levoplant/Sino-implant (II) (Shanghai Dahua Pharmaceuticals, China), Femiplant-II (Techno Drugs Ltd, Bangladesh), and Jadena/Duplant (Harsen Laboratories, Indonesia) generally consisting of two flexible rods containing 150 mg LNG inserted in a V-shape at an angle of approximately 30°, placed 8–10 cm above the elbow on the inner side of the upper arm and available effective for 3–5 years as contraceptives, whereas Implanon NXT/ Nexplanon, a single-rod implant containing 68 mg ENG, provides three years of contraception. However, some recent studies recommend it for five years of effectiveness [3,4]. These devices initially release higher doses of hormone during the first 6–12 months, stabilizing thereafter to approximately 30–35 µg/day throughout the remainder of their effective lifespan [2]. LNG and ENG implants differ from each other in respect of the mechanism of activity, duration of action, side effects, and user satisfaction. In this review, we have attempted to make a comparative investigation of both types of subdermal implants, detailing their individual strengths and weaknesses in terms of safety, efficacy, performance, acceptability, and overall impacts on women's health and lifestyle.

2. Historical Evolution

There is significant progress in the development of LARC subdermal contraceptive implants. The first generation of subdermal implant, known as Norplant, manufactured in Finland in 1983, consisted of six LNG-releasing silicone capsules, giving 5-7 years of contraceptive efficacy and was discontinued worldwide in 2008 [5,6]. Continuing research to ease the insertion and removal procedures directed to the development of Norplant-2 (Jadelle), a two-rod LNG-releasing contraceptive option permitted by the USFDA in the USA in 1996 [7]. In addition, Implanon, a third-generation single-rod ENG-releasing implant with a three-year life span as a contraceptive delivery system, was introduced in 1999 to make it more user-friendly. Its successor, Implanon NXT (Nexplanon), was first introduced in 2010, and included a redesigned applicator to progress the insertion technique, and after that, the original Implanon was replaced by the latter one in most countries [4,8]. The use of Jadelle and Implanon has become limited in many low and middle-income countries due to their high cost, which was then moderately addressed with the breakthrough of Sino-implant (II) in 1999, manufactured by Shanghai Dahua Pharmaceutical Co., Limited of China. and marketed as Levoplant throughout the world [7,9]. Beyond these recognized LARC implants, numerous next-generation contraceptive implants continue under vigorous study, including Nesterone and Capronor, which have discovered biodegradable polymeric rods, pellets, and microcapsule formulations of novel hormones. In addition, further research into male contraceptive implant development, for example, MENT acetate (7α-methyl-19-nortestosterone), has shown prospective but remains in the early clinical phase and is waiting for regulatory authorization [10].

3. Chemistry

The chemical structure information for LNG is as follows: IUPAC name (17α)-17-ethynyl-18-methyl-19-nor-17α-pregn-4-en-20-yn-3-one, molecular formula $C_{21}H_{28}O_2$, molecular weight 312.45 g/mol, synthetic progestogen (19-nortestosterone derivative) [11,12]. For ENG, the IUPAC name is (17α)-13-Ethyl-17-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one, molecular formula $C_{22}H_{28}O_2$, molecular weight 324.46 g/mol, synthetic progestin; active metabolite of desogestrel (19-nortestosterone derivative) [3,12]. Both LNG and ENG are derived from testosterone, with modifications for high oral bioactivity. The ethynyl group (-C≡CH) at C_{17} prevents rapid hepatic metabolism, while the keto group at C_3 and the double bond at C_4-C_5 are critical for receptor binding [11]. Additionally, the methyl group at C_{18} differentiates LNG from norethindrone. ENG is structurally related to LNG but has a 3-keto group modification and an 11-methylene substituent, which enhances oral activity, prevents rapid hepatic metabolism, and distinguishes it from LNG [3]. Like LNG, ENG also retains the C_3 keto group and 4-ene double bond, critical for progesterone receptor binding. These structural modifications give ENG higher receptor affinity and bioavailability compared to its prodrug, desogestrel [12].

4. Mechanism of Action

Both LNG- and ENG-containing implants are inserted subdermally, typically in the upper arm, and are highly effective in suppressing ovulation [4,6]. These implants function by releasing hormones into the body that prevent ovulation, thus averting pregnancy. Both LNG and ENG-releasing implants, synthetic progestogen that inhibits the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), are needed for ovulation, ultimately thickening the cervical mucus, creating a hostile environment for sperm, and altering the endometrial lining to prevent fertilization [2,8,12].

5. Pharmacokinetics

LNG-releasing contraceptive subdermal implants deliver a sustained release of progestin hormone from the implant delivery

system into the systemic circulation immediately after subdermal insertion, ensuring three to five years of reversible birth control. After systemic distribution, it reaches a relatively constant plasma drug concentration compared to the dose given orally [6,12]. On the other hand, ENG implant, the biologically active metabolite of desogestrel, releases progestin hormone uninterruptedly from a single-rod subdermal implant system (Implanon/Nexplanon), intended to offer contraceptive action for up to three years [4,8].

6. Absorption and Distribution

After implant insertion, LNG is absorbed gradually into the systemic circulation. Peak plasma concentrations (Cmax) are characteristically perceived within the first few weeks to months, followed by a steady decline as the release rate decays. Initial serum LNG levels may range between 200-400 pg/mL depending on the type of implant, such as Jadelle or Sino-implant II, women's body mass index, and insertion time [6,12]. The drug is highly bound to plasma proteins, largely albumin and sex hormone-binding globulin (SHBG), with only a small portion remaining as free, being pharmacologically active. On the other hand, ENG is rapidly absorbed into the bloodstream, with peak plasma concentrations (Cmax) of ~800-1000 pg/mL reached within two weeks of implantation. Serum ENG levels then progressively drop but remain adequate to impede ovulation for the intended duration of usage [3]. In addition, ENG is an extremely protein-bound hormone, around 98% binds with plasma proteins, mainly albumin and SHBG, leaving only a small free part biologically effective [6].

7. Metabolism and Elimination

LNG is metabolized primarily in the liver through reduction and conjugation pathways. The metabolites are excreted in both urine and feces. The effective half-life varies, but steady plasma levels are maintained throughout most of the implant's effective lifespan due to continuous release [12]. ENG is metabolized principally in the liver via the cytochrome P450 3A4 (CYP3A4) enzyme system. Metabolites are excreted in urine and feces. The apparent half-life of ENG after subdermal release is approximately 25-30 hours, though stable levels are maintained due to continuous release from the implant matrix [3].

8. Time-Dependent Decrease

The serum LNG decreases gradually with time, though typically remaining above the threshold required to suppress ovulation and provide contraceptive efficacy for up to 5 years (depending on the implant system). Studies show serum levels falling from approximately 300-400 pg/mL in the first year to 150-200 pg/mL by the fifth year. Variability may be observed with higher body weight and BMI, which can influence drug distribution and clearance [6,12]. Contrary, serum ENG level declines progressively with implant duration, from approximately 200-300 pg/mL at the end of year first year to 150–200 pg/mL by the third year, yet still above the threshold level (~90 pg/mL) needed to suppress ovulation. Body mass index (BMI) influences concentrations, with heavier women generally showing lower systemic levels, though contraceptive efficacy is maintained across most populations [3].

9. Clinical Implications

The pharmacokinetic profile of LNG implants ensures effective contraception with minimal user adherence requirements. However, inter-individual variability in serum concentrations may affect side effects (e.g., irregular bleeding patterns) and implant continuation rates. However, the steady PK profile of ENG implants ensures consistent contraceptive efficacy without the need for user adherence. Declining serum concentrations over time correlate with a gradual decrease in ovulation suppression margin, but efficacy remains high throughout the approved three-year duration. Extended use beyond 3 years has been studied, with evidence suggesting sufficient ENG concentrations to maintain ovulation inhibition up to 5 years in many women, though this is not universally recommended. These pharmacodynamics and pharmacokinetics comprise the primary functional components of these contraceptives and amateur the basis for understanding their effects on the biological system. The long-acting, reversible nature of both the implant formulations makes them highly effective, with a failure rate of less than 1%, akin to that of sterilization but with the benefit of reversibility.

10. Duration of Action and User Compliance

The duration of effectiveness and compliance is a critical factor for contraceptive users looking for long-term contraceptive options. Both LNG and ENG implants offer a longer duration of up to 3-5 years, making them a pleasing choice for individuals pursuing prolonged birth spacing without regular follow-up visits in the clinic [6,12]. The prolonged duration of implants decreases the possibility of user mistakes, a very common problem with oral methods of contraception, necessitating everyday adherence. Importantly, both LNG and ENG implants claim effectiveness rates exceeding 99%, mainly eradicating the threat of unplanned pregnancy during their duration . In addition, user compliance is essentially higher in implanted women compared to daily or monthly contraceptive formulation options. The users showed a higher rate of continuation than in tablet users, partly due to the 'set and forget' nature of the implants [13,14]. This benefit is particularly relevant for women with varying healthcare admittance, ensuring continuous contraceptive defense. Studies from the satisfaction perspectives of LNG and ENG implants showed a high degree of acceptability. However, ENG implant materializes preference to some extent for its easier insertion and removal, although both implants have high continuation and satisfaction, demonstrating their pragmatism and user compliance.

11. Side Effects and Health Considerations

The common side effects, including irregular menstruation and bleeding patterns, weight gain, headaches, weakness, and mood fluctuations, are major considerations for LNG and ENG implant users [15,16]. Experimental data demonstrate that irregular and frequent bleeding is the most common cause for implant discontinuation among the users, where around 30% of LNG-implanted and 20% of ENG-implanted women stated persistent irregular bleeding [16]. Among other reported side effects, weight gain presents diverse findings with implant use [15]. Severe health risks are infrequent, though deep vein thrombosis (DVT) is

rarely reported for both types of progestin contraceptives with an acceptable risk profile. Infection at the insertion site or improper implant placement are tremendously rare difficulties, although ENG implants overcome this problem, a redesigned applicator has been developed to facilitate an easier insertion technique.

12. Accessibility and Cost-Effectiveness

Availability and price of implants are key factors influencing contraceptive choices. LNG-releasing implants are more widely available globally. They are often sponsored by donor agencies or governments in many countries and regions with low socio-economic status [7,17]. WHO family planning programs have supported the distribution of LNG implants in underdeveloped areas, helping to close gaps in contraceptive access. ENG implants are mainly available in developed nations because their overall cost is higher than that of LNG implants, often making them less accessible in low-income regions. In terms of cost, both LNG and ENG implants offer an economical option for long-term contraception compared to monthly injectables or daily pills, especially when considering the costs associated with unintentional pregnancies [17]. Additionally, efforts by both government and non-government organizations are subsidized, impacting their availability. The Affordable Care Act mandates insurance coverage for all contraceptive options in the USA. However, in low-resource regions, partnerships between governments and international NGOs help make implants available and accessible to users.

13. Lifestyle and Autonomy

The impact on the lifestyle and self-sufficiency of the implanted women spreads out of common side effects. Since individual, marital, or communal compressions exist, both LNG and ENG implants offer a distinct choice demanding discharge exposure of their use as a contraceptive method [18,19]. These options make them independent to accomplish their obstetric health without external intervention. Both formulations offer incomparable benefits, with the reduction in daily or monthly intake of the hormonal delivery system. They decrease the psychological disturbances associated with other contraceptives [14,20]. For working ladies or those having difficulty with regular intake of contraceptive pills, implants represent a redeeming select, giving a reliable long-term contraception and extensive socio-economic advantages. Research performed by the United Nations Population Fund assumes that access to contraceptive options is directly associated with educational background and personal contribution [21]. In addition, women have the freedom to pursue a career goal independently through the proper selection of contraceptive implants, contribute to their society in terms of financial strength, lifestyle, and familial contribution [22]. Additionally, the reversible characteristics of both types of implants influence family planning decisions. Unlike sterilization, implantation permits the users to return to immediate fertility after implant discontinuation or removal from the body. Importantly, this factor is very crucial for women who face constant familial pressure to conceive a future child.

14. Conclusion

Both LNG and ENG implants offer distinctive benefits in different aspects, demonstrating highly effective and consistent long-acting reversible contraception. LNG implants for 3-5 years' duration are an outstanding choice for contraception, whereas ENG implants are more convenient and slightly shorter in duration (three years) and boast somewhat fewer adverse effects compared to LNG implants, with an insignificant follow-up visit. Several factors, such as duration of use, side effects, price, and availability etc, should be considered during contraceptive implant selection. LNG implants are often more accessible and subsidized in low-income countries, and ENG implants are more prevalent in higher-income regions. As a whole, both implants have overwhelmingly positive impacts on the lifestyle and autonomy of the users, contributing to increased socio-economic prospects. Their demand is increasing day by day due to the preference and access offered by these implants. In addition, since the availability and consciousness of these opportunities remain to be developed, more women will get advantages from the self-dependence benefits provided by both influential methods of birth control.

Declarations

Ethics and Consent to Participant: Not applicable

Conflicts or Competing Interest: The authors declare no conflict of interest.

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