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ORIGINAL ARTICLE

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Lunelle™ monthly injectable contraceptive

An effective, safe, and convenient new birth control option

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Abstract Lunelle™, an injectable estrogen/progestin contraceptive, is administered on a monthly basis and is now available as the first monthly injectable in the United States. International and US clinical trials have established its safety and confirmed its contraceptive efficacy. Fertility returns rapidly after discontinuation of injections. Studies have noted a high level of patient satisfaction with Lunelle, suggesting that monthly injectable contraception will become a first-line contraceptive option in the United States.

Keywords Contraception · Complicance · Benefits · Safety

Introduction

Approaches to birth control used in the United States include barrier methods (male and female condoms, diaphragm, cervical cap, spermicide); oral hormonal regimens (combination and progestin-only oral contraceptives [OCs]); injectable hormonal regimens; implantable hormonal systems; hormonal and nonhormonal intrauterine devices (IUDs); abstinence; withdrawal; natural family planning; sterilization; and postcoital contraception. These methods vary in their efficacy, their reversibility, their safety, and their ability to provide noncontraceptive benefits.

In the 1995 National Survey of Family Growth, sterilization was identified as one of the most common methods of contraception used in the United States (female sterilization, 17.8%; male sterilization, 7.0%) [1]. Although sterilization is extremely effective (typical-use annual failure rates for female and male sterilization are 0.5% and 0.15%, respectively) [28], many individuals prefer reversible methods of contraception. Others choose sterilization because they lack confidence in the safety and efficacy of reversible methods. Of the reversible methods available in the United States, OCs are the most popular. In 1995, OCs were used by 10.4 million women, representing 17% of those using any type of contraception [1]. Used consistently and properly, OCs have one of the highest efficacy rates of all contraceptives. For example, low-dose OC formulations show failure rates of less than 1% in clinical trials [28]. However, with typical use, failure rates are much higher (between 3% and 8%) [9, 25]. This discrepancy is largely due to the fact that, for many women, complicance with the required daily pill-taking routine is difficult; nearly 30% of OC users miss at least 1 pill per cycle, and about 13% miss ≤ 2 pills per cycle [1].

Poor compliance with and discontinuation of OCs accounts for approximately 20% of the annual 3.5 million unintended pregnancies occurring in the United States, representing an annual cost of almost $ 2.6 billion [24]. The strongest single risk factor associated with poor commpliance among OC users is the lack of a daily routine for pill taking, which is essential to satisfy the requirement of daily administration. Other reasons for poor compliance are the occurrence of spotting or intermenstrual bleeding, which can cause the patient to be concerned that an abnormal condition is present, and inadequate reading or understanding of the OC packaging information [23]. In addition, side effects of breast tenderness, nausea, mood changes, weight gain, and headache, whether caused by OC use or not, are often attributed to this method by the users, who may discontinue OCs as a result. In a recently published US prospective cohort study of 1,657 OC users [22], side effects were responsible for 46% of discontinuations, with bleeding irregularities as the leading cause.

These OC compliance issues and resultant unwanted pregnancy statistics illustrate the need for effective, long-acting, reversible, hormonal contraceptives with minimal side effects. In the United States, 2 types of long-acting progestin-only contraceptives are available:

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depot medroxyprogesterone acetate injections (DMPA; Depo-Provera®, Pharmacia) [12] and levonorgestrel implants (Norplant®, Wyeth-Ayerst). Advantages of these methods compared with OCs include greater convenience, improved compliance, and as a result, fewer accidental pregnancies [9]. However, some features of each method may be perceived as disadvantages by some women. For DMPA, irregular bleeding or spotting, followed by amenorrhea may occur. In addition, fertility may not return for up to 18 months after the last injection. Weight gain often occurs with use. The major reasons cited for discontinuing DMPA are irregular menstrual bleeding and weight gain [5]. For Norplant, disadvantages include irregular bleeding [13] and the requirement of surgical procedures for insertion and removal. The system is sometimes visible under the skin, compromising patient privacy, and development of fibrous tissue around the implant can increase patient discomfort during removal as well as add to the technical difficulty and the duration of the removal procedure.

Whereas no available option fully meets the need for an easy-to-use, reversible contraceptive method with minimal side effects, the objective of this review is to describe the features and benefits of a new hormmonal contraceptive now available in the United States, offering many of these attributes. Lunelle™ is a combined estrogen/progestin contraceptive that is administered as a monthly injection. In clinical studies, most women taking Lunelle have had regular bleeding patterns, and a rapid return of fertility is seen after discontinuation [2, 20]. The efficacy of Lunelle in typical users is higher than that of OCs [14]. Finally, Lunelle has safety and side effect profiles that appear to be comparable to those of OCs [7, 11, 14].

Lunelle™ monthly contraceptive injection

Lunelle contains a 17 α-hydroxy derivative of progesterone, medroxyprogesterone acetate (MPA) 25 mg and the natural estrogen ester, estradiol cypionate (E_2C) 5 mg. This preparation provides a full month of protection with 1 injection every 28–30 d, a low serum concentration of MPA, and a cyclic E_2 profile with peak values similar to those of ovulatory women [16]. The contraceptive effect is mediated primarily by MPA, which inhibits ovulation.

Contraceptive efficacy

The efficacy of this monthly injectable contraceptive was demonstrated in 3 well-controlled, 1-year studies sponsored by the World Health Organization (WHO) [18, 26, 29]. In these studies involving over 4,000 women undergoing over 40,000 woman-months of use, only 5 pregnancies occurred, and the overall pregnancy rate was 0.1 per 100 woman-years [18, 26, 29].

In the United States, a recent open-label, multicenter trial was performed to compare the efficacy of Lunelle administered once every 28 ± 5 d with that of the OC Orhto-Novum® 7/7/7 administered once daily for 60 weeks (with placebo pills administered during the fourth week of each cycle) [14]. The participants in the trial (n = 1,103) were sexually active, 18–49 years of age, and had been menstruating regularly for the 3 months prior to enrollment. They were given their choice of the 2 contraceptives being studied. Efficacy was measured by number of pregnancies that occurred during the 13 cycles of treatment. No pregnancies occurred in Lunelle users (n = 782), yielding an overall pregnancy rate of 0.0% per 100 woman-years. In contrast, one pregnancy occurred in the Ortho-Novum 7/7/7 group (n = 321), resulting in an overall pregnancy rate of 0.31% per 100 woman-years.

Return to fertility

Two recent trials have demonstrated that return to fertility after discontinuing injections is rapid [2, 20]. In a US trial assessing time to return of ovulation following discontinuation of Lunelle injections, surgically sterile women (n = 16) with normal menstrual cycles were studied for 1 pretreatment cycle, 3 months of use, and 3–5 months of follow-up after discontinuation of injections [20]. During Lunelle use, ovulation was suppressed in all subjects (indicated by serum progesterone concentrations of ≤ 1 ng/mL). Return of ovulation after Lunelle discontinuation was confirmed by measurement of serum progesterone concentrations of ≥ 4.7 ng/mL. The first normal ovulatory cycle occurred 63–112 d following the last injection (Fig. 1). Thus, Lunelle provided consistent suppression of the hypothalamic-pituitary-ovarian axis that was repidly reversible following dicontinuation.

In a multicenter trial conducted in Brazil, Chile, Colombia, and Peru, 12-month fertility rates were assessed in revious users of this method who had discontinued injection for the purpose of conceiving [2]. Of the 70 women studied, 50% were pregnant by 6 months, and 82.9% were pregnant by 12 months. This 12-month rate is similar to rates observed in untreated women and in previous users of OCs. In women who do not use hormonal contraceptives, the rate is 82% [31]. After discontinuing OCs, there is typically a 2–3 month-delay to return of normal ovulatory cycles [4]. In contrast, the median time for return to fertility after discontinuation of DMPA is 8.5 months after the last injection [12].

Clinical safety and tolerability of Lunelle

Lunelle has well-studied pharmacologic properties; MPA represents a progestin, pharmacologically similar to natural progesterone, with which clinicians and scientists have a wealth of experience. E_2C is hydrolyzed

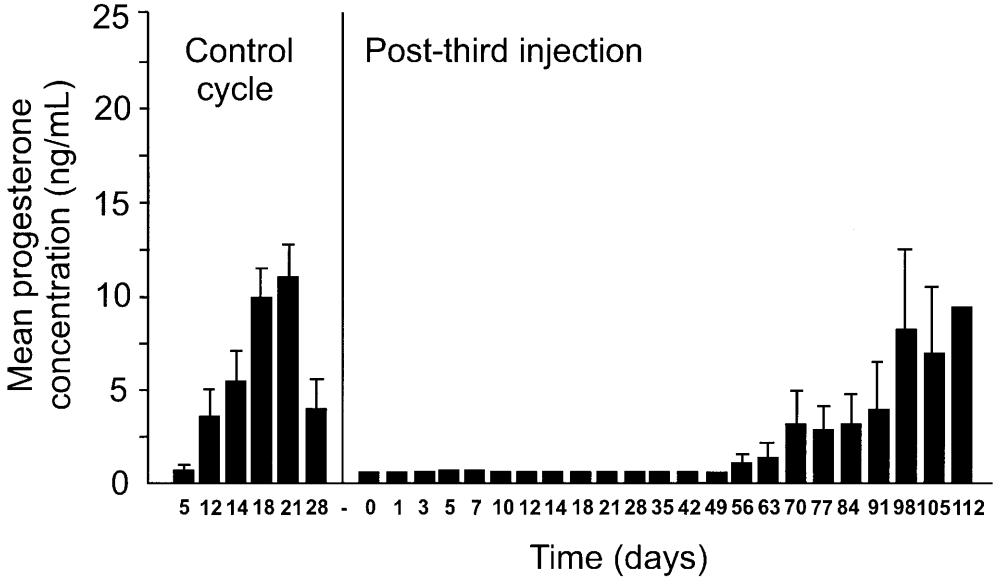

Fig. 1 Mean serum concentration versus time profile of progesterone. Progesterone concentrations were measured during a cycle prior to Lunelle administration and after 3 cycles of Lunelle administration to verify ovulation and return to ovulation. Bars indicate standard error of the mean

into estradiol (E_2), which is physiologically indistinguishable from endogenous estradiol, and E_2 levels in Lunelle users are similar to those noted in ovulatory women [21]. The safety of Lunelle has been demonstrated in over 18,000 women studied by the WHO, for over 156,000 woman-months of use. In the US clinical trial comparing Lunelle with Ortho-Novum 7/7/7 described above [14], the frequency of adverse events with the injections was similar to that noted with combined OCs. At least one adverse event was reported by 89% of women in the Lunelle group and by 84.3% of women in the Ortho-Novum 7/7/7 group. The incidence of adverse events was highest in both groups for the first 3 months and declined with continued use [14]. Types and rates of reported adverse events were consistent with those of other combined hormonal contraceptives.

Coagulation

The increased risk of thromboembolic events associated with use of combination OCs is well established [30]. OC use results in a 10% to 30% increase in fibrinogen, produces variable effects on Factor VII, increases fibrinopeptide A concentrations, and decreases protein S concentrations by 10–20%. In studies to determine the effects of monthly injectable contraceptive use on these parameters, no clinically significant changes were seen in coagulation and fibrinolysis measurements [8, 15]. A WHO study compared the effects of Lunelle and an OC containing 1 mg of norethindrone/35 μg of ethinyl estradiol on coagulation and fibrinolysis, and found that Lunelle did not increase any procoagulant factors and decreased Factor VII activity and plasminogen. In contrast, the combination OC increased Factor VII and Factor X activity, as well as plasminogen and fibrinogen [18].

Blood pressure and lipid metabolism

Increases in blood pressure (BP) have been reported in women using combined OCs [6]. In the US clinical trial described above [14], no clinically significant changes in BP occurred among Lunelle users. Lunelle produced a mean increae in systolic BP of 0.07 m Hg, compared with an increase of 0.23 mm Hg with Ortho-Novum 7/7/7. No mean change in diastolic BP was seen with Lunelle, although a mean increase of 0.83 mm Hg was seen with Ortho-Novum 7/7/7. Three women on Ortho-Novum 7/7/7 discontinued due to hypertension, whereas no patient on Lunelle discontinued due to hypertension [14].

Use of hormonal contraceptives can also cause changes in lipid metabolism. A study of a subpopulation of the US clinical trial [14] participants compared the effect of Lunelle and Ortho-Novum 7/7/7 on lipid parameters [7]. This-open-label, nonrandomized, parallel-controlled study featured assessments of lipid parameters at screening and at Weeks 20, 44, and 60 (or final visit) at 8 centers. Lipid profile measurements included the following: total cholesterol, total triglycerides, LDL cholesterol, HDL cholesterol, apolipoproteins (apo) AI, AII, and B, and total cholesterol/HDL cholesterol ratio. The majority of women in both treatment groups had normal lipid parameters at the beginning of the study. Results in study participants who had switched from a nonhormonal method of contraception were the following: total cholesterol levels, which declined in Lunelle users, increased in Ortho-Novum 7/7/7 users. Total triglyceride levels, which declined in Lunelle users, increased in the OC users ($p \leq 0.05$). The ratio of total cholesterol to HDL-cholesterol changed little in either Lunelle or Ortho-Novum 7/7/7 users. LDL-cholesterol levels, which increased in Ortho-Novum 7/7/7 users ($p < 0.05$), were stable in Lunelle users. Apo B levels, which decreased in Lunelle users ($p < 0.05$), increased in Ortho-Novum 7/7/7 users

($p < 0.05$) [7]. These observations provide reassurance that use of Lunelle does not result in undesirable lipid profile changes, and in fact may produce changes which could favorably impact cardiovascular risk.

Bleeding patterns in Lunelle users

The US clinical study found that, for both Lunelle and Ortho-Novum 7/7/7 users, a regular bleeding pattern was established after an initial transition period in most cases [14]. On average, 1 withdrawal bleeding episode of approximately 6 d occurs each 28 d in Lunelle users. Compared with untreated women, those using Lunelle experience, on average, fewer days of withdrawal bleeding each cycle. Women using OCs experience fewer days of withdrawal bleeding than those using Lunelle (Fig. 2) [3, 14].

A recent re-analysis of the data obtained in the US clinical study [14] compared month-to-month menstrual cycle control in Lunelle and Ortho-Novum 7/7/7 users [10]. Data were divided into one-cycle segments, defined by the time between injections or the time between pill packs. Data from the first and last months were excluded fro the analyses to eliminate confounding variables. Overall, breakthrough bleeding occurred less frequently in women using Lunelle than in those using Ortho-Novum 7/7/7. However, amenorrhea/missed periods occurred more frequently with use of Lunelle. The median day of onset of withdrawal bleeding was 22 d after a Lunelle injection (range 20–25 d) or 24 d after the first pill (range 23–24 d). The broader range in the Lunelle group reflects the less precise decline of hormones with the injection as opposed to the more abrupt decline with the switch from active to placebo pills. The majority of Lunelle-treated women experienced withdrawal bleeding of approximately 6 d in duration, with 14.6% experiencing no bleeding in a given cycle [10].

A recent randomized study compared the effect of Lunelle and a low-dose OC (20 μg EE, 0.1 mg levonorgestrel) on ovarian follicular activity in 30 ovulatory women, 23–44 years of age [11]. Treatment was for 2 cycles, and pelvic sonography was performed every 4 days during the second cycle to measure maximum follicle diameter. Lunelle use was associated with a lower incidence of follicular development than was use of OCs. Only 4/14 Lunelle users developed follicles ≥ 10 mm, compared with 11/13 OC users. None of the Lunelle users developed follicles ≥ 20 mm, compared with 6/13 OC users. I addition, 1 of the 13 OC users developed follicles ≥30 mm. Thus, the use of Lunelle provides more ovarian follicular suppression than a 2-mg EE/0.1-mg levonorgestrel combination OC [11].

Lunelle users: perception and acceptability

Convenience of administration and adverse events are critical in determining whether women use reversible

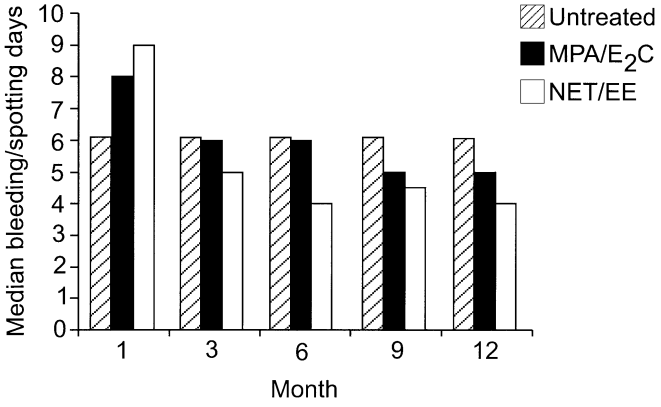

Fig. 2 Median bleeding/spotting days in untreated women, women taking Ortho-Novum 7/7/7 (NET/EE), and women taking Lunelle (MPA/E2C)

contraceptive methods consistently and correctly [27]. Women prefer not to have to think about birth control every day. In a 1999 global survey [19] of women, nearly half (43%) of 500 US women considered the requirement for daily administration of OCs a drawback, and more than half (62%) said they would prefer a monthly contraceptive option. Similarly, a 2000 survey of US women revealed that more than half (56%) were interested in a new method of birth control that is similar to OCs but administered only once a month [17]. A method of contraception that does not require daily administration may be more suitable to the lifestyles of many women and should result in enhanced compliance as well as greater contraceptive efficacy.

Patient acceptance of Lunelle appears to be high. Patient acceptability and satisfaction were assessed in the US comparative clinical trial of Lunelle and Ortho-Novum 7/7/7 [27]. Acceptability was assessed by a User Satisfaction Questionnaire, a Treatment Assessment Questionnaire, and a Global Well-Being Schedule questionnaire. Overall experience with Lunelle was rated as favorable by 84.2% of Lunelle users, which was comparable with ratings by new and previous OC users (86.2% and 83.2%, respectively). More than 90% of Lunelle users responded that they would probably or definitely recommend Lunelle to a friend. Nearly 80% of Lunelle users were not bothered by the need for monthly injections. Nearly 80% of Lunelle users did not think that Lunelle interfered with normal daily activities, and the majority (86.3%) did not think that Lunelle interfered with social or recreational activities. In addition, most women (87%) had no logistical difficulty going for monthly injections.

Patient education and counseling are essential in increasing compliance [23]. Physicians may help women choose a contraceptive method based on their individual needs, background, and concerns. The nature and duration of potential side effects should be explained to the patient before a method is begun. For example, explaining that spotting and breakthrough bleeding are commonly experienced during the initial months of use is appropriate prior to beginning Lunelle or OCs.

Conclusions

Lunelle, a new once-monthly contraceptive now available in the United States, provides many desirable features of OCs, including safety, minimal side effects, and rapid return to fertility, without the requirement of daily administration. Clinical trials indicate that the contraceptive efficacy of Lunelle is higher than that of OCs. Global and US studies have determined that monthly contraceptive injections are well accepted by women.

Monthly contraceptive injections provide users with high efficacy, safety, tolerability, and a rapid return to fertility after discontinuing use. Given these favorable attributes, Lunelle represents a welcome new choice for US women desiring an effective birth control method.

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