

## Long-acting hormonal contraception

Today, a new category of fertility-regulating agents has been created: long-acting, reversible hormonal contraceptives; they minimize compliance, while maximize effectiveness. They comprise subdermal implants and intrauterine devices. Other long-acting agents exist, such as Depo Provera and Noristerat. Use of Depo Provera and Noristerat carries great effectiveness, good clinical safety and usefulness in developing countries. They cause no significant increase in breast cancer risk, but they may carry an increased risk of HIV. Subcutaneous delivery systems have two common features: prolongation of effect is obtained by a drug reservoir and for most of their duration of action they provide a continuous, sustained release of the active hormone. Finally, the intrauterine system Mirena represents both a very effective contraceptive and a specific treatment for menorrhagia.

**Keywords:** Depot–Depo Provera • injectable contraceptives • Implanon • intrauterine contraceptive systems • Jadelle • long-acting contraceptives • Mirena • Noristerat • Uniplant • subcutaneous contraceptive implants

Long-acting, reversible hormonal contraceptive methods have been available for decades: indeed, a 3-monthly injection of medroxyprogesterone acetate in a depot formulation has been marketed since 1960 [1].

Recently, a new category of contraceptive modalities has been identified grouping together methods of family planning affording effective protection for an extended period of time: long-acting, reversible contraception (LARC). In principle, only subdermal implants and intrauterine devices are comprised in this category [2], although, recently Halpern *et al.* [3] have included in the definition also injectable contraceptives and coined the acronym LAI (longer acting injectables). For this reason, in this review, mention will be made also of all methods with duration of action of more than one month. Advantages of LARC include the fact that they minimize problems relating to compliance, since they require users' involvement only at the time of application or re-application; in addition, they are all very effective and completely

reversible. A recent, large prospective cohort study comparing LARC to short-acting methods found the failure rate among users of pills, patches or vaginal rings to be 4.55 per 100 woman/years, compared with 0.27 per 100 woman/years in women using LARC [4].

LARC can also be nonhormonal (i.e., copper-releasing intrauterine devices or Cu-IUDs); here, however, we wish to summarize only hormonal methods: intramuscular injections, intrauterine systems and subdermal implants.

These methods have one common feature: they all utilize only a synthetic progestogen without any estrogen and therefore they all have an effect on menstrual cyclicality, although the nature of such an effect varies depending on the progestogen, the route of administration and whether ovulation is inhibited or not.

### Long-acting injectables

As mentioned, the first attempts at producing long-acting hormonal contraceptives were

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made half a century ago; prolongation of action was obtained utilizing either a microcrystalline aqueous suspension or esterification.

Two injectable preparations are currently marketed: depot-medroxy-progesterone acetate (Depo Provera<sup>®</sup>, or DMPA) administered every 3 months and norethisterone enantate (Noristerat<sup>®</sup>, or NET-EN) administered every 2 months.

A third preparation, utilizing the long-acting progestin levonorgestrel butanoate, seems to continue to experience problems in its development.

### Depo Provera

In the 1950s a new class of potent progestins became available having the same basic moiety of progesterone. One of them was medroxy-progesterone. For clinical use it is esterified as acetate and prepared as a microcrystalline suspension for intramuscular injection. The formulation and the size of microcrystals are critical for optimal duration of action. In the 1960s, it was utilized as a contraceptive and was characterized as a most effective modality with high continuation rates.

In spite of these optimal characteristics, in the seventies a major controversy developed over the safety of DMPA, since toxicology studies had shown that in huge doses it increased the risk of breast tumors in female beagle dogs [5]. For this reason the US FDA refused to approve the drug for contraception, creating a chain reaction, with countries reluctant to approve the use of a modality not sanctioned in its country of origin. At this stage the WHO, through its Special Program of Research in Human Reproduction (HRP), decided to embark in a series of multinational clinical trials [6,7] proving DMPA's great effectiveness, clinical safety and usefulness in the developing world. In addition, to address the specific question of cancer risk, the WHO carried out an extensive multicenter, case-control study clearly showing that use of DMPA was not associated with a significant increase in the risk of breast cancer [8]. Finally, thanks mostly to WHO's studies, in 1992 the FDA approved Depo Provera for contraceptive use.

Another controversy, this time involving combined oral contraceptives (COCs), developed over risk of thromboembolic complications. In this connection, a recent case-control study in Sweden found an odds ratio for current use of COC of 5.3, compared with an odds ratio of 2.2 for Depo Provera [9].

Recently, DMPA has been reformulated for subcutaneous use. The new formulation contains 104 mg of medroxyprogesterone acetate in 0.65 ml suspension and has been found to be as effective as the 150 mg delivered intramuscularly. It is available also with a new delivery system (Uniject<sup>TM</sup>) and is now licensed

under the name Sayana Press<sup>®</sup>. The new formulation is also marketed under the brand names of Depo-SubQ Provera 104<sup>®</sup> in the USA and Sayana<sup>®</sup> in the UK and some other countries.

### Noristerat

The heptanoic ester of norethisterone was synthesized in 1957 and experimental work indicated that its duration of action varies between species; in humans, following injection of 200 mg, NET-EN is detectable in plasma for at least 40 days [10].

For contraceptive purposes, it was initially recommended that, as for DMPA, NET-EN should be administered every 3 months [6]. However, following multicenter studies carried out by WHO-HRP, it was established that the 200 mg dose was effective for only 2 months, with 75% of all pregnancies occurring during the third month after injection [6]. For this reason, today Noristerat is marketed as a bimonthly injection with a cumulative life table used effectiveness rate at 24 months of 0.4 ( $\pm$  0.2) per 100 woman/years of exposure [6].

An issue that came-up with regard to long-term use of long-acting injectables is a negative effect on bone mineral density (BMD) in adolescents. Recently a South African study evaluated over a 5-year period, BMD in 15- to 19-year-old new users of DMPA, NET-EN and COCs versus non users. During follow-up, BMD increased in all groups, but there was evidence of a lower annual increases in NET-EN ( $p = 0.050$ ) and COC ( $p = 0.010$ ) users compared with non users, but no difference between DMPA and non users ( $p = 0.76$ ). Although, BMD increase in adolescents may be lower in NET-EN users, recovery was found following discontinuation [11].

### Research aimed at developing longer acting injectables

There is little doubt that longer intervals between injections make a system more appealing and useful, especially in the developing world [12,13]. For this reason, injectable contraceptives lasting for 6 months or more would make these methods more appealing to a number of women, although their irreversibility once injected, may limit their duration of action to half a year.

Several attempts at developing longer acting injectable contraceptives have been made.

### Levonorgestrel butanoate

In the mid-1970s the already mentioned WHO's Program HRP, set-up a synthetic and screening research network aimed at synthesizing new, long-acting esters of levonorgestrel (and of testosterone). In 1983,

this work was reported in a full issue of the journal *Steroids* [14].

In the end, three progestin derivatives were considered to be of particular interest, although later only levonorgestrel butanoate (LNG-B) was selected for full development. Human pharmacokinetic and pharmacodynamic studies indicate that, as an injection, this progestin – at a dose of 10 mg every 3 months – can provide full contraceptive protection. It is too early to tell whether, imposing a lower body burden than DMPA, it will result in a lower degree of ovarian suppression, less amenorrhea and a more rapid return of fertility. An Investigational New Drug application has been filed with the US FDA for this compound and in 2004 a collaborative effort to further develop this compound was initiated with the US National Institute of Child Health & Development (NICHD) and the Contraceptive Research and Development Programme (CONRAD). This resulted in further optimization of the physical and chemical properties of LNG-B [15]. At present, NICHD and CONRAD are preparing for a clinical evaluation of the latest formulation to begin shortly.

### The Family Health International program

Halpern *et al.* [3] have summarized efforts made by the Family Health International (FHI) to develop long-acting injectables. Their goal is to develop ‘a safe and effective injectable method that would provide 7 months of contraceptive protection (6 months plus a 1-month window for reinjection) to women in the developing world’.

At present they are exploring several alternatives:

- Microspheres composed of poly(glycolide), poly(lactide) and their copolymer poly-lactico-glycolic acid;
- Novel polymers and materials, such as polyanhydrides, already tested for parenteral delivery;
- Porous mineral silicone that can be loaded with a wide range of molecules.

### Long-acting progestins & risk of HIV/AIDS

It has not yet been determined whether during pregnancy there is an increased risk to contract HIV infection, with some studies providing positive and others negative results. This issue is connected with that of a possible relationship between use of long-acting progestins and a potential increase in the risk of HIV.

Several possible mechanisms leading to greater HIV-1 susceptibility have been suggested, based on the fact that both progesterone and estrogen regulate

a number of immune mechanisms that may exert an effect on retroviral infection. These include changes in the epithelial structure of the vagina, modification of cytokine regulation and C–C chemokine receptor type 5 expression, and cervico-vaginal HIV-1 shedding [16].

Recently, Polis and Curtis [17] carried out a systematic review of the subject after identifying eight prospective studies reporting findings for progestin-only injectables.

Three studies assessed risk connected with use of NET-EN and none showed a significant association with HIV acquisition.

On the other hand, they found mixed results analyzing studies of users of DMPA or nonspecified injectable contraceptives: some investigators observed a 1.5- to 2.2-times increased risk of HIV when compared with controls; others reported no association.

Polis and Curtis identified several factors that merit further consideration: length of intersurvey interval, analysis of condom use, analysis of sero-discordant couples and reason for data collection.

Interestingly, before publication, these data were presented at a WHO Consultation where consensus was reached that no restriction should be placed on use of any method of hormonal contraception for women at high risk of HIV. At the same time, the WHO experts stressed the inconclusive nature of existing evidence and recommended that users of progestin-only injectables should be advised to also always use condoms (male or female) [18].

Another recent development took place in January 2013 when the United States Agency for International Development (US AID) called a meeting to develop recommendations for future observational analyses of studies of hormonal contraception and HIV acquisition. The consensus was that implementing these recommendations will enhance interpretation of existing studies and strengthen the overall evidence base in this field [19].

Finally, a just published systematic review concluded that “Overall, uncertainty persists regarding whether an association exists between depot-medroxyprogesterone acetate (DMPA) use and risk of HIV acquisition. Most studies suggested no significantly increased HIV risk with norethisterone enanthate (NET-EN) use” [20]. Under the circumstances, women who select Depo Provera or Noristerat should be advised about the present uncertainty and encouraged to use dual protection: a condom to prevent HIV infection and the progestin-only injection for effective contraception.

In conclusion, it is a fact that while most HIV-seropositive women use contraception, this is mostly limited to condoms; therefore, use of long-acting methods (whether hormonal or not) should be encouraged among these women [21].

### Subcutaneous delivery systems

The first contraceptive device to be implanted subcutaneously was developed more than 40 years ago and released the C<sub>21</sub> progestin megestrol acetate. Unfortunately, in the seventies this class of compounds came under close scrutiny because, when given in large doses, they produced breast tumors in female beagle dogs [5].

Developmental work had to be restarted using a different progestin, levonorgestrel (LNG). Implants releasing this steroid, with duration of action of 5 years (Norplant 1<sup>®</sup>), have been available for some 30 years [22]. More recently, subcutaneous devices releasing other progestins have also become available.

All subcutaneous delivery systems (SDS) have two common features [23]: prolongation of effect of a short-acting progestin is obtained by a drug reservoir, rather than chemical manipulation; zero-order kinetics can be achieved only after a period of time, but – for most of their duration of action – they provide a continuous, sustained release of the active compound.

Since the early days, research activities concentrated on specific aims:

- Reducing the number of implants by increasing the rate of release and the loading of the device, or using more potent progestins;
- Minimizing side effects, particularly bleeding disturbances;
- Gathering evidence on long-term safety and use in specific situations, such as breastfeeding.

Two types of implants have been developed: contraceptive ‘rods,’ where the polymeric matrix (dimethyl-polysiloxane or DPS) is mixed with the steroid and contraceptive ‘capsules,’ being made of a hollow polymer tube filled with free steroid crystals. High research and development costs and the need for provider training in techniques of insertion and removal have substantially slowed-down development of contraceptive implants, although today several devices are available on the market, or are in advanced stage of development.

#### Norplant-1 & -2

Two types of SDS go under the name Norplant. As already mentioned, Norplant 1, developed by the Population Council, was the first subcutaneous implant in widespread use. It consisted of a set of six DPS capsules filled with 36 mg of LNG and duration of action of 5 years. Its use has now been discontinued and substituted with Norplant-2 (Jadelle<sup>®</sup>), capable of deliv-

ering the same daily dose of LNG utilizing only two rods in which the active drug is interspersed within the matrix. Initially, the system was approved for 3 years, but after studies documented a longer duration of action, many countries have now labeled it for a 5-year use. Indeed, in a clinical trial involving 1198 women, none became pregnant in the first four years of use; the failure rate rose to 1 per 100 woman/years in the fifth year of use [24]. The Chinese “Implant system No. 2,” also called Sinoplant or Sino-implant is nearly identical to Jadelle but contains more levonorgestrel (150 mg instead of 140). The duration of action is 5 years.

#### Implanon<sup>®</sup>

The Dutch pharmaceutical Company Organon (now incorporated into Merck, Sharp & Dome) developed a single implant with duration of action of three years, which is marketed in a number of countries. Its benefit over Norplant-2 is that, according to the manufacturer, it is easier and faster to insert. It contains a total of 68 mg of etonogestrel delivering 60 µg/day of steroid initially. In most cases Implanon is capable of blocking ovulation, a fact that can explain its very high effectiveness: in a multicenter clinical trial including 1416 women followed for over 53,530 cycles not a single pregnancy was observed [25]. Recent preliminary findings indicate that Implanon continues to be highly effective for an additional fourth year. This is substantiated by serum etonogestrel levels [26].

A small trial conducted in Brazil evaluated a number of parameters and observed no complaints of dysmenorrhea, breast tenderness or lower leg edema over one year. Mean body weight decreased 1.2 kg on average, and the same occurred to body mass index (a decrease of 0.5 kg/m<sup>2</sup>), but these changes did not reach statistical significance [27].

The device has been introduced into the developing world and a recent study of unmet need for long-acting family planning in Ethiopia, concluded that local provision of Implanon through community health workers is effective in reaching women with the greatest need for contraception.

A newer version of Implanon (still containing 68 mg of etonogestrel) is now available under the trade names of Nexplanon<sup>®</sup> and Implanon NXT<sup>®</sup>. The new device differs from the old in two ways: it has an improved insertion mechanism and contains barium sulphate, so it can be located by x-ray if it is not easily palpated. The FDA has now approved Nexplanon as a contraceptive for a duration of 3 years.

An integrated analysis of Implanon efficacy including 923 nonbreastfeeding women for 24,100 cycles found no in-treatment or pre-treatment pregnancies; 50 post-treatment pregnancies were reported, occur-

ring as early as 14 days after removal, indicating a quick return of fertility [28].

A recent study found that approximately one-fifth of etonogestrel contraceptive implant users requests premature removal due to irregular bleeding; however, the immediate postpartum insertion does not increase removal rates [29]. It seems that Implanon is specifically appreciated by women who value convenience and privacy [30].

In terms of safety, Bahamontes *et al.* [31] found no significant changes of BMD after 1 year of use among Implanon users compared with users on a Cu-IUD, although there was an increase in weight and fat mass.

Recently, a technique has been proposed to ensure easy and steady removal of the implant: ultrasound scan and surface marking [32].

### Uniplant®

This single rod system, containing 38 mg nomegestrol acetate (NGA) has a duration of 1 year, was developed in Brazil and first described in 1993 [33]. In 1997, Devoto *et al.* [34] evaluated hormonal profile, endometrial histology and ovarian function over a one year period and found that 75% of all cycles were anovulatory (mostly during the first months after insertion of the rod). In 63% of these cases a persistent nonluteinized follicle was observed and even in ovulatory cycles abnormalities were common (inadequate luteal phase or dysregulation of follicular growth). These findings indicate that several different mechanisms contribute to the contraceptive effect of Uniplant: follicular growth inhibition; anovulation with a persistent nonluteinized follicle and inadequate luteal phase. Morphologically there was a disruption of endometrial architecture with a predominance of progestogen-induced changes. An additional study by Barbosa *et al.* [35] evaluating the same parameters concluded that 20% of 20 healthy volunteers continued to ovulate, whereas 80% were anovulatory; persistent nonluteinized follicles were present in 40% of all cycles, inadequate luteal phase in 20% and no follicular development in 40%.

In a nonrandomized trial of 240 fully breastfeeding mothers, Uniplant was compared with a copper-releasing intrauterine device and it was found that amenorrhea was significantly more prolonged in the Uniplant group. There were no significant differences in net continuation rates of breastfeeding, the number of breastfeeding episodes, time to weaning, cumulative rates of full and partial breastfeeding, infant weight, weight gain per day or infant linear growth [36].

Over the last decade, not much has occurred with this device.

### Nestorone containing implants

Two subcutaneous implants containing the orally inactive progestin nestorone (NES, Elcometrine®), have been developed.

The first, developed by the Population Council, consists of a single rod releasing NES and has duration of action of 2 years. It has been designed specifically for breastfeeding women, since for practical purposes nestorone it is not absorbed by infants through breast milk. Indeed, babies of breastfeeding mothers who are using the implant have almost undetectable NES in their blood, with concentrations in breast milk ranging between 54 and 135 pmol/l [37].

A comparative clinical trial (including breastfeeding and nonbreastfeeding women) indicated a different performance of the implant in the two groups; in lactating mothers the implant, when compared with the Copper-T-380A intrauterine device, seems to produce significantly less irregular bleeding. In nonlactating women, prolonged and irregular bleeding in implant bearers was worse than in Cu-IUD users. Metabolic effects reported for the implant are minimal and unlikely to be of clinical significance. A 2-year trial of a nestorone implant was conducted some 10 years ago in three Latin American centers. Three pregnancies occurred and the study was halted when 224 women had completed at least 18 months of use, and 99 women had used the implant for more than 24 months. The 2-year cumulative pregnancy rate was 1.7 per 100 women/years [38]. At present nestorone is being tested in combination with ethinyl estradiol as a contraceptive vaginal ring and for male contraception.

The second nestorone-containing system consists of a silastic capsule with the duration of action of 6 months; it was tested in a comparative fashion in Brazil some 15 years ago in 66 breast-feeding women and compared with 69 women using a Cu-IUD. All women and their infants were observed during the entire first postpartum year. No significant differences were found in the growth and development among the infants in the nestorone compared to the control group. Two pregnancies occurred in women using the Cu-IUD, whereas none occurred in those using implants [39]; there were menstrual bleeding irregularities in both.

With regard to the risk of acquiring HIV, to date no studies have been published suggesting any significant increase in the risk of acquiring it with use of implants, although only limited data exist [17].

### Intrauterine delivery systems

An intrauterine system named Progestasert®, releasing 65 mg progesterone daily and exerting good contraceptive activity without inhibiting ovulation (levels of estradiol and progesterone remained within the



normal range), was developed some 40 years ago. In a study of endometrial changes it was clearly found that there was a contrast between the appearance of the superficial portion of the endometrium in the zone immediately adjacent to the device, when compared with areas away from the device. Progesterone and/or its metabolites were abundant in the superficial epithelium and in the portion of the glands adjacent to the surface; and also well distributed in the stroma and in the capillary walls. However, progesterone barely penetrated the deeper portion of the endometrium [40]. Vascularity was decreased and defects in small vessels were observed. Unfortunately, epidemiological data highlighted that failure in women bearing a Progestasert®, caused a disproportionate percentage of extra-uterine pregnancies [41], leading to the withdrawal of the device from the market.

In the meantime, a new, LNG-releasing system (LNG-IUS) was being developed [42]. The system, called Mirena®, releases locally 20 µg of LNG and thereby has a strong direct action on the endometrium. It has a T-shaped polyethylene body with a steroid reservoir on the vertical stem. The recommended duration of use is 5 years, after which the release of LNG is reduced to some 14 µg/day; however, data from randomized trials of contraceptive efficacy show that this dose is effective for up to 7 years [43].

The LNG-IUS represents both a very effective contraceptive and a specific treatment for menorrhagia. The release of LNG has a marked antiproliferative effect on the endometrium that becomes suppressed and insensitive to the stimulus of endogenous estrogens. Meanwhile, no reduction was found in estradiol levels and ovulatory cycles occur in 85% of women. Indeed, the incidence of anovulatory cycles in users of the LNG system does not differ from that observed in women bearing a copper device [44]. Over long-term use (6 years) serum levels of LH, progesterone and estradiol documented ovulation in 11 of 14 women, indicating a local action [45].

Besides a strong effect on the endometrium, progestins released directly in utero exert major peripheral effects: cervical mucus is thickened and sperm mobility is inhibited [46]. This effect seems correlated to ovarian function: when this is fully maintained, cervical mucus characteristics are seemingly normal; however, when luteal activity is inadequate, mucus production is scanty and viscous with a reduction in the mucus penetration test score. Analysis of mucus properties shows that water content in relation to mucin concentration is substantially lower than in women bearing a copper-releasing device.

The LNG-IUS combines the advantages of oral and intrauterine contraception, being very effective and

reversible. Large clinical studies indicate a Pearl index of 0.1 per 100 woman/years [47]. Recent data from randomized trials seem reassuring, with no ectopic pregnancy over a total of 334,944 woman-months of use. Worth of notice, given the Progestasert problem (see above) is the finding that compared with Cu-IUDs users or nonusers, rates of ectopic pregnancy per 100 woman/years were: 0.02 for LNG-IUS; 0.25 for the Cu-IUD (Nova T) and 12–16 with nonusers. Following discontinuation, there is a rapid return of fertility: in the first year after removal the pregnancy rate is 90%, with a mean delay of 4 months [48]. There seem to be no significant difference in side effect incidence (acne, breast tenderness, headaches, nausea) between women using a LNG-IUD or a Cu-IUD [47]. Finally, a recent study evaluated the risk of venous thrombosis and concluded that such a risk was increased for DMPA and not for Mirena [49].

Important noncontraceptive benefits have been observed with the LNG-IUS; among them, the best known is a marked reduction in menstrual blood loss. Their description, however, is outside the scope of this review.

## Conclusion

Long-acting hormonal contraception provides a number of options, especially for women in the developing world with limited access to family-planning service. They have different characteristics and produce different effects on bleeding patterns, but they all share great effectiveness and relative ease of use.

Although, no specific threats to a woman's health have so far surfaced, large epidemiologic studies on their long-term safety have not been carried out and therefore a word of caution is in order.

With the injectable contraceptives Depo Provera and Noristerat there is an unresolved issue concerning whether they may increase the risk of contracting the HIV infection. For this reason, women at risk should be advised to the advantage of using also a condom for their protection against sexually transmitted diseases.

## Future perspective

After more than half a century of clinical use, the 3-monthly injectable contraceptive Depo Provera is still surrounded by controversy. At present the main issue is whether its use may be associated with an increased risk of contracting the HIV infection. Because Depo Provera is a very effective contraceptive it has been recommended that women at risk of contracting sexually-transmitted diseases, including HIV, use a dual method; the injection coupled with a condom. This, however, is not likely to resolve the

controversy and, if past can teach us about the future, for the foreseeable future Depo Provera will continue to be the target of groups opposed to contraception in general. This, in spite of a very recent statement by the WHO that it is safe to use it even younger women.

Subcutaneous implants on the other hand, seem destined to an ever increasing utilization, both in developing countries and in the industrialized world. After major mishaps toward the end of the previous century, the development of single implants and improved insertion procedures provides the basis for predicting increased popularity and widespread use. Bleeding control remains a problem for a number of users, but it can be expected that with proper counselling, this will no longer represent a barrier to utilization.

Long-acting methods based on the intrauterine delivery of hormonal or other substances are bound to receive greater attention over the next decade. Delivering drugs directly into the uterus seems more and more an appealing modality and, after the great success of the levonorgestrel-releasing system, it is likely that other active compounds will be tested and eventually used.

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#### Executive summary

- Long-acting, injectable, progestin-only contraceptives with 2 or 3 months duration remain a valid option, especially in developing countries, in spite of recurring criticism which is mostly scientifically unfounded.
- Subcutaneously implanted, progestin-releasing capsules and rods offer contraceptive protection of 1–5 years duration depending on the type. They are highly effective and are ideally suited for settings with limited infrastructures.
- The intrauterine system continuously releasing levonorgestrel probably has the highest effectiveness of all methods; is particularly suited for women with heavy menstrual bleeding and has a variety of noncontraceptive applications.
- The mechanism of action of these methods is multiple: in the case of injectables it is mostly based on ovulation inhibition; with subcutaneous implants a mixed mechanism is at work: anovulation with persistent nonluteinized follicle, or abnormal ovulatory cycles with inadequate luteal phase or dysregulation of follicular growth; with the intrauterine system the effect is mostly local.
- All long-acting, progestin-only contraceptives cause different degrees of cycle disturbance.

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