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LONG-ACTING HORMONAL CONTRACEPTIVES FOR WOMEN

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Summary—Following the development and widespread use of oral hormonal contraceptives, it became evident that alternative long-acting delivery systems would be required to improve contraceptive practice in some cultural settings where injectable or subdermal routes of administration are preferred. Nowadays, long-acting contraceptives constitute an important option in family planning services in many parts of the world. Indeed, two long-acting injectable contraceptives containing just a synthetic progestogen (depot-medroxyprogesterone acetate (DMPA) and norethisterone enantate (NET-EN)) have been in clinical practice for more than 20 years. The World Health Organization's (WHO) Special Programme of Research in Human Reproduction, in collaboration with the U.S. National Institute of Child Health and Human Development (NICHD) and universities primarily in developing countries undertook a synthesis programme aimed at producing an improved injectable preparation by developing new derivatives of known steroids. One such compound (levonorgestrel 17-butanoate) is now at the stage of Phase II clinical testing. In addition, the Special Programme has developed and improved once-a-month injectable formulations and assessed their safety and efficacy in different countries worldwide. After large scale clinical testing, at least two progestogen–estrogen combinations have reached the point of introductory trials.

INTRODUCTION

More than seven million women around the world are currently using long-acting injectable and implantable steroidal contraceptives, mostly in developing countries and the number of users is increasing [1]. In order to provide improved methods with less disruption of menstrual bleeding patterns or which give a wider choice of long-acting methods, worldwide research efforts during the past 25 yr have focused on developing sustained release formulations of steroids to be used either as injectable or implantable contraceptives.

In addition to DMPA (17α-acetoxy-6-α-methylpregnen-3,20-dione) and NET-EN (17α-ethynyl-17β-heptanoyloxy-4-estren-3-one), which have been in clinical practice for more than 20 yr, a number of long-acting progestogen-only injectable formulations are at present under clinical evaluation. One developed by WHO and NICHD is a microcrystalline suspension of an ester of levonorgestrel [2], while another approach, developed by the Program for Applied Research on Fertility Regulation (PARFR), Family Health International (FHI) and the Contraceptive Development Program (CONRAD), is the microencapsulation of steroids such as norethisterone in a polymer-based matrix of lactic acid or a copolymer of lactic and glycolic acids giving rise to injectable formulations intended for three month duration [16].

Following extensive pharmacokinetic and pharmacodynamic investigations [3–5] and clinical studies [6–8], two once-a-month injectable contraceptives have been assessed by the WHO Task Force on Long-Acting Systemic Agents for Fertility Regulation in collaboration with many institutions around the world, which have advantages over progestogen-only preparations in improving vaginal bleeding patterns [6].

Among implantable contraceptives, the Norplant® system developed by the Population Council has been used by more than 30,000 women throughout the world and is currently registered in some 15 countries. Norplant® consists of six 3.4 cm × 2.4 mm silastic capsules and releases levonorgestrel in contraceptive quantities for a minimum of 5 yr [10]. Work is continuing on an improved device, Norplant-2,

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which is made up of two 4.4 cm × 2.4 mm covered rods. This device will release levonorgestrel for more than 3 yr. Single device implantable contraceptives are also being developed, the most advanced being Implanon, manufactured by Organon, which releases 3-ketodesogestrel.

Biodegradable implants have been under extensive investigation during the past 10 yr. One of the most promising approaches is the Capronor device developed by the Research and Triangle Institute with support from NICHD. The Capronor implantable device consists of a poly (ϵ-caprolactone) tube which releases levonorgestrel. A single 4.0-cm implant, releasing 100 μg of levonorgestrel per 24 h showed inhibition of ovulation for 3–6 months [11]. Phase II clinical studies of Capronor have recently been completed.

Vaginal delivery systems have many advantages, such as self-insertion and self-removal and minimal steroid load. The WHO Special Programme has developed and tested a vaginal ring manufactured from a silicone rubber of 56 mm outside diameter and 9.55 cross-section diameter. It provides constant blood levels and contraceptive protection for a minimum of 3 months by releasing as little as 20 μg levonorgestrel per 24 h [13]. Other vaginal rings under development include combined progestogen-estrogen rings which remain *in vivo* for three weeks in four. These are being developed by both the Population Council and by Organon. In addition, a ring releasing progesterone is being developed by the Population Council for postpartum contraception [2].

Intrauterine devices are also used as sustained delivery systems for progestogens, one example is Progestasert, produced by the Alza Corporation, which releases 65 μg per day for 1 yr duration [14]. Another intrauterine system developed by the Population Council releases levonorgestrel at a daily dose of 20 μg [15].

The purpose of this review is to describe the new developments in long-acting hormonal contraceptives with emphasis on the multicentred assessment of various long-acting injectable contraceptives.

EXISTING PROGESTOGEN-ONLY INJECTABLES—DOSE REDUCTION STUDIES

Results from many clinical trials have shown that both the progestogens MPA and NET-EN are highly effective contraceptive agents. Pregnancies due to method failures have been consistently low (cumulative life-table rates at 12 months of 0.0–0.1) with the use of 150 mg DMPA administered every 90 days. The pregnancy rates reported with NET-EN use have varied according to the injection schedule used (cumulative life-table rates at 12 months of 0.4–0.6). Table 1 shows the discontinuation rates at 12 months of subjects participating in three large multicentred Phase III clinical trials undertaken by WHO [16, 17].

In its assessment of the safety and efficacy of DMPA, the WHO Task Force on Long-Acting Systemic Agents for Fertility Regulation undertook studies on the pharmacokinetics and pharmacodynamic effects of 25, 50, 100 and 150 mg of DMPA in centres in Mexico City [18] and Bangkok [19]. The results from both studies showed no significant differences in the ability of either 100 or 150 mg of DMPA to inhibit ovulation for a minimum of 90 days. From these data it was postulated that a dose of 100 mg of DMPA would be more than adequate to provide full 3-month contraceptive coverage. To answer this question, a multicentred study comparing 100 mg or 150 mg DMPA was recently completed [20]. The results are summarized in Table 1 and showed little difference in efficacy and side-effects between the two DMPA treatment groups. Except for discontinuation of method use for amenorrhea, which was 7.2% for the 100 mg group and 12.5% for the 150 mg group, the rates for all medical and non-medical reasons given were comparable between the two

Table 1. Cumulative life-table discontinuation rates in Phase III clinical trials on injectable contraceptives. Modified from [6]

Treatment regimen	Woman months	Total discontinuations		Pregnancy		Bleeding irregularities		Amenorrhea	
		Rate %	SE	Rate %	SE	Rate %	SE	Rate %	SE
DMPA 150 mg (90 days)	20,498	51.4	1.3	0.1	0.1	15.0	1.0	11.9	1.0
NET-EN 200 mg (60 days)	10,339	49.7	1.8	0.4	0.2	13.6	1.4	6.8	1.1
NET-EN 200 mg (60/84 days)	10,315	50.3	1.8	0.6	0.2	13.7	1.4	8.4	1.1
DMPA 150 mg (90 days)	5,434	41.2	2.0	0.0	—	13.3	1.5	12.5	1.5
DMPA 100 mg	5,514	40.7	2.0	0.4	0.2	14.7	1.5	7.2	1.2
DMPA 25 mg	10,969	35.5	1.4	0.0	—	6.3	0.8	2.1	0.5
E_2-Cyp 5 mg NET-EN 50 mg E_2-Val 5 mg	10,608	36.8	1.5	0.2	0.1	7.5	0.9	1.6	0.4

treatment groups. Despite the similar performance of the two doses, a reduction of the dose of DMPA was not recommended before the assessment of additional pharmacokinetic data from several populations was completed [2].

For some years, it has been obvious that certain injectable steroids such as DMPA give rise to differing pharmacokinetic profiles in different populations. In the above mentioned dose reduction studies undertaken in Mexico City and Bangkok with 25, 50, 100 and 150 mg DMPA, higher peak levels of MPA, more rapid disappearance of MPA from the blood and more rapid return of ovulation were seen in all dose groups in the Thai women compared with those observed in Mexican women [18]. Further analysis of these studies are presented in Fig. 1. Indeed, major differences were evident when pharmacokinetic parameters were compared.

Some years ago, it was reported in Chiang Mai that there was an increase in method failure with DMPA when a locally produced formulation was utilized by the Thai National Family Planning Programme instead of Depo-provera [21]. It was found that the batches locally manufactured, whilst being to pharmacopeia specifications, gave a smaller particle size distribution of the micronized crystals than the previously used batches of Depo-provera. It was postulated that the smaller particles are more rapidly dissolved than larger ones and hence MPA appears more rapidly in the circulation, which coupled with the more rapid elimination of MPA in Thai women, could potentially give rise to a situation whereby small particle formulations provide less than 90-day contraceptive protection in this population.

In order to provide data on this problem, a multicentered pharmacokinetic study was designed in which the influence of particle size on the absorption and duration of action of DMPA was investigated in Thai and Mexican populations. The preliminary data analysis as presented in Table 2 confirmed the differences previously observed in different populations and suggested that the particle size of the DMPA formulation is important for its duration of action and therefore contraceptive protection [22].

NET-EN, first used as an intramuscular contraceptive in 1966, is formulated in an oily solution of benzyl benzoate and castor oil [23]. An intramuscular injection of 200 mg of NET-EN was shown to result in peak serum levels of NET within the first week followed by a gradual decline. Considerable individual variations have been reported [24]. Moreover, it has been reported that after a single 200 mg injection, there are some differences in blood levels between Indian and Swedish women [25]. The variability

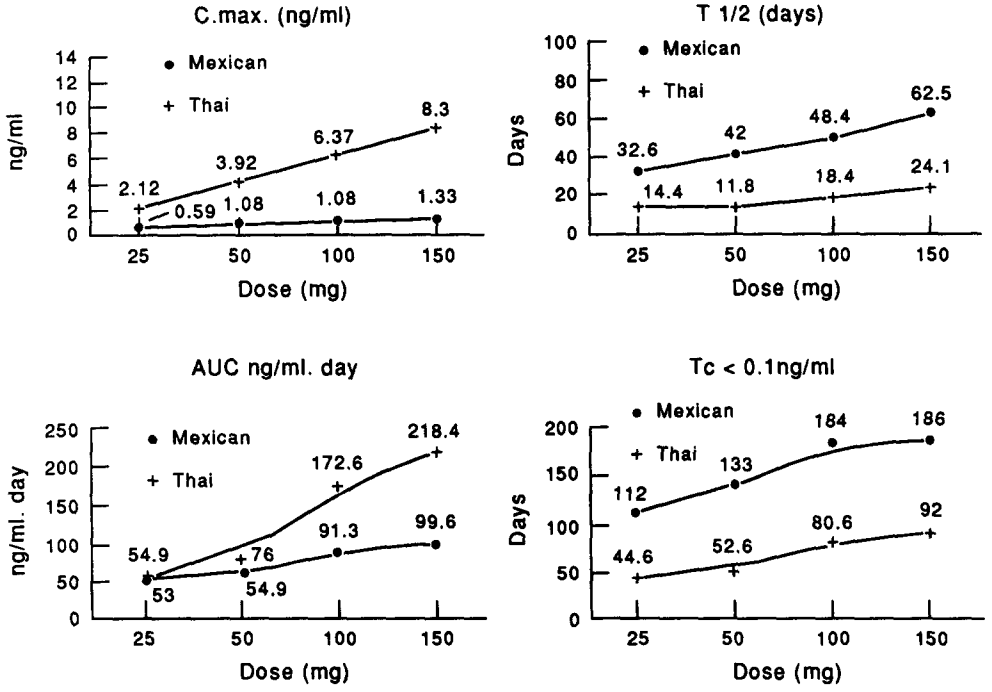

Fig. 1. Comparison of some pharmacokinetic parameters, maximum concentration in serum (C_{max}), elimination half-life ($T_{1/2}$), area under the serum concentration curve (AUC) and time to reach MPA serum levels below 0.1 ng/ml (T,C < 0.1 ng/ml), of different doses of DMPA in Mexican and Thai women.

Table 2. Preliminary analysis of DMPA (150 mg) of different particle sizes administered to women from Thailand and Mexico [22]

Centre	Formulation 1 (0–5 μm) C_{max} (nmol/l)	T_{max} (days)	$C_{170\ days}$ (nmol/l)	Formulation 2 (10–25 μm) C_{max} (nmol/l)	T_{max} (days)	$C_{170\ days}$ (nmol/l)
Chiang Mai						
Mean	17.1	3.7	1.0	8.3	4.3	1.2
SD	12.0	2.0	1.0	4.9	3.2	0.6
($n = 10$ per group)						
Mexico City						
Mean	5.6	4.6	1.9	4.4	6.7	1.5
SD	1.6	3.3	0.5	0.8	3.5	1.1
($n = 8$ per group)						

between subjects reflects the large number of factors that can influence the absorption rate from the depot site.

Results on Chinese women who received 200 mg NET-EN were compared with those previously obtained by the same investigator in British women [26]. There was no difference between Chinese and British women in the absorption after intramuscular injection, but elimination rate was significantly lower and the bioavailability higher in Chinese women than in British women [27].

Recent studies in Mexican women addressed at assessing the pharmacokinetics and pharmacodynamics of NET-EN have demonstrated that, unlike with DMPA, no major differences are observed with those obtained in European women except that there is a tendency for ovulation to return later in Mexican women. Overall, as can be seen in Table 3, comparable values were obtained in different populations, however, further studies in large numbers of subjects would be required to draw definitive conclusions [28].

LEVONORGESTREL DERIVATIVES AS LONG-ACTING INJECTABLE CONTRACEPTIVES

During the last 10 yr, 213 esters of norethisterone (17α-ethynyl-17β-hydroxyestr-4-en-3-one) and levonorgestrel (D-(−)-13β-ethynyl-17α-ethynyl-17β-hydroxygon-4-en-3-one) have been synthesized by investigators of a chemical synthesis programme organized by WHO. All esters were prepared by esterification of the tertiary hydroxyl group at C-17 of the parent steroid [29, 30]. Figure 2 shows the structural formula of three of the levonorgestrel esters. After quality control, the steroid esters were formulated as microcrystalline aqueous suspensions and assessed in a rat model by NICHD and the most promising ones in non-human primates [31]. Based upon data from the rat screening test and subsequent studies in the rhesus and cynomolgus monkeys, two of the esters, namely levonorgestrel cyclobutylcarboxylate (HRP001) and levonorgestrel butanoate (HRP002) underwent pharmacokinetic/pharmacodynamic studies in humans in Mexico City and London, at doses of 12.5, 25 and 50 mg [32]. The results showed that both compounds have very similar pharmacokinetic properties and similar duration of action in inhibiting ovulation in both populations.

Table 3. Pharmacokinetic/pharmacodynamic parameters after NET-EN (200 mg) in different populations

Population	C_{max} (ng/ml)	T_{max} (days)	Return to ovulation (days after injection)	Reference
U.S.A. ($n = 5$)	13.4	7.1	98	[38]
U.K. ($n = 8$)	11.1	4.3	—	[26]
Sweden ($n = 14$)	10.2	6.0	—	[39]
($n = 4$)	14.2	3.5	85	[25]
India ($n = 4$)	15.2	5.0	99	[25]
Mexico ($n = 11$)	15.3	4.3	107	[28]

As shown in Table 4, a single dose of 50 mg of either HRP001 or HRP002 was found to suppress ovulation for 5–6 months. Further reduction to 12.5 mg inhibited ovulation for 2–3 months. Comparison of the toxicological data, pharmacokinetic profiles, pharmacodynamic effects and bleeding patterns led to the selection of one of the esters, the HRP002 (levonorgestrel butanoate) for further assessment. Accordingly, a Phase II clinical trial comparing 12.5 mg HRP002 with 200 mg NET-EN given at 2-monthly intervals for a period of 1 yr is being undertaken with the support of WHO [2].

A third compound, levonorgestrel cyclopentylcarboxylate (HRP003) was also tested in humans at doses of 10 and 20 mg. However, HRP003 did not suppress ovulation at either dose studied due to barely measurable levels of levonorgestrel. These low levonorgestrel serum levels suggested that HRP003 was poorly

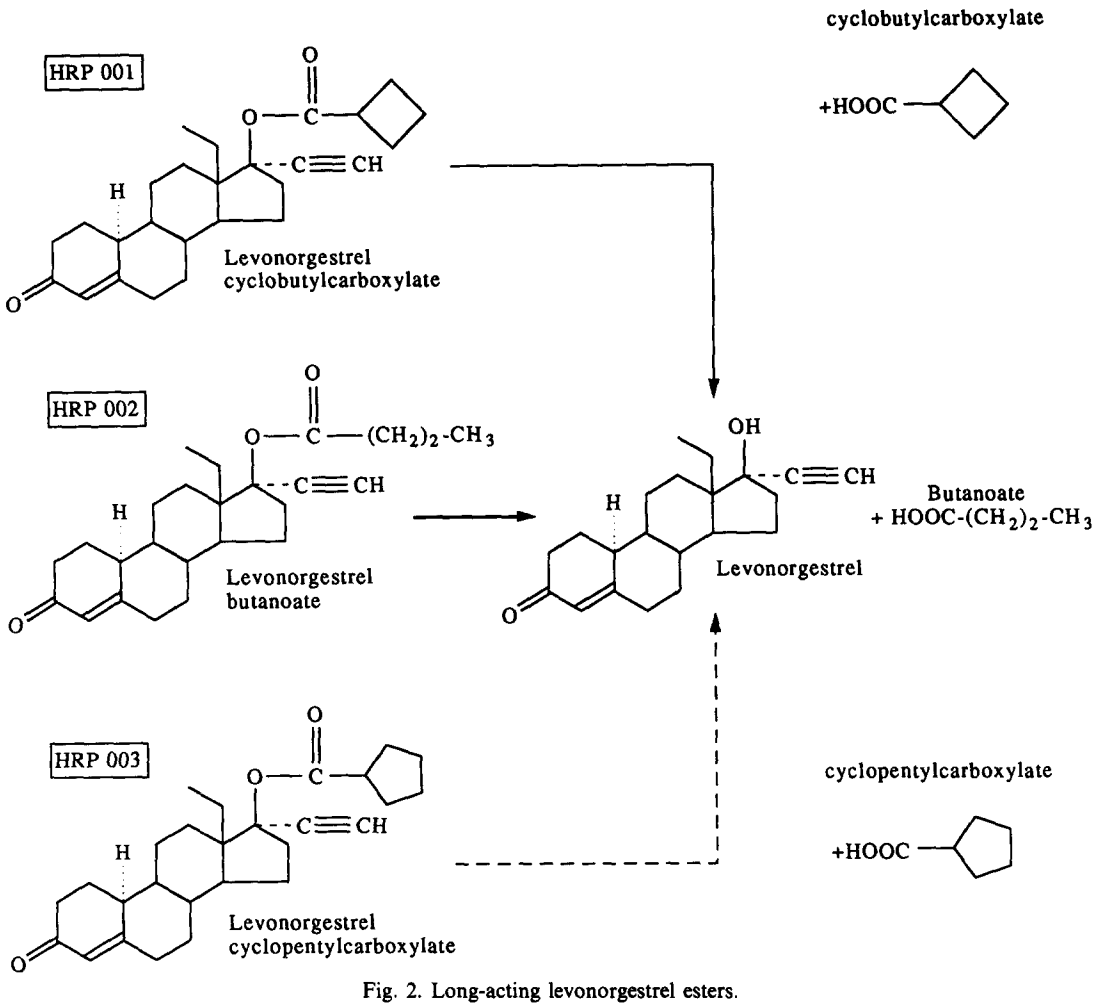

Fig. 2. Long-acting levonorgestrel esters.

metabolized *in vivo*, therefore its further development was abandoned [2].

ONCE-A-MONTH INJECTABLE PREPARATIONS

The addition of estrogens to long-acting progestogens to produce combined injectable formulations has proven to be a successful strategy for overcoming the endometrial bleeding problems associated with the use of long-acting progestogen-only contraceptives.

Table 4. Return to ovulation in normal women ($n = 5$ per group per dose) after a single injection of new long-acting levonorgestrel esters [32]

Compound	Dose (mg)	Ovulation return (days)
Levonorgestrel 17-β	12.5	114 ± 5
Cyclobutylcarboxylate	25.0	204 ± 26
HRP 001	50.0	266 ± 25
Levonorgestrel 17-β	12.5	105 ± 34
Butanoate	25.0	231 ± 22
HRP 002	50.0	265*
Levonorgestrel 17-β	10.0	**
Cyclopentylcarboxylate	20.0	**
HRP 003		

*$n = 2$; **immediate since no ovulation inhibition was achieved.

The development of combined progestogen-estrogen injectables was initiated early in the 1960s with preparations containing medroxyprogesterone acetate plus estradiol cypionate; 17α-hydroxyprogesterone caproate plus estradiol valerate; and dihydroxyprogesterone acetophenide combined with estradiol enantate (Table 5) [34]. Clinical information on once-a-month contraceptives indicates that this method is an effective fertility regulating method that appeals to certain populations [33, 34].

Research undertaken by WHO over the last 10 yr, aimed at the development of improved once-a-month injectable contraceptives, has assessed two combinations, one containing DMPA 25 mg, estradiol cypionate 5 mg and the other NET-EN 50 mg, estradiol valerate 5 mg, which were effective in inhibiting ovulation. However, measurable amounts of the synthetic progestogens were found 90 days after injection [3, 4]. This led to the design of studies to

Table 5. Combined once-a-month injectable preparations

Progestogen	Dose (mg)	Estrogen	Dose (mg)	Stage of development
Dihydroxyprogesterone acetophenide	150	Estradiol enantate	10	Available in Latin America
Hydroxyprogesterone caproate	250	Estradiol cypionate	5	Available in China as Injectable No. 1
Medroxyprogesterone acetate	25	Estradiol cypionate	5	Introductory trials began in 1989
Norethisterone enantate	50	Estradiol valerate	5	Introductory trials planned

test reduced doses and alternative progestogen–estrogen ratios [35–37]. The results from these studies in terms of ovulation inhibition capacity are summarized in Table 6. Both DMPA and NET-EN either alone or combined with estradiol esters resulted in effective ovulation inhibition at all doses studied. However, when the progestogen–estrogen ratio was decreased, 42% of the women ovulated with the DMPA combination (Formulation 5 in Table 6) and 32% of the women ovulated with the NET-EN preparation (Formulation 10 in Table 6). These results underline the importance of not only the absolute amounts of the steroids but also the appropriate ratios employed. Furthermore, the combined full dose preparations (Formulations 3 and 8 from Table 6) induced better bleeding patterns than the half-dose formulations (Formulations 4 and 9).

With this background information, a large multicentred trial was undertaken to evaluate the effectiveness, safety and acceptability of DMPA 25 mg, estradiol cypionate 5 mg and NET-EN 50 mg, estradiol valerate 5 mg. The study included a total of 2328 women from 12 different countries [6, 7]. The main results are presented in Table 1. Life-table cumulative pregnancy rates at 1 yr were comparable to or lower than those previously reported for progestogen-only preparations. Furthermore, the total discontinuation rates reported were less than progestogen-only injectables as well as discontinuations due to bleeding problems. The results gave further support to the concept that both preparations could be safely used on a large scale in family planning programmes. For this purpose, introductory trials with one of the formulations (DMPA 25 mg, estradiol cypionate 5 mg), now called "Cyclofem", began in 1989 in several countries and are planned with the other.

Table 6. Percentage of ovulatory cycles after administration of DMPA or NET-EN-based once-a-month injectable formulations [WHO, Refs 35–37]

Compound formulated	Dose (mg)	3rd Treatment month	1st Follow-up month	2nd Follow-up month
1. DMPA ($n = 21$)	25.0	0	24	48
2. DMPA ($n = 20$)	12.5	0	40	75
3. DMPA E_2-Cyp ($n = 21$)	25.0 5.0	0	60	71
4. DMPA E_2-Cyp ($n = 20$)	12.5 2.5	0	60	90
5. DMPA E_2-Cyp ($n = 24$)	12.5 5.0	42	100	100
6. NET-EN ($n = 22$)	50.0	0	23	60
7. NET-EN ($n = 21$)	25.0	0	71	86
8. NET-EN E_2-Val ($n = 21$)	50.0 5.0	0	19	67
9. NET-EN E_2-Val ($n = 23$)	25.0 2.5	0	26	70
10. NET-EN E_2-Val ($n = 22$)	25.0 5.0	32	73	100

CONCLUSIONS

It is generally agreed that there is a major need for a wide variety of safe and effective methods of fertility regulation that will suit the individual situation, the socioeconomic condition and the cultural values of different couples around the world. The role of long-acting steroidal contraceptives can be summarized by the fact that more than seven million women around the world are using them. Despite the drawback of disturbances in menstrual bleeding observed with progestogen-only formulations their use and demand show a constant increase. In this new decade, family planning programmes will benefit from the introduction of new long-acting steroids which will contribute to a wider selection of contraceptive options.

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