HORMONAL CONTRACEPTIVES, PROGESTOGENS ONLY

1. Exposure

'Progestogen-only' contraceptives are available as injections, implants, oral preparations, hormone-releasing intrauterine devices and emergency contraceptives. These compounds can be used by women who are breast feeding or have other contra-indications to oestrogen therapy, such as immediately *post partum*, those with thalassaemia, sickle-cell disease, gall-bladder disease, past or present thrombo-embolic disorders, valvular heart disease, ischaemic heart disease, recent surgery, migraine or hypertension, and older women, particularly those over 35 who smoke (WHO Family Planning and Population Unit, 1996; see Annex 1 for guidelines for use). Parenteral methods of administration generally result in more effective contraception than oral routes, as they provide more constant concentrations of the hormone in the blood. Use of progestogen-only oral contraceptives leads to the peaks and troughs in concentration characteristic of oral medication but involves greater potential errors by the users, as placebo is given during seven days of the cycle.

The progestogens that are or have been used in 'progestogen-only' contraceptives are chlormadinone acetate, desogestrel, ethynodiol diacetate, levonorgestrel, lynoestrenol, medroxyprogesterone acetate, norethisterone, norethisterone acetate, norethisterone oenanthate, norgestrel, norgestrienone and progesterone. Of these, medroxyprogesterone acetate, norethisterone oenanthate and progesterone are used only in this way; the remaining progestogens are also used in combination with oestrogens. Thus, information on the progestogens used only in 'progestogen-only' hormonal contraceptives is given in this monograph, and studies on other progestogens are summarized in the monograph on 'Oral contraceptives, combined'.

1.1 Historical overview

The development of injectable progestogen-only contraceptives resulted from a growing understanding of steroid hormones and from the research that eventually led to the development of combined oral contraceptives. In 1953, Karl Junkman and colleagues synthesized the first injectable progestogens and then developed the first injectable contraceptive, norethisterone oenanthate, in 1957. This compound is now approved for contraceptive use in over 60 countries. Medroxyprogesterone acetate was synthesized in the late 1950s, and its depot form was subjected to clinical trials in 1963, before being released onto the international market. It has been approved for use as a contraceptive in

a steadily increasing number of countries over the last 30 years and is now available in over 100 countries worldwide. Concern about an association with cancers of the breast, endometrium and cervix and other possible side-effects meant that depot medroxyprogesterone acetate was approved as a contraceptive in the United States only in 1992, some 25 years after the manufacturer's first application (Lande, 1995); however, it had already been approved for the treatment of conditions such as endometrial cancer, and legislation in the United States does not prohibit the use of approved drugs for non-approved indications. Nevertheless, there are still concerns in the international community about issues of informed consent for the use of these long-acting methods and the potential abuse of their administration to poorly educated groups (Kleinman, 1990).

Although the very first oral contraceptive, which was tested in Puerto Rico in 1955, contained only norethynodrel and was, technically speaking, a progestogen-only oral contraceptive (McLaughlin, 1982), it was superseded by the combination of mestranol and norethynodrel during development, as the combination was shown to prevent ovulation consistently. Progestogen-only oral contraceptives were developed in response to concern raised in the late 1960s about the side-effects of oestrogens in combined oral contraceptives. The prototype progestogen-only oral contraceptive contained chlormadinone acetate and was introduced in 1969. It was withdrawn in 1970 because of evidence that it induced breast nodules in laboratory animals. Other progestogen-only oral contraceptives were developed subsequently, containing progestogens of the norethisterone and levonorgestrel groups (Kleinman, 1990).

Subcutaneous progestogen implants were developed in the late 1960s and 1970s and were approved in Finland in 1983, in Sweden in 1985, the Dominican Republic, Ecuador, Indonesia and Thailand in 1986, China, Colombia, Peru and Venezuela in 1987, Chile and Sri Lanka in 1988 and the United States in 1990 (McCauley & Geller, 1992).

A device that releases progesterone into the uterus was developed in the early 1970s and has been available since 1976. This had the disadvantage of a high rate of hormone release, necessitating annual replacement (Kleinman, 1990; Treiman *et al*., 1995). An intrauterine device that releases effective concentrations of levonorgestrel over a five-year period was approved in Finland in 1990 and in Sweden in 1992 (Chi, 1995); it has since been approved in Belgium, Denmark, France, Iceland, Norway, Singapore, Switzerland and the United Kingdom (Treiman *et al.*, 1995).

1.2 Injectable progestogens

Two progestogen-only injectable contraceptives are available worldwide, and their formulations have remained unchanged since their development in the late 1950s and early 1960s (Table 1).

Norethisterone oenanthate is a long-chain ester of norethisterone which is formulated in a solution of castor oil and benzyl benzoate and given intramuscularly into the gluteal or deltoid muscle. The ester is then distributed to adipose tissue throughout the body and is slowly released back into the bloodstream. It then undergoes hydrolysis in the liver to produce norethisterone, the active progestogen (Kleinman, 1990). It is most commonly

Table 1. Formulation and availability of injectable progestogen-only contraceptives

Brand name	Composition	Dose (mg) and schedule	No. of countries in which registered
Depo-Provera[a]	Medroxyprogesterone acetate	150, every 3 months	100
Dugen	Medroxyprogesterone acetate	150, every 3 months	100
Megestron	Medroxyprogesterone acetate	150, every 3 months	100
Noristerat, Norigest	Norethisterone oenanthate	200, every 2 months	60
Doryxus	Norethisterone oenanthate	200, every 2 months	60

From Kleinman (1990); Lande (1995)

[a] Other names include Depo-Cliovir, Depocon, Depo-Gestin, Depo-Geston, Depo-Prodasone, Depo-Progesta, Depo-Progestin, Depo-Progevera, Medroksiprogesteron

used as a 200-mg dose given every eight weeks or two months, although in some programmes it is given on a two-month schedule for the first six months and then every three months (Lande, 1995).

Depot medroxyprogesterone acetate is administered in an aqueous microcrystalline suspension by deep intramuscular injection into the gluteal or deltoid muscle. This depot results in a high plasma concentration of medroxyprogesterone acetate initially, which declines exponentially thereafter. It is given at a dose of 150 mg every 90 days or three months (Lande, 1995).

Menstrual disturbances are common in women using these compounds and may take the form of amenorrhoea or frequent and/or irregular bleeding. Weight gain is also a common side-effect.

1.2.1 *Patterns of use*

About 12 million women worldwide currently use injectable contraceptives, and the vast majority of these are progestogen-only preparations (Lande, 1995). Table 2 shows the percentage of married women or women in union, aged 15–49, currently using any method of contraception (including traditional methods) and the percentage currently using injectable contraceptives. The overall proportion of women using injectable contraceptives is low in most regions, except in Indonesia, Jamaica, Kenya, Namibia, New Zealand, Rwanda, South Africa and Thailand.

In a survey conducted in New Zealand between 1983 and 1987, 14% of women aged 25–54 reported ever having used depot medroxyprogesterone acetate; however, 26% of these had only ever received one injection (Paul *et al*., 1997). In 1994, the Planned Parenthood Federation of America supplied depot medroxyprogesterone acetate to 141 000 women, representing around 7% of their clients (Lande, 1995).

Table 2. Use of injectable contraceptives by married women or women in union aged 15–49, by country

Country	Year	Any contraceptive (%)	Injectable contraceptives (%)
Africa			
Algeria	1992	51	0.1
Benin	1996	16	0.7
Botswana	1988	33	5.4
Burkina Faso	1993	8	0.1
Cameroon	1991	16	0.4
Côte d'Ivoire	1994	11	0.8
Egypt	1995	48	2.4
Eritrea	1995	8	0.8
Ghana	1993	20	1.6
Kenya	1993	33	7.2
Madagascar	1992	17	1.6
Malawi	1992	13	1.5
Mali	1995–96	7	0.2
Mauritius	1985	75	6
Morocco	1995	50	0.1
Namibia	1992	29	7.7
Niger	1992	4	0.5
Nigeria	1990	6	0.7
Rwanda	1992	21	8.4
Senegal	1992	7	0.2
South Africa	1987–89	50	23
Black		49	27
White		79	3
Sudan	1992–93	10	0.2
Swaziland	1988	20	4
Tunisia	1988	50	1
Uganda	1995	15	2.5
Zimbabwe	1994	48	3.2
Europe			
Austria	1981–82	71	0
Belgium	1982	81	0
Hungary	1986	73	0
Italy	1979	78	0
Portugal	1979–80	66	2
United Kingdom	1983	83	0
England	1995	Not reported	1.2
North America			
Canada	1984	73	0
United States	1988	74	0

Table 2 (contd)

Country	Year	Any contraceptive (%)	Injectable contraceptives (%)
Latin America and the Caribbean			
Bolivia	1994	45	0.8
Brazil	1996	77	1.2
Colombia	1995	72	2.5
Costa Rica	1981	65	2
Dominican Republic	1991	56	< 1
Ecuador	1987	44	< 1
El Salvador	1985	47	1
Guatemala	1995	31	2.5
Haiti	1994	18	2.7
Jamaica	1993	62	8
Mexico	1987	53	1
Nicaragua	1981	27	1
Panama	1984	58	1
Paraguay	1990	48	5.2
Peru	1996	64	8
Trinidad and Tobago	1987	53	0.8
Asia and Pacific			
Bangladesh	1993	45	4.5
China	1988	71	< 1
Hong Kong	1987	81	3
Indonesia	1994	55	15
Nepal	1991	25	2
Pakistan	1990–91	12	0.1
Philippines	1993	40	0.1
Sri Lanka	1987	62	3
Syria	1993	40	0
Thailand	1991	69	12
Turkey	1993	63	0.1
Yemen	1991–92	7	0.6

From Population Council (1994); Lande (1995); Population Council (1995, 1996a,b); Bost *et al.* (1997); Population Council (1997a,b,c,d,e,f, 1998a,b); United States Census Bureau (1998)

1.2.2 *Action*

Injectable progestogen-only contraceptives prevent ovulation (Lande, 1995) by inhibiting follicle-stimulating hormone and luteinizing hormone in a similar way to combined oral contraceptives. They also thicken the cervical mucus, making it relatively impenetrable to sperm, and make the endometrium less receptive to implantation (Kleinman, 1990). They are very effective contraceptives, with 0.3 pregnancies per 100 women per

year for depot medroxyprogesterone acetate and 0.4 pregnancies per 100 women per year for norethisterone oenanthate, in the first year of use (Lande, 1995).

1.3 Progestogen implants

Subdermal implants release progestogen slowly over a long period and provide long-term, reversible contraception. The prototype is Norplant, which consists of six silicone rubber (Silastic) capsules 2.4 mm in diameter and 3.4 cm long which are inserted under the skin of the forearm or upper arm and provide contraception for five years. The capsules are each packed with 36 mg crystalline levonorgestrel, which is released at a rate of 85 μg/day initially, falling to 50 μg/day by nine months of use, to 35 μg/day by 18 months and then 30 μg/day during the third, fourth and fifth year of use (McCauley & Geller, 1992). They are non-biodegradable and must be removed in a minor surgical procedure. Implants consisting of two Silastic rods with similar release rates are effective for three years (Reynolds, 1996), and biodegradable implants that do not require removal are being developed.

Like the injectable progestogen-only contraceptives, progestogen implants cause amenorrhoea or frequent or irregular bleeding in most users. Implants are also more costly than many other methods (McCauley & Geller, 1992).

1.3.1 *Patterns of use*

Although implants are approved as a contraceptive in many countries, their use is not widespread. The country with the largest number of users is Indonesia, where over 1 million women had used them by 1992, and in 1994 they were currently being used by around 5% of married women aged 15–49 (United States Census Bureau, 1998). In the two years after their approval by the United States Food and Drug Administration in 1990, about 500 000 women in the United States obtained implants (McCauley & Geller, 1992). By mid-1992, 150 000 women in Thailand had used Norplant; in a survey in 1994, 1.2% of married women or women in union aged 15–49 in Haiti were reported to be currently using it (McCauley & Geller, 1992; United States Census Bureau, 1998).

1.3.2 *Action*

Implants suppress ovulation in up to 50% of women and have progestogenic effects on the cervical mucus and the endometrium (Kleinman, 1990; McCauley & Geller, 1992). The pregnancy rate is less than one per 100 women per year, averaged over five years of use (McCauley & Geller, 1992).

1.4 Progestogen-only oral contraceptives

Progestogen-only oral contraceptives generally contain a progestogen of the norethisterone or levonorgestrel group, given at a constant dose, to be taken at the same time every day, without a break. They are also called ‘mini-pills’. Annex 2 (Table 2) lists the common brand names of progestogen-only oral contraceptives with their compositions. Typical pills contain 0.3–0.35 mg norethisterone or 30–37.5 μg levonorgestrel (Kleinman, 1996).

1.4.1 *Patterns of use*

Few systematic data are available on the prevalence of use of progestogen-only oral contraceptives worldwide, as in most surveys women are asked about their use of 'oral contraceptive pills' with no distinction between combined and progestogen-only oral contraceptive pills. Use is probably more common in Australia–New Zealand, Scandinavia and the United Kingdom than it is in the United States and other parts of Europe, but use has been increasing over the last 20 years. In the United Kingdom, progestogen-only oral contraceptives represented 0.9% of all oral contraceptives used in 1973 and 8.8% in 1987 (Thorogood & Villard-Mackintosh, 1993). The *Health Survey for England 1995* showed that 4% of English women aged 16–54 were currently using progestogen-only oral contraceptives and 19% were using combined oral contraceptives; in the age group 35–44 years, 4% of women were using progestogen-only oral contraceptives and 9% were using combined oral contraceptives (Bost *et al*., 1997). In the United States, progestogen-only oral contraceptives accounted for less than 1% of oral contraceptive sales in 1984 (Piper & Kennedy, 1987). Table 3 indicates the percentages of women among the population-based controls in studies of oral contraceptives and breast cancer in Denmark, New Zealand, Sweden and the United Kingdom who reported any use of progestogen-only oral contraceptives (Collaborative Group on Hormonal Factors in Breast Cancer, 1996). In 1987, about 2% of oral contraceptives bought by pharmacies in 'developed' countries were progesterone-only pills, while they accounted for less than 1% of such sales in 'developing' countries (Wharton & Blackburn, 1988) .

Table 3. Percentages of women reporting any use of progestogen-only oral contraceptives in selected studies

Country	Study	Any use of progestogen-only oral contraceptives (%)
Denmark	Ewertz (1992)	5
Sweden	Meirik *et al*. (1986)	13
New Zealand	Paul *et al*. (1990)	9
United Kingdom	UK National Case–Control Study Group (1989)	15

From Collaborative Group on Hormonal Factors in Breast Cancer (1996)

1.4.2 *Action*

Progestogen-only oral contraceptives have variable effects on ovulation, suppressing it in about 40% of users. Their main contraceptive action is through a progestogenic effect on cervical mucus and, to a lesser extent, the endometrium. As the effect on cervical mucus lessens 20–22 h after administration of a pill, the user must be careful to take it regularly at a time that maximizes its effectiveness. The pregnancy rate is 0.3–5

per 100 women per year of use, with lower failure rates among older women, probably because of their lower overall fertility (Kleinman, 1990).

1.5 Other sources of exposure to progestogen-only contraceptives

The hormone-releasing intrauterine device 'Progestasert' contains 38 mg progesterone, which is released at a rate of 65 μg/day for one year, after which time it should be replaced (Treiman *et al*., 1995). The more recently developed LNG-20 intrauterine device contains 52 mg levonorgestrel which is released at a rate of 20–30 μg/day and lasts for at least five years (Treiman *et al*., 1995; Kleinman, 1996). The progestogen enhances the contraceptive efficacy of the intrauterine device and also reduces menstrual loss. Although worldwide use of intrauterine devices is high, with at least 72 million users in China alone (Treiman *et al*., 1995), only a small proportion of these contain progestogen. Hormone-impregnated contraceptive vaginal rings which release levonorgestrel into the systemic circulation have been developed but are not widely used (Kleinman, 1990).

Progestogen-only emergency contraception involves the administration of two doses of 750 μg levonorgestrel orally 12 h apart within 48 h of unprotected intercourse (Cullins & Garcia, 1997).