

Facts about once-a-month injectable contraceptives: Memorandum from a WHO meeting*

This Memorandum reviews the results of research undertaken in animals and human subjects on once-a-month injectable contraceptives containing a progestogen and an estrogen, in particular the products Cyclofem and Mesigyna. Results from clinical trials, including effectiveness and side-effects, are evaluated and issues arising from health service research are discussed. The Memorandum concludes with a statement regarding the use of Cyclofem and Mesigyna as options for potential contraceptive users.

Introduction

In 1981 WHO convened a meeting of experts to review progestogen-only injectable contraception; the report of the meeting stressed the need for long-acting reversible contraceptive methods but gave menstrual irregularity as the major reason for discontinuation of these progestogen-only methods (1). In order to try to overcome this problem, combined progestogen/estrogen formulations have been developed and extensively reviewed (2-7). In 1993, approximately 2 million women were using once-a-month combined injectable contraceptives mainly in Latin

America and China, with several other countries participating in the development and introduction of two new preparations.

Development of once-a-month combined injectables

Since the first report of a long-acting combined preparation by Siegel in 1963 (8), several different preparations have been tested. Of these preparations, two are now widely used: (1) one, known as *Chinese Injectable No. 1*, is used in China and a few neighbouring countries and is said to be used by at least 1% of all contraceptive users in China; and (2) the other, used in Latin America, is marketed under different brand names. Two new preparations will soon be available to national family planning programmes: (1) *Cyclofem*, previously known as HRP112 or Cycloprovera (this formulation originated with Upjohn and was further developed by WHO); and (2) *Mesigyna*, previously called HRP102 (this was developed by WHO and made available by Schering AG) (see Table 1). Both preparations have been tested in phase-III studies and some introductory studies undertaken on Cyclofem. Registration has been approved in some countries and further registrations are imminent.

17 α -Hydroxyprogesterone caproate plus estradiol valerate. This formulation is only manufactured in China. Two injections are given during the first month, the second 10 to 12 days after the first to achieve high efficacy. Some 5500 women have been studied in Shanghai for some 54 200 months of use and it was found to be acceptable, despite short cycles, and to be relatively free from side-effects (9). It was subsequently assessed in comparison with Cyclofem and Mesigyna (see below).

* This Memorandum is based on the report of a WHO meeting that was held in Geneva on 1-3 June 1993. The participants were A. Andrade, Juiz de Fora, Brazil; S. Bassol, Torreón, Mexico; Wisut Boonkasemsanti, Bangkok, Thailand; L. Dorflinger, Research Triangle Park, NC, USA; J. Findlay, Clayton, Victoria, Australia (Co-Chairman); I.S. Fraser, Sydney, New South Wales, Australia; H.L. Gabelnick, Arlington, VA, USA; O.F. Giwa-Osagie, Lagos, Nigeria; Lely N.E. Hadjar, Jakarta, Indonesia; K. Hagenfeldt, Stockholm, Sweden (Co-Chairman); S. Hajri, Tunis, Tunisia; R. Heywood, Huntingdon, Cambridgeshire, England; R. Holt, Seattle, WA, USA; C. Huezio, London, England; M. El Hussein, Cairo, Egypt; Suporn Koetsawang, Bangkok, Thailand; F. Lubis, Jakarta Pusat, Indonesia; R.F. McConnell, Flemington, NJ, USA; J.R. Newton, Birmingham, England (Rapporteur); E.S.P. Pandi, Jakarta, Indonesia; Sang G.-W., Hangzhou, Zhejiang, China; B.N. Saxena, New Delhi, India; R. Simmons, Ann Arbor, MI, USA; D.C.G. Skegg, Dunedin, New Zealand; and M. Topozada, Alexandria, Egypt. Representative from Drug Regulatory Authority: P.A. Corfman. Representatives from the Pharmaceutical Industry: K.M. Cookson, P. Günzel, B. Seibert and K. Schmidt-Gollwitzer. Observer: R. Lande. WHO Secretariat: C. d'Arcangues (Secretary) and P.E. Hall, Special Programme of Research, Development and Research Training in Human Reproduction, World Health Organization, 1211 Geneva 27, Switzerland. Requests for reprints should be sent to this address. A French translation of this article will appear in a later issue of the *Bulletin*.

Table 1: Once-a-month combined injectable preparations

Name	Progestogen		Estrogen	
	Name	Dose	Name	Dose
Chinese Injectable No. 1	17 α -Hydroxyprogesterone caproate	250 mg	Estradiol valerate	5 mg
Topasel/Patector/Perluta (and various others)	Dihydroxyprogesterone acetophenide	150 mg	Estradiol enanthate	10 mg
Cyclofem	Medroxyprogesterone acetate	25 mg	Estradiol cypionate	5 mg
Mesigyna	Norethisterone enanthate	50 mg	Estradiol valerate	5 mg

Dihydroxyprogesterone acetophenide plus estradiol enanthate. It was shown that 16 α , 17 α -dihydroxyprogesterone acetophenide (DHPA) was a potent inhibitor of ovulation at a dose of 150 mg (10) and that by adding 10 mg of estradiol enanthate (E₂EN) fairly regular cycles were achieved. The total database up to 1983 on the combined product was some 22 889 woman-months of use by 2403 women. It had high efficacy and the mean incidence of cycle irregularities was 22.4%. Continuation rates varied but, after 2 years of use, were 39.7% to 43.6% (11, 12). The main side-effects were menstrual irregularity and short cycles, which ranged from 7.5% to 24.4% (12, 13). Return to fertility was slightly delayed (14, 15).

At the time of development of this progestogen the beagle dog was still a required animal toxicology model. Considering the results of 2-year toxicity studies with DHPA on this animal, the original manufacturer withdrew this combination from further clinical testing. However, subsequent studies of the natural history of breast lumps and other tumours in beagle dogs led to the removal of this species from animal test studies (16).

Nevertheless, this and similar formulations, including half-dose preparations, have been manufactured for many years by several pharmaceutical companies in Brazil, Chile and Mexico and marketed in Spain and Latin America. It is estimated that up to 0.5 million women are using this group of preparations each year in Mexico.

Medroxyprogesterone acetate plus estradiol cypionate and norethisterone enanthate plus estradiol valerate. An initial study by Coutinho & de Souza in 1968 investigated the combined preparation of 25 mg medroxyprogesterone acetate (MPA) and 5 mg estradiol cypionate (E₂C), and found that 74% of the cycles were of normal duration (17).

Further work with a higher dose, MPA 50 mg and E₂C 10 mg, showed that more than 70% of users had normal cycles (2). However, the results from Coutinho & de Souza (17) and subsequent studies

(2, 18) showed that the lower dose of 25 mg MPA and 5 mg of E₂C was likely to give better results and was therefore used in later studies. This product was originally developed by Upjohn and a significant amount of research was subsequently undertaken by WHO. It is now known as Cyclofem.

In the late 1970s WHO's Task Force on Long-acting Systemic Agents for Fertility Regulation investigated norethisterone enanthate (NET-EN) with estradiol valerate (E₂V) as an alternative once-a-month injectable. In a series of optimization studies different dose combinations of NET-EN and E₂V were assessed, which gave rise to a final product formulation of 50 mg NET-EN plus 5 mg E₂V (known as Mesigyna). At this time similar studies were ongoing on NET-EN and E₂V in China by Sang who reached similar conclusions (9). In addition, WHO also undertook a similar series of studies on MPA and E₂C and the final product formulation of 25 mg MPA plus 5 mg E₂C was chosen.

With both products the first injection is given up to day 5 of the cycle by deep intramuscular injection into the deltoid or the gluteal muscle. A bleeding episode will occur after the first injection, usually within 10 to 15 days, owing to the declining level of plasma estrogen. Subsequent injections need to be given every 30 \pm 3 days (27 to 33 days).

Animal studies

The toxicology of estrogens and progestogens contained in Cyclofem and Mesigyna has been reviewed (1, 19) and these compounds are considered to be safe. All clinical animal safety studies were conducted under the standard guidelines in use up until the late 1980s. Dosage selection was based on multiples of human clinical usage without regard to pharmacodynamic and pharmacokinetic parameters of the individual species. These dosages caused exaggerated pharmacological and endocrinological responses resulting in species-specific pathologies. The tumours induced occurred in the endocrine organs, gonads

and accessory sex glands, and can be related to the known pharmacological activity of estrogens and progestogens in the test animal species used.

Experience with the toxicology of combined progestogen-estrogen preparations has shown marked differences between species and in their responses to different ratios of these two steroids. For example, the optimum ratio of estrogen to progestogen for the induction of decidual reaction or secretory transformation of the endometrium is 1:20 000 in rats and 1:50 in women. Toxicological studies have been conducted on Cyclofem (20) and Mesigyna (21). No additional or unexpected information was gained from these studies.

Human studies

A large number of clinical trials, including multi-centre studies organized by WHO, have been carried out in many countries with once-a-month injectables, the largest data sets being with Cyclofem, Mesigyna and Chinese Injectable No. 1. Several dose-finding, other phase-I and phase-II trials have been reported (see below, section on pharmacology); clinical and pharmacological data from two phase-II studies with Mesigyna have been reported (22, 23).

Five phase-III studies have been completed, of which four were comparative: the WHO multicentre, multinational trial (24); the Egyptian Fertility Care Society study (25); the Chinese/WHO multicentre study (26); the Indian Council of Medical Research (ICMR) study on Mesigyna and NET-EN alone (27); and a Latin American multicentre study on Mesigyna (28, and unpublished data). The results of these studies are shown in Table 2. The total database from these phase-III studies now includes information on 4234 Cyclofem users (41 226 woman-months of use) and 5559 Mesigyna users (60 832 woman-months of use).

Pharmacology

Available data on these once-a-month injectables have been reviewed (4-6). A series of studies have investigated the dosage and ratio of doses of the progestogen and estrogen components of the combination preparations containing MPA and NET-EN. In 1980, Oriowo et al. studied three esters of estradiol (the valerate, cypionate and benzoate) (29). The cypionate gave lower peak levels of estradiol with increased levels for 11 days, compared with the valerate which gave measurable estradiol levels for 7-8 days; the benzoate had the shortest duration of elevated estrogen levels, 4-5 days. There was wide subject variation but the valerate provided the most predictable pharmacokinetic behaviour.

There are no reported studies on the pharmacokinetics of preparations containing dihydroxyprogesterone acetophenide or 17 α -hydroxyprogesterone caproate. One pharmacodynamic study was conducted on DHPA 150 mg and E₂EN 10 mg and a half-dose preparation, and ovulation was inhibited at both dose levels in all subjects (30).

The pharmacokinetic profiles of MPA in women receiving Cyclofem were studied by Fotherby et al. (31). Wide intersubject variation of plasma steroid levels was seen, but ovulation was suppressed in all subjects. In the post-treatment phase, follicular activity returned in 3 of the 11 subjects by 28 days and in all subjects by 50 days. Plasma progesterone levels suggested that luteal activity did not occur until after day 63 following the last injection.

The pharmacokinetics of MPA or NET and of estradiol (E₂) in subjects receiving a single injection of either Cyclofem or Mesigyna were compared by Aedo et al. (32). Despite large intersubject variation both preparations inhibited ovulation. Significant levels of both progestogens were measurable at 30 days. Levels of estradiol equivalent to a pre-ovulatory estradiol peak were seen with both esters, being higher with the valerate than the cypionate. In all cases estradiol levels returned to baseline before the end of the treatment cycle. Studies on the endometrium revealed suppressed or early proliferative patterns.

Because of these studies, a reduction in dose of MPA to 12.5 mg (half-dose) and estradiol cypionate to 2.5 mg was investigated in comparison with Cyclofem by WHO (33). In the study, ovulation was only assessed during the third month of treatment and was inhibited by the reduced-dose preparation in 19 out of 20 subjects. There were marked differences in the pharmacokinetic profiles between the centres participating in this study. A deterioration in bleeding patterns was observed with the half-dose preparation.

A similar study was undertaken with Mesigyna and a half-dose preparation containing 25 mg of NET-EN plus 2.5 mg estradiol valerate (34); while the latter preparation inhibited ovulation in all 23 subjects during the third treatment month, it also gave rise to a deterioration in bleeding patterns.

A final dose-finding study was undertaken in which the dose of progestogen was halved (MPA 12.5 mg or NET-EN 25 mg) and the estrogen maintained at 5 mg (34). This change in dose resulted in breakthrough ovulation with both preparations during the third treatment month in 10 out of 24 subjects on the MPA-containing preparation and in 7 out of 22 on the NET-EN-containing preparation.

Additional studies have been undertaken on Mesigyna in China by Sang (9) and have shown similar pharmacokinetic characteristics to those discussed

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above. In one of these studies, 17 subjects were followed through the 1st, 6th and 12th injection intervals and no accumulation of NET was observed with time (9). No similar study has been undertaken with Cyclofem.

In summary, assessment of some 190 women in pharmacokinetic studies led to the chosen formulations of Cyclofem and Mesigyna, which showed complete suppression of ovulation and the least disturbance of vaginal bleeding patterns.

Contraceptive efficacy

Mesigyna and Cyclofem have both proved to be highly effective contraceptives with 12-month pregnancy rates of 0.4% or less for Mesigyna and 0.2% or less for Cyclofem (Table 2). There were no statistically significant differences between the rates found with the two preparations, although rates were slightly higher for Mesigyna. There was one ectopic pregnancy with Mesigyna. The majority of the small number of method-failure pregnancies occurred in the first few cycles of use. The timing of injection (once every 30 ± 3 days) is likely to be extremely important to maintain high contraceptive efficacy. These figures for efficacy are very similar to those recorded in phase-III WHO studies with longer-acting progestogen-only injectables, e.g., 0.1% for depot-medroxyprogesterone acetate, DMPA (given once every 84 ± 7 days) and 0.4% for NET-EN (given once every 60 ± 5 days) (35, 36).

The 12-month life-table contraceptive failure rate with Chinese Injectable No. 1 was 0.8% when it was given on the following schedule: first injection on day 1–5 of the cycle with an additional injection 9

(± 1) days later. Subsequent injections were given on day 10–12 after the onset of withdrawal bleeding, or 28 days after the previous injection if no bleeding occurred. When used on a strict once-a-month schedule the failure rate was high, at 6.0%.

In the case of the only other extensively studied formulation, the combination of dihydroxyprogesterone acetophenide with estradiol enanthate, no pregnancy was recorded in any of the clinical trials (2).

Vaginal bleeding patterns

In all phase-III trials WHO utilized daily menstrual diary cards to record the occurrence of bleeding and spotting and analysed them using a 90-day reference period (37). The three comparative phase-III trials of Cyclofem and Mesigyna found no major difference between the formulations in discontinuation rates for vaginal bleeding problems (Table 2), and around 70% experienced regular monthly vaginal bleeding at the end of one year of use. These studies confirmed that the first cycle after injection was usually very short with bleeding beginning 10–20 days following the injection. This pattern of bleeding, beginning 10–20 days post-injection, continued in all subsequent cycles, thereby inducing a regular monthly pattern. The volume of flow was usually described as less than normal for each woman.

There are very few large-scale studies of the menstrual experience of groups of normal women not using hormonal or intrauterine contraception. WHO has obtained access to the very large database of menstrual patterns of non-contraceptive-using American women collected by Treloar (38). These

Table 2: Summary of phase-III studies of Cyclofem (Cyclo) and Mesigyna (Mes), by use-related terminations (one-year life-table rates)

Event	WHO Phase-III study		EFCS ^a		Chinese study		Latin America	ICMR ^a
	Cyclo	Mes	Cyclo	Mes	Cyclo	Mes	Mes	Mes
Unexpected intrauterine pregnancy	0	0.2	0.2	0.4	0.1	0.3 ^b	0.1 ^c	0.2
Amenorrhoea	2.1	1.6	2.7	1.4	5.2	0.8	2.3	4.2
Bleeding-related problems	6.3	7.5	7.4	11.5	12.7	7.9	5.4	12.0
Other medical	6.2	6.6	7.8	4.7	3.4	3.6	ND ^d	9.4
Non-medical	15.0	16.6	12.4	12.8	6.7	6.7	ND	17.2
Total discontinuation	35.4	36.8	38.9	38.0	26.4	18.8	26.5	44.1
No. of women enrolled	1168	1152	1111	1093	1955	1960	931	423
Woman-months of use	10 969	10 608	10 492	10 033	19 765	20 688	15 787	3 716

^a EFCS = Egyptian Fertility Care Society study. ICMR = Indian Council of Medical Research (Task Force on Hormonal Contraception) study.

^b One was an ectopic pregnancy.

^c Subjects were instructed to use a barrier method in the first month of use.

^d ND = not determined.

data have been reanalysed so that they are comparable to the data for women treated in phase-III WHO studies (39, and unpublished data). The reanalysis has demonstrated that frequency of bleeding is very similar between untreated women and oral contraceptive users (3.2 to 3.3 episodes of bleeding and spotting per 92 days), while once-a-month injectable users had slightly fewer episodes (3.0 for 90 days). The duration of bleeding/spotting episodes was similar for untreated women and once-a-month injectable users at about 5 days, while it was shorter (about 4 days) for oral contraceptive users.

Reanalysis of the data on normal women has allowed a precise statistical evaluation of the variation of normal vaginal bleeding patterns (39). This has also permitted a soundly based assessment of a range of variations from normal regular patterns. These were originally termed "clinically important" patterns (37), but it may be more realistic to call them "variations from the regular pattern" because they have been determined as variations greater than 2 standard deviations from the mean. This new set of variations from the normal, regular pattern is defined as shown in Table 3.

One year of study of women using Cyclofem and Mesigyna showed little difference between the two preparations with respect to the incidence of amenorrhoea and infrequent, frequent, irregular or prolonged bleeding (Table 4). Women using either preparation had a very low incidence of amenorrhoea, which only increased slightly during one year of use. This contrasted dramatically with the increase in amenorrhoea in DMPA users. Cyclofem and Mesigyna users both had a high incidence of frequent, irregular and prolonged bleeding in the first three months of use, which was associated with the short cycle following the first injection. The incidence of these variations decreased greatly during one year of use.

By the end of one year of use around 70% of Cyclofem and Mesigyna users were experiencing

regular bleeding patterns compared with only 8% of DMPA users. The incidence of most variations from regular patterns tended to decrease with time in once-a-month injectable users. In comparison with untreated women, the longer-term once-a-month injectable users had a lower incidence of amenorrhoea, an equal incidence of infrequent bleeding, and a significantly increased incidence of frequent, irregular and prolonged bleeding.

Reasons for discontinuation

The total 12-month discontinuation rates shown in Table 2 ranged from 18.8% to 44.1%. These discontinuation rates are significantly less than those seen with the long-acting progestogen-only injectables, DMPA and NET-EN.

Variations from the normal, regular pattern of vaginal bleeding accounted for the majority of women discontinuing once-a-month injectable use for medical reasons, although these discontinuations were much less than those usually seen with long-acting progestogen-only injectables. Twelve-month life-table discontinuation rates for amenorrhoea and bleeding-related problems with Mesigyna and Cyclofem in phase-III studies are summarized in Table 2. Discontinuation for the stated reason of amenorrhoea varied between 0.8% and 4.2% for Mesigyna and 2.1% and 5.2% for Cyclofem, compared with 5.4% and 12.0% for bleeding-related reasons with Mesigyna and 6.3% and 12.7% with Cyclofem. The main bleeding disturbances were given as heavy, prolonged and irregular bleeding.

Major differences have been seen in the discontinuation rates for different stated reasons in individual centres in most countries. For example, in the phase-III studies amenorrhoea discontinuation rates have varied between 0 and 17.5 per 100 woman-years, while discontinuation for bleeding disturbances varied between 0 and 34.0 per 100 woman-years. A small part of this variation may be explained by actual differences in menstrual patterns, but the major part appears to be due to cultural and counselling factors. Appropriate detailed pre-treatment counselling about possible variations in vaginal bleeding patterns appears to result in much lower discontinuation rates for menstrual reasons.

Discontinuation rates for other medical reasons, shown in Table 2, were low and very similar in all studies. The reasons given were diverse and were similar for both formulations. They included headache, dizziness, body aches, mastalgia, body weight changes, etc. and often appeared to vary with ethnic background. Body weight tended to increase but was less than a mean of 1 kg after 12 months in most centres. Non-medical reasons (8-17% of total)

Table 3: Variations from a normal regular pattern of vaginal bleeding^a

Condition	Definition (for a 90-day reference period)
Amenorrhoea	No bleeding
Infrequent bleeding	Fewer than 2 bleeding/spotting episodes
Frequent bleeding	More than 4 bleeding/spotting episodes
Irregular bleeding	A range of lengths of bleeding-free intervals exceeding 17 days
Prolonged bleeding	At least one bleeding/spotting episode lasting 10 days or more

^a Previously termed "clinically important bleeding patterns".

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included termination of the study, moving away, planned pregnancy, and no further need.

Introductory trials

Introductory trials were carried out on Cyclofem to evaluate whether, under more routine service conditions, the use-effectiveness and reasons for discontinuation were similar to the findings in earlier clinical studies of safety and efficacy, described above. These trials have been undertaken in Indonesia, Jamaica, Mexico, Thailand, and Tunisia and are ongoing in Chile. More than 9000 women were recruited into these studies at urban and semi-urban, primary or secondary health care centres, and more than 70 000 woman-months of experience accumulated (40).

The cumulative 12-month life-table discontinuation rates for all reasons ranged from 33.5% to 71.8% (Table 5). The rates of discontinuation in all countries were similar or lower than those found for DMPA in general use, except in Thailand where discontinuation rates were higher than for general use of other hormonal contraceptives.

With regard to efficacy, in Mexico, more than 20 000 women-months of experience were accumulated with only one pregnancy attributed to the method. In Indonesia four pregnancies occurred, while in Jamaica one pregnancy was reported, giving

a total life-table pregnancy rate of less than 0.1% per 100 woman-years.

Reasons for discontinuation from the study varied greatly between the five countries (Table 5). The phase-III clinical trial of Cyclofem had shown a major difference between centres in discontinuation rates for bleeding-related reasons and amenorrhoea. Similar differences were reflected in the introductory trials where a large range of discontinuation rates was observed for bleeding-related reasons, from 1.4% in Indonesia to 24.8% in Tunisia, and from 1.4% to 13.2% in the same two countries for amenorrhoea. Lack of tolerance, even to minor spotting episodes, was observed in Tunisia where bleeding-related reasons were the most frequent reason for discontinuation.

In Thailand, women were asked whether they had experienced any bleeding since the last injection. For those women who had switched from DMPA with amenorrhoea, some 70% experienced a menstrual bleeding episode by the end of the third month of treatment with Cyclofem.

Discontinuations for other medical reasons reflected the major concerns about side-effects. The rates were lowest in Indonesia and highest in Tunisia. In Indonesia the most common reason was dizziness. In Thailand, weight gain, headaches and dizziness were the most common reasons. In Tunisia, a

Table 4: Proportions (%) of women experiencing different types of bleeding patterns

Group	Days	Number of diaries	Bleeding pattern					Total variations from regular pattern ^a	Regular patterns
			Amenorrhoea	Infrequent bleeding	Frequent bleeding	Irregular bleeding	Prolonged bleeding		
Untreated	1-90	3893	1.3	3.4	0.2	4.5	2.6	9.7	90.3
	91-180	3893	1.5	2.9	0.3	4.8	2.3	9.2	90.8
	181-270	3893	1.3	2.8	0.1	5.4	2.6	9.9	90.1
	271-360	3893	1.6	3.1	0.3	8.6	4.3	14.9	85.1
Cyclofem	1-90	1001	0.1	0.1	22.3	39.6	20.8	57.0	43.0
	91-180	885	0.2	3.4	3.3	23.5	13.3	36.8	63.2
	181-270	802	1.1	5.4	2.8	25.4	9.4	38.7	61.3
	271-360	730	2.3	3.7	6.5	13.6	10.1	30.0	70.0
Mesigyna	1-90	1000	0.2	0.1	29.6	34.6	16.2	52.8	47.2
	91-180	860	0.6	2.2	5.5	25.2	11.1	37.2	62.8
	181-270	766	1.3	2.9	4.9	24.8	12.6	36.7	63.3
	271-360	713	2.0	5.0	6.2	14.6	12.7	31.6	68.4
DMPA	1-90	509	10.6	15.7	17.7	46.0	43.4	91.0	9.0
	91-180	406	23.9	25.8	10.5	35.7	27.7	93.1	6.9
	181-270	311	37.0	24.8	8.3	27.7	17.3	93.6	6.4
	271-360	241	38.6	27.8	6.6	17.9	16.5	91.7	8.3

^a Some subjects may have appeared in more than one category of bleeding pattern

large number of women discontinued because of headaches followed by backache, nervousness, heaviness of limbs and weight gain.

Personal reasons for discontinuation (Table 5) included those reasons which were not due directly to method-attributable side-effects. A woman's reason to discontinue for personal reasons may be influenced by other users or members of the community, or may reflect the subject's treatment or perception of treatment by service delivery staff, or the inconvenience of the services. The personal reasons were greater than seen in the phase-III clinical trials. They included "inconvenience and timing", "moved away", "desire for pregnancy" and, in the case of Thailand, "no further need" and "change of method", and in Tunisia, "negative perceptions" on the part of both users and providers.

"Inconvenience and timing" reflected problems caused by the injection being available in only a limited number of clinics, the distance to those clinics, their opening hours, the need to visit once-a-month, and mobility of the populations. Discontinuation for this reason ranged from 7.2% in Indonesia to 16.2% in Thailand. In all countries there was a large number of women who migrated to the cities or to other provinces, often for limited periods of time. "Moved away" was an important reason in Thailand (13.3%).

While "desire for pregnancy" can be an easy reason to give for discontinuation it also reflects the

use of the method for spacing purposes since this reason increased with time. "No further need" reflected divorce, death of husband, husband's vasectomy, or a temporary separation of partners.

The studies confirmed the high efficacy of Cyclofem but showed, like the phase-III clinical trials, major variations between countries in discontinuation on account of amenorrhoea, and bleeding-related, or other medical reasons. Other reasons for discontinuation were influenced by the limited availability of the method and other service delivery issues.

Return to ovulation and fertility

Data on return to ovulation following use of the new combined injectable preparations are sparse, and data on return to fertility are limited. The return of ovulation between 60 and 90 days was shown after an injection of DHPA 150 mg and estradiol enanthate 10 mg (41); similar results were seen in some nine other studies (42). With Cyclofem and Mesigyna, pharmacodynamic studies in Sweden showed follicular activity with both these preparations by 41–49 days, with time to achieve competent luteal activity taking 59–87 days (32). In a study of 21 women who received Cyclofem for three months, 52% ovulated during the first month post-treatment and 71% in the second post-treatment month (33). In a similar study of 21 women on Mesigyna, 19% ovulated in the first

Table 5: Cyclofem introductory studies. Number of subjects discontinuing and cumulative 12-month life-table discontinuation rates, by country and major reasons

Reason for discontinuation	Indonesia		Jamaica		Thailand		Tunisia		Mexico	
	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate
All reasons	376	33.5	150	40.4	762	58.3	621	71.8	2467	71.4
All medical reasons:	82	8.5	42	14.8	231	22.8	353	52.3	457	20.8
Pregnancy	4	0.5	1	0.7	0	0	0	0	1	0.1
Bleeding-related	13	1.4	15	5.8	49	5.1	144	24.8	271	12.5
Amenorrhoea	11	1.4	3	1.2	43	5.0	63	13.2	99	5.2
Other medical reasons	49	5.0	23	7.7	139	14.3	146	26.5	86	4.4
All personal reasons:	222	21.6	75	24.0	430	39.5	198	31.5	1839	59.1
Inconvenience and timing	67	7.2	30	8.9	153	16.2	51	8.1	—	OPR ^a
Moved away	43	4.7	9	4.0	123	13.3	36	6.5	—	OPR ^a
Desire for pregnancy	65	7.2	6	2.5	66	7.7	27	6.2	206	10.5
No further need	6	0.6	9	4.4	45	4.6	—	—	—	OPR ^a
Negative perceptions	—	—	—	—	—	—	60	11.2	—	OPR ^a
Change of method	1	0.1	14	4.2	33	4.1	—	—	590	26.3
Other personal reasons	40	3.8	7	2.6	10	1.2	24	4.1	1043	39.4
Lost to follow-up	70	6.9	33	7.8	101	10.5	70	11.9	142	6.4

^a Included under "other personal reasons".

month post-treatment and 67% during the second month (34).

After two years of use of Cyclofem or Mesigyna, 54% of the subjects receiving Mesigyna ovulated at least once during the three months following discontinuation, and with Cyclofem 60% had ovulated by the third follow-up month (42). Sang showed no long-term inhibition of the pituitary-ovarian axis in women who had used Mesigyna for 2–3 years (9). The first post-ovulatory peak of progesterone occurred between 43 and 108 days after the last injection interval in 14 out of 15 subjects.

All 19 women who had received a Mesigyna preparation produced in China, became pregnant within three months of terminating treatment (9). It would be prudent, however, to collect further data on return to both ovulation and fertility in women currently participating in introductory trials who intend discontinuing for a planned pregnancy, and women who discontinue on account of bleeding disorders and amenorrhoea.

Effects on lactation

There have been extensive studies on the effects of progestogen-only contraception on breast milk, and no ill-effects were seen on the infants of breast-feeding mothers (43–45). There are no data on combined injectable formulations. Combined progestogen-estrogen injectables can be started after weaning, but further studies of their effects on lactation and infant welfare are required before they can be given during breast-feeding.

Metabolic studies

Information on dihydroxyprogesterone acetophenide plus estradiol enanthate is sparse. One study monitored lipid metabolism, sex-hormone-binding globulin, cortisol and testosterone. In a comparison of test and control subjects the only findings with this combined preparation were higher levels of triglycerides and free testosterone (46). Other parameters were unchanged, in contrast to the variable responses seen with combined oral contraceptive users.

Studies on Cyclofem and Mesigyna have investigated several metabolic parameters over the first year of use.

Coagulation and fibrinolysis. A cross-sectional study undertaken in China compared seven parameters of haemostasis and showed no significant differences between Mesigyna users and control subjects (47). A one-year longitudinal study on Mesigyna users showed a decrease in factor X and antithrombin III; however, these changes were considered to be of no clinical significance (48).

WHO undertook a large multicentre study and compared a combined oral contraceptive with Cyclofem and Mesigyna in respect of 11 parameters of haemostasis (49). This study followed an intensive laboratory standardization programme using matched reagents and a quality assurance scheme. The combined oral contraceptive induced increases in fibrinogen, factor VII and X activities, and plasminogen. These prothrombotic changes were reflected in a shortening of the activated partial thromboplastin time. By contrast, protein C was increased by nearly 10%. Decreased levels of tissue plasminogen activator inhibitor (t-PAI) suggested an increase in fibrinolysis compensating for the rise in pro-coagulant factors. In comparison, neither of the injectable contraceptives induced a rise of pro-coagulant factors. Both, but particularly Mesigyna, induced a reduction in factor VII and X activities, and this was thought to reflect the more antiestrogenic effect of NET compared with MPA. An increase in t-PAI was noted in both groups, reaching 12% by the end of the treatment period. Small decreases in antithrombin III activity and in protein C were not considered to be clinically relevant.

The data indicated that Cyclofem and Mesigyna had less effect on haemostasis than the combined oral contraceptive. They did not induce an increase in pro-coagulants and did not have any clear-cut effect on the fibrinolytic system. All changes observed were within the normal range and most had reversed by three months after discontinuation.

Lipid metabolism. One study found no change in total cholesterol but a reduction in high-density lipoprotein (HDL) cholesterol after 6 months' use of Cyclofem; no significant changes were found with Mesigyna (50). In comparison, another study found a marked decrease in total cholesterol with Mesigyna when compared with an IUD control group (23). No difference was seen in HDL cholesterol, but there was a reduction in low-density lipoprotein (LDL) cholesterol and triglycerides. However, the control sample was taken in the early follicular phase and the subsequent samples were taken at the end of the injection cycle (day 30), which could explain these results, and is consistent with the findings reported below (49).

A WHO study undertaken in five centres was carefully designed to investigate blood lipid levels in the pretreatment cycle and the possible effects of estrogen in the first 11 to 12 days of the third and ninth treatment cycles (49). With both Cyclofem and Mesigyna, total cholesterol decreased during the period of treatment, particularly one week after each injection. The estrogen effect dominated during the

first week of the injection interval, when levels of LDL cholesterol and apolipoprotein B decreased by up to 10% to return to baseline at the end of each injection interval. In the second and third weeks of the injection interval, decreases in HDL cholesterol and apolipoprotein AI were observed, consistent with a dominant progestogen effect. Triglyceride levels were decreased, particularly one week after each injection. All parameters had returned to pre-treatment levels by three months post-treatment.

With both preparations, the HDL-cholesterol:total cholesterol ratio was increased in the first week following each injection, to decrease by no more than 6% from the baseline in the third week. Conversely, the LDL-cholesterol:total cholesterol ratio was decreased in the week that followed each injection, by 4–6% from the baseline in the third week. The HDL-cholesterol:LDL-cholesterol ratio increased during the first week following each injection and decreased in the third week. This drop was more marked in the Cyclofem group than in the Mesigyna group. The apolipoprotein AI:B and AI:III ratios varied in parallel with the HDL-cholesterol:total cholesterol ratio and did not vary by more than 10% during the follow-up period. All ratios returned to baseline by the third post-treatment month.

No clinically significant changes in lipid metabolism were seen. Both Cyclofem and Mesigyna induced only minor changes, which reflected the circulating levels of the two components of each preparation and which reverted promptly to baseline after discontinuation of treatment.

Carbohydrate metabolism. Two studies on Mesigyna, one using the euglycaemic glucose clamp technique over 6 treatment cycles (unpublished data) and the other using the oral glucose tolerance test up to one year, showed no significant changes (9). There are no published studies on Cyclofem.

Prolactin. Prolactin measurements during one injection interval after one year of use of Deladroxate, Cyclofem and Mesigyna showed a slight, but not significant, temporary rise in prolactin (51). The measurement of prolactin after one year of use of Mesigyna showed an increase of prolactin in the early part of the treatment cycle, with levels returning to baseline in the second half of the cycle (52). Both studies showed changes consistent with the stimulatory influence of the peak of estrogen on prolactin secretion during the injection interval.

● In summary, there were no adverse or clinically relevant metabolic changes observed in studies of one year of use of Cyclofem or Mesigyna.

Epidemiological studies of neoplasia

There is considerable information on the relation between combined oral contraceptives and the risk of neoplasia, which has recently been reviewed (53). However, close analogies with monthly injectables cannot be drawn, and there will be a need for epidemiological studies of these preparations as they become more widely used.

The only published study that has specifically examined the effect of monthly injectable contraceptives was a case-control study of cervical cancer in Chile and Mexico (54). The monthly injectables used in these populations contained dihydroxyprogesterone acetophenide and an ester of estradiol. While the results from Chile were consistent with an increase in risk in users of monthly injectables comparable to that reported in users of oral contraceptives, the results from Mexico showed no increase in risk. The authors concluded that the differing results were probably due to chance, but called for further studies.

Indications and contraindications

Indications

Cyclofem and Mesigyna are reversible once-a-month combined injectable preparations for contraceptive use. They are an appropriate choice for all women provided there are no contraindications. They may be particularly suitable for women who wish to delay their first birth or those seeking to space or limit births and who:

- want a highly effective method and prefer injections to other forms of contraception;
- do not want a method that requires use daily or at each act of intercourse; and
- are able and willing to have injections on a monthly basis.

Contraindications

Absolute contraindications are current breast cancer and genital tract malignancy.

Temporary contraindications for monthly injectables apply to clients:

- who are known or suspected to be pregnant (until they become non-pregnant);
- with undiagnosed abnormal genital tract bleeding (until the diagnosis is clear, particularly to exclude a malignancy);
- with suspected malignancy of the breast (until the diagnosis rules this out);
- with active thromboembolic disease (until clinical recovery);

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- with acute liver disease such as viral hepatitis (until liver function tests are normal or, in the absence of liver function tests, 2–3 months after clinical recovery);
- who are breast-feeding (until the beginning of weaning).

Special situations

Some situations may require special consideration before monthly injectables are provided; some on the basis of theoretical concerns projected from the effects of oral contraceptives and some because they constitute good health care practice. Decisions will depend on the circumstances and clinical assessment of each case. The potential risks should be adequately explained to the client and possible alternative methods should be discussed. If monthly injectables are chosen, good follow-up care is important. Such situations include:

- smoking (if over age 35 years);
- a personal history of diabetes mellitus or gestational diabetes, cardiovascular disease, thromboembolic disease or hypertension, gall bladder disease or chronic liver disease, or a known coagulation disorder;
- presence of abnormal cervical cytology requiring further investigation, but not necessarily cessation of the injectable methods;
- possibility of elective surgery (present knowledge raises no concerns about continued use of these injectables prior to surgery);
- concurrent drug use. While no formal studies have been undertaken on the interaction of rifampicin and some anticonvulsants with Cyclofem, it is not expected that these drugs would cause any decrease in efficacy; however, should any subjects be using these drugs this should be recorded. The use of malaria prophylaxis and systemic steroids concurrently with Cyclofem or Mesigyna is acceptable.

Management and health service research

Prior to considering wide-scale introduction of these injectables it is essential to conduct research which examines the opportunities inherent in new contraceptive technology as well as the operational constraints and burdens which arise from their introduction into ongoing service delivery settings. Introductory trials revealed some issues relating to the service environment into which Cyclofem was being delivered, but were not designed to specifically address service delivery issues.

Service delivery research begins with an assessment of the managerial and quality-of-care implications of adding a method into an initial group of service delivery sites participating in the introductory process. It also attempts to assess the managerial requirements and/or adaptations that would be necessary in the event of more wide-scale introduction of the product into both public and private sectors.

A study in one of the countries participating in the introduction of Cyclofem highlights the need to carefully evaluate under what circumstances the addition of a new method contributes to expanding contraceptive options and improving the quality of care (55, 56). Since new methods enter into existing health infrastructures which will have an impact on the appropriate provision of methods, several issues must be considered. Specifically with regard to the addition of a new injectable in situations where other injectables are already available, there are important implications for counselling, logistics management, and maintaining appropriate technical standards of care. It was noted that women's access to informed choice is constrained when the logistic systems do not differentiate between the available injectables and when counselling skills are weak. Adequate logistic systems for managing supplies of disposable needles and syringes are needed to maintain technical standards. It is also important to note that when programmes emphasize long-acting methods, women's access to effective monthly injectables could be curtailed.

Given that service delivery research is specific to a particular context and the results are not generalizable to other institutional and sociocultural settings, it is recommended that future introductory activities on once-a-month injectables focus on country-specific service delivery studies of the type discussed above.

Acceptability studies

Acceptability of a contraceptive method is known to be multifactorial and to depend not only on the characteristics of the method and the service delivery setting but also on the sociodemographic and economic factors that pertain to a given country. A study conducted in parallel to the Egyptian Fertility Care Society phase-III clinical trial is the only acceptability study to be completed on combined, monthly injectable preparations (57).

There was a significant difference between discontinuers and continuers in all measures of acceptability: discontinuers had less method satisfaction, less desire to give advice to others, and less willingness to pay for injections. "Service" satisfaction was also lower in this group. Side-effects were more frequently reported by discontinuers, while users were more tolerant of the same side-effects.

The following factors were found to be important in determining acceptability among Egyptian women: age, contraceptive history, learning about injectables, the husband's attitude, and knowing about another user's satisfaction with the service. The determinants favouring discontinuation included: young mothers used to a large family size, first-time contraceptive users and previous users with menstrual problems that led to termination of the previous method, women who were dissatisfied with the service and did not receive counselling, women lacking social support (from their husbands, relatives or neighbours), and women who encountered problems of any type during contraceptive use.

New product development

A variety of alternatives to ester-based monthly injectables have been explored. The two methods which have received the greatest effort consist of microspheres containing either natural or synthetic steroids. One approach has relied on poly(lactic-co-glycolic acid) as the excipient which controls the rate of release. This method, which has been used extensively for delivery systems of longer duration, has not been successfully developed as a monthly preparation. More promising is the modification of a technology originally used for norethisterone and mestranol which yields microspheres of steroids alone with slow dissolution properties. This technology has been applied to progesterone and 17β -estradiol and preliminary clinical studies are under way (58).

Conclusions

Injectable progestogen-only contraception has proved to be a useful method of contraception with high efficacy. Its main side-effect is menstrual irregularity leading, in some cases, to discontinuation of the method. In an attempt to overcome this, once-a-month injectables combining a progestogen with an estrogen have been developed. Two formulations are currently being used by approximately two million women: 17α -hydroxyprogesterone caproate 250 mg plus estradiol valerate 5 mg (known as Chinese Injectable No. 1, used almost exclusively in China) and dihydroxyprogesterone acetophenide 150 mg plus estradiol enanthate 10 mg (used in Latin America). Limited preclinical and clinical data are available on these preparations.

Two new preparations are now becoming available: Cyclofem (medroxyprogesterone acetate 25 mg plus estradiol cypionate 5 mg) and Mesigyna (norethisterone enanthate 50 mg plus estradiol valerate 5 mg). Pharmacokinetic studies have explored the dosage levels of MPA and NET-EN and of the

respective estrogens. The final doses of Mesigyna and Cyclofem were chosen on the basis of high efficacy and acceptable vaginal bleeding patterns.

Five large-scale, clinical phase-III studies have confirmed the high efficacy of both Cyclofem and Mesigyna in some 9793 women for 102 058 woman-months of use. The pregnancy life-table rates were all below 0.4% for Mesigyna and below 0.2% for Cyclofem. More than 65% of women had predictable regular cycles. Discontinuations for bleeding-related problems were less than half those seen with progestogen-only injectables, and the discontinuation rates for amenorrhoea were low. Data on return to ovulation are limited but indicate a return to normality within a few months of discontinuation. Data on return to fertility are being collected in ongoing studies.

Animal studies on these preparations and their individual components have been reviewed and have not raised safety concerns. There are, at present, no long-term data in humans on combined monthly injectables and neoplasia. The data from progestogen-only injectables and oral contraceptives are reassuring, but close analogies with monthly injectables cannot be drawn, and there will be a need for epidemiological studies of these preparations as they become more widely used.

Observations with Cyclofem in six countries on more than 9000 women with more than 70 000 woman-months of use have confirmed the high efficacy of the product; these studies addressed management and service issues as well as medical surveillance. The results of health service research stressed the need for the following: adequate patient information, staff trained in the new methods, presentation of the monthly injectables as part of a free choice of contraceptive methods, suitable distribution and storage, and adequate supplies of the product.

Both Cyclofem and Mesigyna are thus safe and effective products for fertility regulation, which can be added to the existing range of contraceptive methods. They can be used by all potential contraceptive users provided that precautions are taken to assess potential risk factors. They provide high efficacy and a low incidence of side-effects, and the vaginal bleeding patterns are better than those seen with progestogen-only injectables.

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