INDIAN COUNCIL OF MEDICAL RESEARCH

REPORT

Phase III- Clinical trial with once a month combined injectable contraceptive "Lunelle/Cyclofem" (MPA-25 mg + oestradiol cypionate- 5mg).

Introduction:

Intramuscular administration of a long-acting (LA) fertility control agents is an attractive and desirable contraceptive modality. It suits a significant sector of the population as it fills a gap in the currently available technologies. The injection as a method of delivering drugs fulfills many of the features of an ideal contraceptive as they are relatively long-acting, simple to use, unrelated to coitus, and are highly efficacious.

Injectable contraceptives given every 2-3 monthly contain long acting progestins which has prolonged action such as norethisterone enantate NET-EN and depot medroxyprogesterone acetate DMPA. Although these formulations provide very high use-effectiveness in preventing pregnancy, they induce menstrual cycle disruptions such as heavy and prolonged bleeding, irregular bleeding including amenorrhea. Such side-effects discourage women to accept these methods for long term use.

Long-acting contraceptives delivered through monthly intramuscular injection is an alternate method for family planning which fills the desired gap in birth control methods. The main advantage of this approach over long-acting (2-6 months) progestin only injectables is better cycle control with their use.

Once-a-month combined injectable contraceptives currently used or studied are Deladroxate, Lunelle, Cyclofem, Mesigyna and Chinese Injectable No.1. Chinese Injectable No.1 is being used mainly in China; it has good efficacy when doubling the dose in the first month of use.

The most promising once-a-month combined injectable Contraceptives at present are Cyclofem/ Lunelle and Mesigyna. Both preparations are highly efficacious and compare favourably with the efficacy of other available. One major advantage of both these once-a-month injectables is much better cycle control than with the 3-monthly injectable DMPA.

Cycloprovera/Cyclofem, combines 25mg of progestogen MPA and 5mg estrogen ethinyl estradiol cypionate. The Upjohn Company developed Cycloprovera and turned it over to WHO in 1984. Lunelle containing the same combination is marketted by Pharmacia Pharmaceuticals USA and is registered in USA and few other countries and is available in Indonesia and other countries as Cyclofem.

Mesigyna, developed by WHO, combines 50mg NET EN and 5mg estrogen estradiol valerate. Schering AG is handling registration, distribution, and marketing of Mesigyna. Mesigyna is manufactured in Mexico and has been registered in Argentina and Brazil as well as Mexico.

Introductory trials of Cyclofem have been conducted in Chile, Indonesia, Jamaica, Mexico, Thailand and Tunisia and many other countries

It is expected that the addition of a once-a-month combined injectable contraceptive to the existing cafeteria of family planning methods could possibly increase the contraceptive prevalence. However, one disadvantage of the monthly injectable is the need for frequent visits and would also increase the staff work load. If well planned and with proper selection of the users and with good counseling, the introduction of a once-a-month injectable contraceptive should offer another useful family planning option for the couples.

In a WHO comparative multicentric study of Cyclofem and Mesigyna, a total of 2320 women were recruited from 17 centres from Africa, Asia and South America (1108 Cyclofem, 1152 mesigyna). The data from over 1 year Follow up was collected; 10,969 woman months for Cyclofem 10,608 women month for mesigyna.There was no significant difference between the two preparations. There was no pregnancy with Cyclofem and two pregnancies occurred with mesigyna. Discontinuation rate with both the preparations were around 36/100 women users. There was some de.iation from the normal menstrual pattern for both these preparations, eg. 23.3 and 25.2% experienced rregular bleedings with Cyclofem and mesigyna respectively and 13.3 and 11.0% of Cyclofem and mesigyna users experienced prolonged bleedings at 3-6 months of use. Moreover 63% women had acceptable bleeding pattern during the same period. Discontinuation due to bleeding irregularity and amenorrhea has been low in WHO trials; 6.3 and 7.5 % for Cyclofem and mesigyna discontinued due to heavy /prolonged or irregular bleedings and 2.1 & 1.6% discontinued due to amenorrhea at 12 months.

Trials with Cyclofem and Mesigyna have also been carried out in Egypt and China. All the studies indicate that both the preparations were highly effective and there was no significant difference between the two groups.

ICMR carried out a phase III clinical trial with once a month injectable contraceptive Mesigyna v/s two monthly injectable contraceptive NET-OEN 200 mg. The result indicated that the monthly injection was found to be equally efficacious as two monthly injection (pregnancy rate of 1.1/100 users at 1 yr). Although subjects using monthly injections had better bleeding pattern as compared to two monthly injectable but the discontinuations due bleeding related reasons were similar with both the preparations, whereas the WHO trials indicated better continuation rates with monthly injectables.

In order to study the efficacy , side effects and acceptability of monthly injectable contraceptive Lunnele/Cyclofem in our population a clinical trial was conducted through our network of Human Reproduction Research Centres (HRRCs) with the following :

Objectives

- To evaluate the contraceptive efficacy, side effects, continuation rate and the bleeding pattern of one monthly injectable contraceptive.

- To assess women's perception for monthly injectable contraceptive.

- To study the return of fertility after discontinuation of the method .

Methodology

The study was carried out at 15 HRRCs of the ICMR through cafeteria approach. Women attending family planning clinic of the participating HRRCs seeking spacing methods were given balanced presentation of the advantages & disadvantages of the currently available methods in the clinic namely IUD, OC, Condom, Sterilisation (Male & Female) and one monthly injectable contraceptive Lunelle / Cyclofem. Pamphlets in local languages and pictorial charts were used to explain the methods to the women. Special efforts were made to find out whether they have understood the advantages & disadvantages of the methods and help them to make right choice. Women were enrolled in this study who accepted Lunelle / Cyclofem as a method of spacing after Screening for inclusion / exclusion criteria.

All women accepting Lunelle signed an informed "consent form". A thorough systemic and pelvic examination was performed to exclude conditions listed in subject exclusion criteria. Haemoglobin estimation (done by cyanmethhaemoglobin method), urine for albumin and sugar, B.P. and weight was recorded at registration and at three monthly follow-up for a period of one year. Each women was provided with a menstrual diary card to record the bleeding pattern and bring it along with her to the clinic for follow up and for subsequent injections.

Injection Lunelle / Cyclofrm was given within five days of LMP / MTP as deep intramuscular injection in the Deltoid / Gluteal region (gluteal maximus) or anterior thigh. Women were instructed to come for subsequent follow-up and administration of Injection of Lunelle / Cyclofem at one monthly interval (28-30 days) ± 3 days. Women were informed that they would receive 12 injections provided she does not discontinue the method earlier for any reason. All subjects who discontinued the use of Lunelle / Cyclofem and did not opt for any family planning method including conventional methods were followed up for one year for Return of Fertility. Those women who became pregnant (method failure) during the follow up period of the study and continued with the pregnancy were followed until delivery to record the pregnancy outcome. Women who did not wish to continue with the pregnancy were offered medical termination of pregnancy. Special efforts were made to ensure that all women are followed up at home by the Social Worker if they failed to report to the clinic for any reason. To ensure this, the women's address as well as address of near relatives or a friend was clearly recorded at the time of registration so that even if the subject migrated to other place without information to the clinic she could be traced and followed up.

At any point during the trial if the women wanted to discontinue the injections she was allowed to do so. However, efforts were made not only to ascertain the actual reasons for discontinuation but also to provide her with alternative method of contraception (whenever injection was discontinued for reasons other then planning pregnancy).

As expected with combined Injectable Contraceptives bleeding problems are expected to be few. However, some bleeding irregularities are expected in women using these contraceptives. If the women had amenorrhoea of more than 45 days urine pregnancy test (mandatory) was performed to exclude pregnancy and reassure her that she is not pregnant. In case of bleeding irregularities women were examined/reassessed and reassured. She was provided with haematinics if she wished to continue with the method. Women were also provided with "Health Care" cards for all illnesses including those unconnected with monthly injectable contraceptive use so that they are assured of good quality health care

services. This ensured a regular and timely follow-up for subsequent injections and reporting of any side effects or complications during the use of this method.

CRITERIA FOR SUBJECT SELECTION:

Subjects were recruited in this study only if they met the criteria specified below .

Married women exposed to the risk of pregnancy **if they met the following criteria:**

1. Willing to participate in the trial.
2. Age between 20 - 38 years.
3. Has at least one living child.
4. Had not used any long acting hormonal contraceptive for last 6 months.
5. Regular menstrual period (28 ± 7 days).
   a. If interval case, then menstrual cycles of 28 ± 7 days during last 3 months.
   b. If post delivery case who is not lactating, then at least two menstrual periods following delivery with an interval of 28 ± 7 days.
   c. If post MTP, then either concurrent with MTP (first trimester) within 5 days or after one menstrual period within 35 days of MTP. If first period after MTP does not occur within 35 days then wait till normal menstrual period i.e., one cycle of 28 ±7 days.
   d. Lactating women enrolled after 6 months of delivery provided she has at least one menstrual period following delivery.
   e. For those who had discontinued IUD or Oral Pills or any other steroidal hormone at least two menstrual periods i.e., one cycle of 28 ± 7 days after discontinuation.
7. Ability to maintain menstrual diary card.
8. Living within a distance of 10 km. from the HRRC, i.e. accessible for follow-up for home visits.
9. Is judged to be co-operative for clinical assessment and clinic visits on scheduled dates and is agreeable to home visits by Social Worker.

The following were the **contraindications to the use** of Lunelle/Cyclofem injection:

1. **Suspected pregnancy**
2. History of menstrual disorder (s)
3. History of Thromboembolic disorders.

4. Jaundice (during last 6 months) or during any pregnancy.
5. Severe liver disease.
6. Diabetes Mellitus.or any other metabolic disorder
7. Heart disease.
8. Hypertension (systolic> 130 mm/Hg, (diastolic>90 mm/Hg).
9. Tuberculosis / Leprosy.
10. History of allergies (e.g. Asthma, hay fever).
11. Known or suspected malignancy any where.
12. Depression, epilepsy,migraine.
13. On Rifampicin, Phenytoin or Butazolidine.
14. Haemoglobin less than 8 gm %.
15. Cervical Cytology dyspiasia moderate/severe.
16. Known or suspected pregnancy

SAMPLE SIZE

The reported pregnancy rate with Lunelle/Cyclofem is 0.2 to 0.7 per 100 users at one year. To estimate a pregnancy rate of 0.5 per 100 users (with an absolute error of 0.5 per 100 users) the sample size required is 764 cases (α = 0.05).The reported continuation rate is 55 to 80 per 100 women. Assuming a continuation rate of about 65 per 100 users at the end of one year, a sample of 1200 women will be adequate for the study.

Enrolment procedure:

The subject were screened for suitability for inclusion in the study after they volunteered to use Lunelle/Cyclofem after being informed of the nature of the study and after signing the informed Consent Form.

Complete medical history was recorded to ascertain any conditions listed in the exclusion criteria. A full medical and gynaecological examination was performed to ascertain the suitability for inclusion in the study. Blood sample were taken for haemoglobin estimation and urine examination was done for albumin and sugar. A pap smear was also taken at the time of admission and at 6 monthly thereafter.

If the subject was found suitable to enter the study, the monthly injectable contraceptive Lunelle / Cyclofem was given within 5 days of onset of menstrual period taking first day of the menstrual bleeding as day one or concurrent with MTP or within 5 days of MTP. Lunelle / Cyclofem was administered by deep intramuscular injection by a sterilised

disposable syringe following all a septic precautions. If the subject was not menstruating at the time of screening, she was asked to report to the clinic within 5 days of the next menstrual period. The subject was admitted to the study only after administration of the injection and not in advance. The registration record was completed at the time of enrolment.

The study subjects were provided with a menstrual diary card and were explained how to fill it accurately. The subjects were given appointment to report to the clinic at one monthly interval (± 3 days) for the next injection provided she did not require to report earlier for any other reason (unscheduled visit).

Follow-up procedures

Each women was followed up at one monthly interval for a period of 12 months for giving injections and for return of fertility for another period of 12 months, if not using any method of contraception, if women discontinued earlier for any reason she wasl also followed for return of fertility and pregnancy outcome.

Each study subject was examined at the prescribed intervals. At each follow up visit, detaiis were obtained on the subjects menstrual history since her last visit and recorded on the follow up form. Each subject was asked for symptoms or complaints that she can recall since her last visit. For each subject breast examination, systemic examination and pelvic examination was perfrmed after every three months. Blood pressure and weight were also monitored regularly. Haemoglobin was estimated at 6 monthly interval or earlier if clinically indicated.

Cervical cytology was repeated at 6 monthly interval ie. at admission, at 6 mths and at the last injection (11 month) or earlier if clinically indicated.

Non-specific questions were asked, e.g. "How have you been since your last visit" If she volunteers any complaints the same were recorded. Efforts was made to contact women if overdue by more than two days by making home visits by a health visitors/social worker. Vigorous adherence to follow-up dates was done to minimize discontinuations due to " Lost to follow up" and "late for follow-up ". The women were encouraged to report to the clinic on any day in case she has any complaints or side effects.

The filled menstrual diary card was collected and new one provided to record the menstrual data.

A follow-up appointment was given and it was emphasized to come back to the clinic within the stipulated date so as to avoid failure of the method.

Criteria for discontinuation

(i) Discontinuation of a subject:

It is conceivable that Lunelle/ Cyclofem may be discontinued before the prescribed duration due to side effects or method failure. If the subject develops any condition during use listed under contra-indication, she was advised to discontinue the use of Lunelle/Cyclofem and alternative method provided. In addition the subject may request discontinuation for planning pregnancy, switch over to other methods or for any other reason. If woman desired to discontinue no further injections were given to her and the reasons for discontinuation appropriately elicited and recorded in the data recording forms.

(ii) Discontinuation of centre

The center to be discontinued from the study if women who are "late-to-follow-up" or "Lost to follow up "exceed more than 10% in either category .

(iii) Discontinuation of the study

In order to safeguard against an unexpectedly high method failures, the number of women becoming pregnant during the use of Lunelle / Cyclofem was monitored very closely.
The study to be discontinued if the lower limit of 95% confidence interval of cumulative life table pregnancy rate exceeds 3 per 100 users. This was to come into effect only after (a) 100 women have enrolled in the study or (b) 1200 women months of experience has been observed.

ADVERSE REACTIONS - In case of occurrence of any life threatening side effects directly related to the method use, the women were instructed to report to respective HRRC who in turn would report to the ICMR Hqrs, further Lunelle / Cyclofem injection was stopped and the women were appropriately treated and closely monitored.

PREGNANCY - Any suspicion of pregnancy (amenorrhoea more than 6 weeks) it was confirmed by a urinary pregnancy test or ultrasound. If confirmed, the pregnancy report form duly filled was to be sent to ICMR Hqrs by fax or e-mail. Further injections of Lunelle were stopped and woman advised to undergo MTP.

Return of Fertility:

All the women who did not adopt any method of contraception after discontinuation of Lunelle and were exposed to the risk of pregnancy were followed up at three monthly intervals for return of fertility for a period of one year. Women who became pregnant were followed up for outcome of pregnancy.

ETHICAL ASPECTS:

Toxicological studies have shown that monthly injectable has no toxicological risk to the subject. Prior to the initiation of the study, approval has been obtained from the Toxicology Review Panel, the Central Ethics Committee of ICMR and the Drugs Controller General of India. All the participating centres obtained clearance from their local Institutional ethical committees.

Results:

A total of 63784 women attended family planning clinics at 15 HRRCs of the Council, out of these 26856(42.3%) accepted Tubectomy, 116(0.2%) couples opted for the Vasectomy , 25% accepted Condoms, 15.8 accepted IUD, 14.7% accepted Oral pills and monthly injectable Cyclofem was opted by 1330 (2.1%) of total family planning seekers (Table 1).

Table 1 : Relative acceptability

	No of Subjects	%
Tubectomy	26856	42.3
Vasectomy	116	0.2
IUD	10049	15.8
Oral Pills	9358	14.7
Condoms	15865	25
Monthly injectable	1330	2.1
Others	218	0.3

Total acceptors	**63784**	

A total of 1330 women have been enrolled in the study. Mean age of acceptors is 26.0±4.1 years and mean parity of 1.8±1.0. Mean weight and height of acceptors is recorded as 48.2±10.9 kgs and 152.3±17.7cms respectively. 87% of the acceptors are literate and 17.8% are employed (Table 2).

Table 2: Profile of acceptors	
No of acceptors	1330
Mean age (yrs.)	26.0 ± 4.1
Literate (%)	87
Employed(%)	17.8
Mean Parity	1.8_ 1.0
Mean age of youngest child (mths)	27.9 ± 24.1
Mean weight (kgs)	48.2 ± 10.9
Mean Height (cms)	152.3 ± 17.7

These women have been observed for a total of 11518 women months of use. 539 women have completed one year of use i.e. have used 12 injections. The continuation rates at 6, 9 and 12 months are 79.2, 73.9 and 70.3 per 100 users respectively (Table 3).

Table 3 : Continuation rate per 100 users			
	6 months	**9 months**	**12 months**
Continuation rate	79.2 %	73.9 %	70.3 %
Woman months of use	6759	9446	11518
No. of women completed	1056	953	539

Majority of the users discontinued the method due to personnel reasons 4.7, 7.0 and 8.4 at 6, 9 and 12 months of use. In contrast to progestin only methods discontinuation rates due to

menstrual irregularities was very less i.e. 9.2 per 100 users at one year. Discontinuation rate due to ammenorrhoea was 2.2, 2.4 and 2.7 at 6, 9 and 12 months, discontinuation due to heavy and prolonged bleeding were 1.9, 2.1 and 2.7(Table 4).

Table 4 : Net Cumulative discontinuation rate per 100 users			
Pain at injection	0.1 ± 0.1	0.1 ± 0.1	0.1 ± 0.1
Infection of injection site	0.3 ± 0.1	0.3 ± 0.1	0.3 ± 0.1
Involuntary pregnancy	**0.0 ± 0.0**	**0.0 ± 0.0**	**0.0 ± 0.0**
All menstrual reasons	7.1 ± 0.7	8.0 ± 0.8	9.2 ± 0.9
Other medical reasons	2.2 ± 0.4	3.5 ± 0.6	3.7 ± 0.6
Planning Pregnancy	0.7 ± 0.2	0.8 ± 0.3	1.4 ± 0.4
Opting permanent method	0.5 ± 0.2	0.8 ± 0.3	1.1 ± 0.3
Opting for other FP method	0.7 ± 0.3	1.1 ± 0.3	1.7 ± 0.4
Other personal reasons	4.7 ± 0.6	7.0±0.8	8.4 ± 0.9
Late for F.U	2.0+0.4	2.7± 0.5	2.7 ± 0.5
Lost to F.U	0.9± 0.3	1.2±0.3	1.2± 0.3

Menstrual data on 1118 women was analysed and normal bleeding pattern (menstrual cycle of 25 -35 days) was observed in about 38 per cent of acceptors and reduced infrequent bleeding was observed 60 per cent of the women. Infrequent and reduced bleeding did not result in women discontinuing the method. **No method failure has been reported in this study.** Discontinuation rate due to other medical reasons is 2.2, 3.5 and 3.8 at 6, 9 and 12 months(Table 5)

Table 5 : MEDICAL REASONS FOR DISCONTINUATIONS	
Nausea, Giddiness and vomiting	7
High Blood Pressure	6
Rashes and itching	2
Dysmenorrhoea	2
Painful boils present at vulva	1
Weight gain	3
Breast tenderness	3
Atypical Squamous cells in cytology	1

Hair loss	4
Others	23
Total	**52**

Few women (116) discontinued from the study due to personal reasons like transfer to other city (56), husband separated (18), objection from family members (16) and illness of the husband (12) were the major personal reasons for discontinuations (Table 6).

Table 6 : Personal Reasons For Discontinuation	
Husband illness	12
Transfer	56
Husband separated	18
Family objection	16
Religious reason	2
Feel shy for examination	1
Others	11
Total	**116**

33 acceptors could not come to the clinic at the scheduled,time for taking injection due to illness in the family (5 cases), being out of station for social commitments (27 cases) and family problem (1 case) Table 7.

Table 7 : Reasons for Late for follow-up (28 to 33 days)	
Illness in family	5
Out of station	27
Family problem	1
Total	**33**

Return of Fertility

All women discontinuing the use of the monthly contraceptive injection Cyclofem and not using any contraceptive method (exposed to the risk of pregnancy) were followed up for a period of 12 months for return of fertility and outcome of pregnancy. A total of 223 women

were enrolled who have met the above criteria but majority of them accepted another FP method after completion of study period and a total of 23,women were recruited for the return of fertility as they met all the criterion for enrollment ie not using any method of contraception and exposed to the risk of pregnancy. Out of these 23 women , all became pregnant at the end of 12 months(mean 5.5 months) earliest at 1month and the last at 12 months after discontinuation. Out of these 23 pregnancies 21 delivered normal live babies, 1 was a still birth and 1 women opted for termination of pregnancy(8wks).

Vaginal bleeding patterns

The menstrual pattern was analysed using the approach recommended by Rodriguez et al. Analysis has been done on 4 different menstrual bleeding indicators given below:

No of bleeding runs: Number of times the women starts bleeding in a reference period of 90 days. 2- 4 bleeding runs are taken as normal.

No of bleeding days: Gives the total number of days in which the menstrual bleeding occurs in a reference period of 90 days. 6-20 days of bleeding are considered normal.

Average episode length: Gives the number of days after, which the next cycle starts. A period of 22-35 days is considered normal in a reference period of 90 days.

Based on the above-mentioned indicators, another indicator is generated which summarizes the bleeding pattern of a subject in a given reference period.

1. **Frequent/prolonged bleeding:** if a subject has either of the following:
   - Bleeding runs > 5 number
   - Average episode length < 21 days
   - Total bleeding days >20 days
   - Longest bleeding run >10 days
2. **Reduced/infrequent bleeding:** If the subject has none of the above but has either of the following:
   - Bleeding runs 0 – 1
   - Average episode length > 35 days
   - Total bleeding days < 5 days
3. **Acceptable/normal bleeding pattern:** If the subject has none of the above.

Result of analysis of Menstrual Bleeding Pattern:

62.5% of the women using Cyclofem had 2-4 (normal) bleeding runs in the first reference period and increased to 70.3% at the end of 4th reference period (Table5).

54.6% of women had normal number of bleeding days (6-20) in a reference period which increased to 61.7% at the end of 4th reference period. Average episode length (22-35) was

seen in 35.3% of the women at 1st reference period which increased to 46.8% at the end of 4th reference period.(Table-5), the data reveals that only 2.4 % women have frequent / prolonged bleeding in 1 year use of Cyclofem. The majority of the acceptors have either normal bleeding pattern (41.5%) or reduced / infrequent bleeding pattern (56.2%) (Table 5).

Table 5: VAGINAL BLEEDING PATTERNS OF CYCLOFEM USERS

	Number of Reference Periods (each reference period = 90 days)			
PARAMETERS	**1st (3 mths)**	**2nd (6 mths)**	**3rd (9 mths)**	**4th(12 mths)**
No. of Diaries	1136	954	831	507
No. of bleeding runs (%)				
0	13.6	13.3	10.3	11.6
1	21.4	14.8	16.7	16.5
2-4	62.5	70.5	71.6	70.3
5+	2.5	1.4	1.3	1.6
Mean ± SD	2.0 ± 1.3	2.2 ± 1.2	2.2 ± 1.2	2.1 ± 1.2
No. of bleeding days (%)				
0	13.6	13.3	10.3	11.6
1-5	29.8	21.9	25.8	25.9
6-20	54.6	63.3	62.8	61.7
21+	2.0	1.5	1.1	0.8
Mean ± SD	6.9 ± 5.4	7.8 ± 5.3	7.5 ± 4.9	7.2 ± 4.9
Average Episode Length (%)				
1-21	4.8	3.6	2.2	2.0
22-35	35.3	46.9	46.7	46.8
36-63	34.7	23.7	25.0	27.5
64+	25.2	25.9	26.1	23.8
Mean ± SD	63.1 ± 62.7	70.6±76.7	70.4 ±77.8	65.0 ± 73.4
Summaries of Bleeding pattern%				
Frequent/prolong	7.3	5.2	3.4	2.4
Normal (Acceptable pattern)	29.4	42.3	41.6	41.5
Reduced/ infrequent	63.3	52.4	55.0	56.2

Discussion :

Combined injectable contraceptives containing both progesterone and Oesterogens were developed to overcome menstrual irregularities which was commonly seen with progesterone only contraceptives**(1)**. Two very popular combined preparations Mesigyna and Cyclofem have been clinically evaluated and programme introductive studies have already been undertaken in different parts of the word including Latin America. Another popular monthly injectable contraceptive Chinese No. 1 is very popular in China. Combined once-a-month injectables contain a synthetic oestrogen in addition to protestogen. This allows them to keep the contraceptive effect of progestogen together with the added benefit of oestrogen to provide bleeding simulating regular menstrual bleeding. Different combined once-a – month injectable contraceptive formulations have been evaluated and used over the last four decades. In China and neighbouring countries, the so-called injectable No. 1 has been developed,is made up of 17 α hydroxyprogesterone caproate and estradiol valerate, and this has been used by approximately 1 million women throughout the world **(2)**. Deladroxate, an injectable formulation made up of dihydroxyprogesterone acetophenide and estradiol enanthate, has been used for years in Latin America **(3,4)**, It is known in different countries under the names of Perlutal, Unalmes or Agurin. Two new combined once-a-month injectable contraceptives have been studied by the WHO and others during the last 20-30 years, namely Cyclofem (previously known as Cycloprovera) and Mesigyna (registered in some countries as Norigynon). Safety and efficacy studies for Cyclofem began in 1968 and the first clinical trials with Mesigyna started in 1974. Subsequent introductory studies of these two combined injectable contraceptives, carried out in different countries, confirmed the results of the clinical trials and supported their commercialization. Cyclofem and Mesigyna have demonstrated benefits and advantages compared with other once-a-month injectables, as indicated by the multicentre studies carried out by the WHO, and they are currently being accepted by an ever-increasing number of countries as a good and effective contraceptive option for women opting for spacing methods **(3,5,6)**

Once-a-month combined injectables

1. Cyclofem / Cycloprovea : 25 mg. medroxyproges terone acetate and 5mg estradiol cipionate.
2. Mesigyna / Norigynon : 50 mg NET-EN and 5 mg. estradiol valerate.

Both preparations are administered by deep intramuscular injection. The first dose is administered during the first 5 days of menstrual bleeding and thereafter every 30 days, plus or minus 3 days. None of the Cyclofem and Mesigyna studies have found them to induce any adverse or clinically relevant metabolic changes. Once-a-month combined estrogen and progestogen injectables do not cause any significant delay in return to ovulation.

Use in the post partum period

Progestogen only injectables have not shown any adverse effects on lactation with regard to quality of the milk, duration of lactation and infant growth**(7,8,9,10)**. However, the progestogen is present in maternal milk in the same concentration as in maternal plasma. DMPA reaches concentrations of 10 ng/ml in the first week after its administration, decreasing to 0.5 ng/ml in the third month. The concentrations of NET-EN in maternal milk are lower than those of medroxyprogesterone because of the 19 nor derivatives which are less soluble in milk. The estimated daily progestogen dose ingested by the infants of mothers using progestogen only injectable contraceptives is 0.3-10 microgram DMPA and 0.5-2.4 microgram NET-EN. These amounts have been estimated by taking the concentrations in maternal milk and assuming that the infant ingests 600-700 ml. milk a day **(11,12)**. No health problems were found in children whose mothers had used these methods, but the possible long term effects on neuroendocrine mechanisms regulating the reproductive process are not yet fully understood. More studies and long term follow up are required to answer this questions ..

Oestrogen containing once a month combined injectables would behave in the same way as the oral combined contraceptive pill and are therefore not recommended during this period due to their possible adverse effects on the duration of lactation and infant growth.**(13,14)**

WHO accelerated the development of Cyclofem for use in developing countries in response to request from India, Mexico, and other countries in the 1970s for a safe and effective monthly injectable **(1)**. Today Cyclofem is available in 18 countries, mostly in Latin America and Asia **(31)**.

While even the newer combind injectables have been on the market for years, they have become more widely known and used in recent years because new safety and effectiveness data have become available. The US FDA has approved Lunelle, although it is currently not available in the US **(31)**. It delivers 25 mg of MPA and 5 mg estradiol cypionate.

The following discussion focuses on the newer combined injectables: Cyclofem® (also known as Lunelle®, Lunella®, Cyclo-Provera®, Novafem®). Combined injectables have been studied since the 1960s, and several formations have been used in some countries for the past two decades. Older combined injectable formulations that are still in use include Chinese Injectable No. 1 (also known as Gravibinon®) and deladroxate (available in Latin America under various trade names, including Pelutal®, Patectro, and Topasel®) **(1,5)**.

In order to study the efficacy, side effect and acceptability, the Council initiated a Phase – III Clinical Trial in 15 HRRCs located in the dept of Obs/Gynae of the medical colleges in different parts of the country from 2001-2005

Efficacy

Both progestogen only injectables and once a month combined injectables are highly effective, with pregnancy rates between 0.1 and 0.4 after 12 months **(5,15,16)**. The efficacy of the injectable methods depends on the timing of the first injection, adherence to the schedule and on the injection technique. A study carried out in Thailand shows that delaying the first injection from the fifth to the eighth day of the cycle, increases the pregnancy rate from 0.16 to 0.62 after 3 months of use **(17)**. The maximum delay for the next DMPA injection should not exceed 2 weeks, 1 week for NET-EN and 3 days for the once a month injectables. In a programme introductive study done in Mexico on 3,457 women and observed for 20,316 women months of use found only one pregnancy (rate 0.03%) **(18)**. This is comparable to what we observed in our study , no pregnancies have been reported shows that the method is highly efficacious. In a systematic review by the World Health Organisation of the once a month injectable contraceptives found the life table pregnancy rates in 5 Phase-III Clinical Trials in which 9,793 women were observed for a total of 102,058 women months of use were 0.2% for Cyclofem and 0.4% for Mesigyna **(19)**. In a review by Koetsawang have found that monthly injectables to be very effective for preventing pregnancy(0.23 /100 women years of use).**(16)** In an open label, non-randomised, parallel, controlled study compared the efficacy of Lunelle and Orthonovem oral contraceptives conducted in the USA found no pregnancies in Lunelle users as compared to 1 pregnancy reported in the Oral Contraceptive users.**(20)** In a large multicentre WHO sponsored introductory study of Cyclofem in Indonesia, Jamaica, Mexico, Thailand and Tunisia revealed it to be highly efficacious with 12 months pregnancy rates ranging from 0 to 0.7% **(21)**. In a review by Peter Hall and others of WHO reported Cyclofem to be highly efficacious in preventing pregnancies.**(22)** Another WHO sponsored Phase-III Clinical Trial with Cyclofem in which 2,328 women were observed for a total of 10,969 women months of use found no pregnancies as compared to cumulative life table pregnancy rate at 12 months of 0.18 per 100 users with a combination of norethistrone enantate, 50mg and estradiol valerate 5 mg.**(23)** In a comparative Phase-III Clinical Trial of 2 injectable contraceptives DMPA and Cyclofem in 600 Vietnamese women randomized revealed no pregnancy during the study period.**(24)** In a large multicentre comparative clinical trial of Mesigyna, Cyclofem and injectable No. 1 in Chinese women showed that out

of 990 women who used Cyclofem, the life table pregnancy rates were 0 as compared to 0.4% with Mesigyna and 0.77% with injectable No. 1 showing very high relative efficacy in women using Cyclofem.**(25)**

Acceptability

In a programme introductory study conducted with Cyclofem in Mexico in which 3457 healthy women participated (645 women from rural area and 2817 women from urban and suburban areas) were observed for a total of 20316 women months of use over a period of one year. The overall continuation rate was 36.6% in rural areas and 23.7 % in urban and suburban areas. The most common reason for discontinuation was loss to follow up as the women had changed their address and shifted to new places.**(18)** In our study the continuation rates was observed to be 79 per 100 users at six months and 70 per 100 users at the end of one year, which indicates a very high acceptability of the method in the teaching hospitals where good motivation and counseling skills are available through the trained research staff.

Another study on acceptability conducted in Cairo (Egypt) between Nov. 89 to July 92 on 1091 women using Cyclofem and Mesigyna. The overall continuation rates was more than 60% with the range of 45 to 87 in different locations. The logistic regression analysis showed that the most important determinant of discontinuation was service dissatisfaction, the others being desire for pregnancy and other personal reasons. **(26)**

A programme introductory study conducted in Indonesia between March 90 and Feb 92 showed a life time continuation rate of 80 and 66 percents at the end of 6 month and one year respectively. Personal reasons accounted for most discontinuations followed by desire for pregnancy and loss to follow up. **(27)**

In a study conducted in Egypt on a sample of continuous and discontinuous of monthly injectable contraceptive Cyclofem and Mesigyna as well as with the providing physicians. Providing dedicated staff and counseling were crucial to the success of clinical trial. The most satisfied users were those who had tolerated well the oral contraceptives but had difficulty in daily compliance.**(26)**

Side effect of injectable contraceptives

Irregular bleeding

Irregular bleeding is the main side effect of progestogen only contraceptive methods. The initial use of injectables may cause irregular unpredictable bleeding,, with or without intermittent spotting. Only 10% of women who use DMPA report normal cycles during the

first year of use. Irregular bleeding is usual during the first 6 months, followed by delayed bleeding and / or amenorrhoea in the months thereafter.

Menstrual irregularities with NET-EN are similar but of a lower intensity. The rate of discontinuation after 1 year is estimated at 15% due to irregular bleeding and 12% due to amenorrhoea, but these figures vary considerably from one area to another.**(5,15,25)**

Once a month combined injectables

There are no major differences between the bleeding patterns of cyclofem and mesigyna users. During 10-15 days after the first injection, most women have a bleeding pattern similar to menstrual bleeding and then they will bleed very 30 days in a regular manner, differentiating once a month combined injectables from progestogen only injectables. During the first 3-6 months of use, only 25% of women experience some form of irregular bleeding and 12% develop prolonged bleeding. The discontinuation rate due to irregular bleeding is between 5 and 12% per year. **(5,28)**

The most common side effects observed with Injectable contraceptives are menstrual irregularities which includes irregular and prolonged bleeding, heavy bleeding and in frequent bleeding. The idea of adding oestrogen is to reduce these side effects and make them more acceptable to women. In a large multicentre study by WHO in collaboration with Family Planning Research Institute and Academy of Medical Science in China, 41.4% of the women using Cyclofem had bleeding patterns similar to their untreated pattern in first 90 days of observation as compared to 63.7% of mesigyna user and 60.6% using injectable No. 1. This percentage increased to 67.8, 82.2 & 75.0 in the forth reference period of 90 days.**(2)**

Between October 1988 and July 1990, a randomized multicentered Phase III Clinical Trial was conducted in three provinces of China to compare three monthly injectable contraceptives (Mesigyna, Cyclofem and injectable No. 1. A detailed analysis of the menstrual diaries of 5098 women aged 18-35 years compared the vaginal bleeding patterns associated with the injectables. Women in all three groups experienced more bleeding/spotting days, more bleeding episodes, shorter bleeding free intervals, and larger variability during the first 90 days than during the following three 90-day periods. 90% of Cyclofem users had 1-4 B/S episodes. 90% of Mesigyna users had 2-4.2 B/S episodes. Cyclofem users had more spotting days than did Mesigyna users in each 90 day period. Acceptable bleeding patterns predominated, on the most part in all four periods. Acceptability increased with each 90 day period for all three injectables. Acceptability of

bleeding patterns was much higher among Mesigyna users than Cyclofem users. Prolonged bleeding, followed by irregular bleeding and frequent bleeding, were the most common bleeding disturbances. Irregular bleeding decreased with time. 79.1% of Mesigyna and Cyclofem users who finished the study had an acceptable pattern. 70.7% of women who stopped for non-bleeding reasons had an acceptable pattern compared to 31.3% of those who stopped for bleeding reasons. These findings show that Mesigyna users experienced better cycle control and more acceptable bleeding patterns than did the users of the other two injectables. **(2)**

In our study 62.5% of the women using Cyclofem had 2-4 (normal) bleeding runs in the first reference period and increased to 70.3% at the end of 4th reference period (Table5).

54.6% of women had normal number of bleeding days (6-20) in a reference period which increased to 61.7% at the end of 4th reference period. Average episode length (22-35) was seen in 35.3% of the women at 1st reference period which increased to 46.8% at the end of 4th reference period.(Table-5), the data reveals that only 2.4 % women have frequent / prolonged bleeding in 1 year use of Cyclofem. The majority of the acceptors have either normal bleeding pattern (41.5%) or reduced / infrequent bleeding pattern (56.2%) . The menstrual pattern in majority of the users indicates a shift towards normal bleeding pattern from frequent and reduced / infrequent bleeding pattern.

In our study the other common reason apart from menstrual reasons was, other personal reasons like transfer to another place, objection from husband/other family members etc. which rose from 4.7 per 100 user at six month rose to 8.4 per 100 user at one year. These rates are comparable to studies conducted elsewhere. Other predominat reson was late for follow up to get their monthly supply of injectable. This rate increased from 2 per 100 user at 6 month to 2.7 at the end of one year.

Most of the side effects associated with the use of progestogen only injectables are subjective and difficult to quantify. Some users gain weight during the first year of use and some may subsequently continue to gain weight at the same rate [7-8]. **(15,25)** Between 3 and 19% of users report headaches or dizziness, a percentage similar to that seen in the general population; few women discontinue this method for these reasons.

Side effects are less common than those reported with progestogen only injectables and are similar to those reported by the users of combined pills: headaches, dizziness, mastalgia, changes in body weight, etc. **(29)**

Medical reasons like Nausea, Vomitting, High Blood pressure, weight gain, breast tenderness observed in a total of 52 cases i.e an acceptable number and none of these side

effects were serious or life threatening and were transitory. These rates are comparable to other studies in which it was found to be decreasing with increased duration of use.

Return of Fertility

After discontinuation of progestogen only injectbales, there is generally a delay in the return to fertility in comparison with combined pill or with non-hormonal methods. The extent of this delay varies between different regions, communities and women. After discontinuing use of DMPA 50% of women became pregnant in the 9 months following the last injection. After discontinuing once a month combined injectables, ovarian function recovers quickly 39% of women ovulated within the first 3 months and 78% within 6 months after discontinuing the method. The return to fertility is considerably shorter with these injectables, most women becoming pregnant during the first 6 months after discontinuing the use of injection. **(2,7,8,13,30)**

In the present study a total of 23 women were recruited for the return of fertility as they met all the criterion for enrollment ie not using any method of contraception and exposed to the risk of pregnancy. Out of these 23 women , all became pregnant at the end of 12 months(mean 5.5 months) earliest at 1month and the last at 12 months after discontinuation. Out of these 23 pregnancies, 21 delivered normal live babies, 1 had a still birth and 1 women opted for termination of pregnancy (8wks).

Service delivery issues play an important role in acceptability and continuations/discontinuations. The family planning programs which have responsive service delivery and good quality of care in contraceptive service delivery have managed to motivate women in accepting and continuing with method. Changes are needed in techniques and content of counseling and information provision, technical provision of care, training of staff, supervision, record keeping, logistics and supplies and the support from the program and policies. Research is required in service delivery of the injectable contraceptives to assess managerial requirements/adaptations that would be required if these are to be introduced on a large scale especially in the public sector. There are issues of accessibility and availability of these contraceptives as the women will have to leave the family and work to go to a facility to get injections on a regular basis

Conclusions

The results of the study indicate that the method is highly efficacious as no pregnancy is reported in the study and the method is acceptable method of contraception for women desiring spacing (continuation rate 70.3%) at the end of 1 year. The menstrual bleeding

pattern is not very significantly disrupted and women experience near normal menstrual cycles.

As the present study was conducted at teaching hospital in which trained staff and researchers conducted the study, the continuation rates may not be replicable at other service delivery systems. The data on return of fertility is not enough to make conclusive inferences although the studies conducted elsewhere have shown that most women would become pregnant within first six months after discontinuing the method. In order to validate the results of the present study and to study other logistics and supplies, training requirements, follow up needs and mechanisms it is imperative that a pre- program introductory study is carried out at the post partum (B&C) centres,community health and primary health centres through the existing health care delivery system.

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Supply Meets Demand With Forecasting and Ingenuity

"No product, no program," say logistics professionals (53). Increasing demand for injectables challenges programs to maintain a steady flow of supplies and to respond quickly as more clients ask for injectables. Maintaining a continuous supply of injectables—vials of the contraceptive, needles, syringes, and sharps containers for disposal of used equipment—requires adequate supplies at the warehouse and a well-run logistics system to distribute supplies to clinics and other service delivery locations (see *Population Reports*, "Family Planning Logistics: Strengthening the Supply Chain," Series J, No. 51, Winter 2002).

Forecasting Maintains a Steady and Sufficient Flow of Injectables

Forecasts of demand for injectables enable programs to place accurate and timely orders to manufacturers, donors, or procurement agents. With demand rising, accurate forecasting is especially important. The most accurate forecasts use several types of information. These include expected increases in use of injectables (for example, as a result of a communication campaign), past trends in use, numbers of new and returning clients, and changes in population due to migration. Forecasting needs to be done at least once a year and adjusted every six months based on actual use. Stock levels and trends in use of injectables should be reviewed every month at service sites and additional orders placed to maintain supplies (53). Many countries have computerized logistics management information systems at the central warehouse to help with forecasting (85, *94*) (for forecasting tools, see Table 3, p. 22).

With demand for injectables rising, accurate forecasting is especially important.

Forecasting several years into the future alerts programs to potential shortfalls and helps governments and donors plan procurements. For example, the Kenya Ministry of Health (MOH) projects that the share of injectables in the contraceptive method mix will increase from 40% in 2002 to 50% in 2010. In 2003 the MOH's reproductive health advisory board projected a shortfall of injectables beginning in mid-2004 and recommended that the MOH seek more funds from the government and donors (158). As a result of the forecasting, the government for the first time allocated funds in the budget specifically for injectables and covered part of the shortfall. Also, a donor agreed to provide funding for injectables and the MOH ordered injectables from UNFPA (97).

Choosing which injectables to offer. Programs forecast demand for each type of injectable that they offer. A number of organizations involved in international family planning suggest carrying one or at most two injectables (*142*). Carrying multiple injectables complicates forecasting, distribution of supplies, training, and service delivery. Differing injection schedules can confuse providers and clients (*18, 156*). To avoid confusion IPPF recommends that programs offer one progestin-only injectable and, if available, one combined injectable (84).

Some programs offer DMPA and NET-EN because donors supply them or clients ask for both (*121, 156, 177*). The two injectables differ in several ways. NET-EN requires more frequent injections than DMPA, which increases costs (*177*). Injections of NET-EN may be more painful because, in contrast to the water-based DMPA, NET-EN is oil-based and a larger-gauge needle is appropriate. NET-EN can be injected with a narrower needle, but the injection takes longer to administer and, as a result, may also be painful (*175*, 176).

At times, switching a client's injectable may be necessary due to supply shortages. Switching injectables is safe and does not decrease effectiveness. Switching clients routinely between injectables is not recommended, however (*215*). When clients switch to a different injectable, the schedule for repeat injections changes and side effects may change. Such changes led some women in Nepal to stop using injectables, a country assessment has reported (*156*).

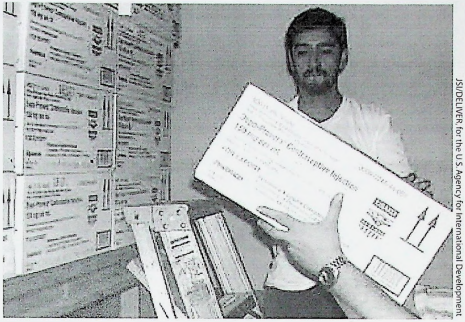
Cooperation and Conservation Meet Unexpected Demand

Logistics managers can plan their response to unexpected demand for injectables. When supplies run low, managers can:

- **Order an emergency shipment.** USAID-funded programs can order emergency shipments of DMPA through the USAID Mission in their country to help prevent stockouts (21). UNFPA's Global Contraceptive Commodity Program stores injectables and other contraceptives with their suppliers to facilitate fast shipment in the case of stockouts and emergencies such as earthquakes or wars. The normal, non-emergency lead time for ordering injectables from UNFPA is 10 weeks (91, *197*) (see Table 3, p. 22).
- **Borrow supplies.** When delayed shipments of contraceptives led to stockouts at a health care facility in Kenya, staff borrowed contraceptives from a nearby district hospital and other facilities. This was one reason that this facility was identified as one of 13 high-performing facilities in Kenya (157).

- **Mobilize suppliers, volunteers, and shippers.** When stockouts of contraceptives plagued the national family planning program in Nepal in 1993, the Ministry of Health and UNFPA organized 75 graduate students to pack contraceptives and other supplies for maternal and child health. UNFPA supplied DMPA through its commodity distribution program (29). A private shipping company delivered the packages by road, air, and porter, and within 60 days every health facility in Nepal's 75 health districts had reproductive health supplies (196).

- **Share clients.** If a facility or program is running out of injectables, it can encourage clients to go to other sources for their injections and save its own supplies for those with no other source of supply. Public and private providers can work together to provide injectables when either has a stockout. Providers should be able to give clients directions to other sources of injectables.



JSI/DELIVER for the U.S. Agency for International Development

An inspector at the central warehouse of the Ministry of Health in El Salvador checks that injectables are stored properly to avoid wastage. DMPA must be stored upright so that any precipitate collects on the bottom of the vial and can be completely dissolved with gentle shaking. If a vial is used with sediment on the bottom, the injection may not be effective for three months.

- **Avoid losses** due to passed expiration dates and ruined stock. The First-to-Expire First-Out (FEFO) method—using supplies with the earliest expiry date first—helps to avoid loss through expiration. The shelf-life of progestin-only injectables is three to five years, and of combined injectables, at least three years (*45*, 98). Injectables should be stored between 20° and 25°C (68° and 77°F) away from direct sunlight and protected from freezing. Changes in temperature can affect the size and solubility of particles in DMPA and the combined injectable *Cyclofem*. Usually, any sediment at the bottom of a vial dissolves with gentle shaking. If sediment does not dissolve or has collected into a solid mass, perhaps because of low temperatures in the storage area, the vial should be thrown away (92). Injectables should be stored upright so that any sediment settles on the bottom of the vial and can be dissolved again by shaking. Heat can decrease the effectiveness of NET-EN without changing its odor or appearance. Stock that has been exposed to high heat, such as fire, should be thrown away (127).

If injectables are out of stock, providers typically give clients their second or third choice of contraceptive, or they may give them oral contraceptives and ask them to return in a month or more (61). Clients are more likely to stop using a contraceptive that is not the one they wanted, however (132). Faced with rising demand for injectables, programs and providers need to look for ways of supplying clients with their first choice.

Training to Meet Demand

As demand for injectables increases, programs need more health care workers who can provide injectables. Staffing decisions and training content depend on a program's specific needs. An assessment in advance can help to determine who most needs training and in what (110, 136).

Method Introduction or New Providers May Require Comprehensive Training

Comprehensive training to provide injectables may be needed if a program is adding injectables as a new method or if a program already offers injectables but is training new health care workers to provide them. Depending on providers' skill levels and on program needs, comprehensive training on injectables may include:

- Characteristics of injectable contraceptives and the importance of returning on time for the next injection,
- Giving injections using the universal precautions (see p. 8),
- Counseling clients, with emphasis on bleeding changes,
- Screening clients using the Medical Eligibility Criteria (see the *Checklist for Screening Clients Who Want to Initiate DMPA (or NET-EN)* in the companion issue of *INFO Reports*),

Give Injections and Dispose of Waste Safely

Illustration: Rafael Avila/CCP

As more providers give injectable contraceptives to more clients, injection safety remains crucial (208). The spread of infection from clients to other clients, health care providers, and the community can be avoided by:

- Ensuring an adequate continual supply of disposable injection equipment and sharps containers for safe disposal of needles and syringes,
- Following safe injection practices and universal precautions for infection prevention, and
- Establishing a safe waste management procedure.

Safety guidelines for contraceptive injections are the same guidelines that apply to all medical injections.

WHO defines a safe injection as one that does not harm the recipient, does not expose the provider to any avoidable risk, and does not result in waste that is dangerous to people (*209*). Of the 16 billion injections given for all purposes in developing countries each year, nearly two in every five are thought to be unsafe (*81*). WHO estimates that each year unsafe medical injections cause an estimated 21 million hepatitis B infections, 2 million hepatitis C infections, and 260,000 HIV infections (71). Every year these infections result in an estimated 1.3 million early deaths, 20 years of life lost per person, and US$535 million in medical costs (115). Injections remain an important delivery method for curative and preventive purposes, so improving injection safety is necessary.

In 2005 contraceptive injections accounted for an estimated 1% of all injections. No statistics are available on the percentage of contraceptive injections that are thought to be unsafe.

Auto-Disable Syringes Now Preferred

In the past it was common practice to use, sterilize, and reuse sterilizable injection equipment. More recently, single-use syringes, if disposed of as intended, have eliminated risk of client-to-client transmission of infection. The latest development is disposable auto-disable (AD) syringes. Unlike conventional disposable syringes, the AD syringe cannot be reused because it inactivates after a single use. Depending on the design, either the needle retracts or the plunger breaks or locks (149). WHO recommends AD syringes for all immunizations and recommends disposable syringes—ideally AD syringes—for all other medical injections, including contraceptive injections (*210, 223*). Purchased in bulk, AD syringes cost approximately US$0.06 each, about $0.02 apiece more than conventional disposable syringes (150, 195). USAID began including the AD syringes with all shipments of DMPA in 2002 (95, *128*).

A safe injection is one that does not harm the recipient, does not expose the provider to any unavoidable risk, and does not result in waste that is dangerous to people.

Sterilizable needles and syringes should be considered only when disposable injection equipment is not available and if programs can ensure that sterilization conforms to WHO guidelines. Sterilization of reusable syringes and needles requires heating to 121°C (250°F) in high-pressure steam for at least 20 minutes (14, 206).

Universal Precautions Prevent Infection Transmission

Safe injections require not only the proper equipment but also that providers understand and follow the universal precautions for infection control and best practices for injections (160). Developed in 1987 by the U.S. Centers for Disease Control and Prevention, universal precautions are a simple set of practices designed to protect health care workers and their clients from infection in health care settings. Under the universal precautions principle, health care workers assume that all blood and body fluids are infectious, regardless of actual infectiousness (*192*, 218).

Rules for injections include:

- Prepare each injection in a clean designated area where contamination from blood or body fluid is unlikely.
- Wash hands with soap and water before and after giving an injection, if possible. Gloves are not needed unless there is a chance of direct contact with blood and other body fluids.
- Use a sterile syringe and needle for each injection. Use an AD syringe, if possible. If only sterilizable equipment is available, sterilize according to WHO guidelines.
- Discard used disposable needles and syringes in sharps containers immediately after use. Do not recap used needles.
- Safely dispose of sharps waste according to local or regional environmental regulations (*80*, 211, 218).

Proper Waste Disposal Keeps Clients, Staff, and Communities Safe

Disposable injectable equipment can generate a large amount of waste. Programs offering injectable contraceptives must have a

procedure in place for collecting, storing, transporting, and disposing of sharps waste (*207*).

Used disposable needles and syringes should be placed in a sharps container immediately after use to prevent needlestick injuries and access to used needles. When a sharps container is three-fourths full, it should be destroyed. Overfilling the container can lead to needlestick injuries. WHO-approved sharps containers distributed by USAID are designed to hold 100 syringes (*45*). Donors promote injection safety by "bundling"—that is, shipping matching quantities of sharps containers with vials of contraceptive injectables and AD syringes.

Methods for destroying sharps containers and their contents include burial, burning, and incineration (burning at high temperature) (*128*). Unfortunately, there are no easy nonpolluting methods for destroying used injection equipment. Programs should choose the method that is most appropriate for their local conditions, taking into account cost, safety risks, and local and national environmental regulations (*207*, 213, *217*).

Burying sharps waste in a protected pit at least two meters deep is a simple and inexpensive method of disposal. Some programs build special pits for sharps waste near the clinic. Pits must be fenced to prevent community members and scavengers from entering. Encapsulation—sealing sharps containers with concrete or other substances before burial—can ensure that buried waste is not unearthed.

Incineration, at temperatures above 800°C (1472°F), minimizes the volume of waste and reduces the pollutants produced. It requires special equipment and fuel, such as propane or natural gas. Programs with on-site incinerators should position incinerators in a convenient outdoor location, away from crops and homes, and far enough away so that smoke does not blow into the facility. Where an incinerator is not available on site, some programs transport waste to a central health facility or use incinerators at other facilities, such as cement factories (*151*).

Burning sharps waste in a metal container or a protected hearth at low temperatures is a commonly used option. Fuel such as kerosene is added to the container, and the waste is burned until the fire goes out. After burning, the ash and noncombustible material are buried in a protected pit at least one meter deep. This method is relatively inexpensive and can reduce the weight and volume of waste (*151*). Burning should be done only when no other options are available since it produces harmful substances. Some countries have banned this method of waste disposal.

Illustration: *Immediately after giving the injection and without recapping the needle, a provider deposits the used syringe and needle in a conveniently located sharps disposal container. Safely disposing of used injection equipment prevents accidental needlesticks, which can lead to infection.*

- Counteracting myths and correcting misperceptions,
- Conducting return visits and ensuring continuity of care (see forthcoming *Population Reports*, "Developing a Continuing Client Strategy"), and
- Managing side effects.

The time needed for training depends on the amount of content, the initial skill level of trainees, program needs, and policy requirements. The Pathfinder International DMPA Training Module (see Table 3, p. 22) covers characteristics of DMPA, counseling, giving the injection, conducting return visits, and managing side effects. The module is designed for trainees to practice and demonstrate competence in each skill. It requires about 16 hours to complete (*181*). In contrast, in a pilot community distribution program in Uganda (see p. 12), community providers who had been providing oral contraceptives and condoms received comprehensive injectables training that included one week of classroom sessions and two weeks in hospitals and health centers (123, *183*).

Focused Training Meets Specific Needs

To meet demand quickly, programs may consider training current staff members, such as assistant or auxiliary workers, to give only routine repeat injections. This would free doctors and nurses to handle special needs (see box, p. 10). A short training course for providing repeat injections might focus on the first three topics listed on page 7: characteristics of injectables, giving safe injections, and counseling.

Any health care provider who is appropriately trained can give injections safely.

Focused training also can be used to address a specific component of service delivery that needs strengthening, such as counseling. For example, when Vietnam was scaling up the provision of DMPA in 1999, an assessment of an earlier pilot project found that client visits typically involved little counseling and that providers and program managers believed that a woman's choice about contraceptives was best made by the provider. As a result of this finding, providers received focused training in providing balanced information, listening to clients' concerns, and offering individually tailored guidance. This training improved counseling and helped women make an informed choice of DMPA and other contraceptives (224).

Refresher training maintains skills. Regular retraining can help maintain safe injection practices and maintain good quality of care generally (218). For example, in a 2005 survey of 526 nurses and midwives in Uganda, the reported frequency of needlestick injuries was lower among those who had attended safe injection training in their workplace than among those who had not had workplace training (129).

Depending on program needs, refresher training may be offered one or two times per year (74). Retraining also may address clinic staff other than providers, such as waste handlers (*93*).

Competency-Based Training Works Best

Training that develops the skills, knowledge, and attitudes required to meet standards—known as competency-based training—has proved more effective than conventional training approaches, in which trainees may have little opportunity to practice skills (185). With this approach, training continues until each trainee is competent to provide injectables. The training uses techniques such as role playing, discussion, use of job aids, and simulation (93). Vietnam used the competency-based approach to training when scaling up DMPA services in 1999 (224).

Supportive Supervision Can Encourage Good-Quality Services

Supportive supervisors are those who meet the needs of the staff they supervise, thus enabling providers to perform well and meet the needs of their clients (47). By giving constructive performance feedback, supportive supervisors can help staff correctly follow injection guidelines, improve their performance, identify operational barriers, and maintain standards (189). Ongoing supportive supervision is particularly important when programs increase the number of providers giving injections.

Program managers and providers together can use the Standards-Based Management and Recognition (SBM-R) approach to help improve performance and the quality of services (*24, 125*) (see Table 3, p. 22). In this approach supervisors and staff work together to define standards for service and performance, and they determine how to meet those standards. For example, if a supervisor sees that injection safety practices need improvement, SBM-R can guide the supervisor and provider in (1) setting performance standards for safe injections that detail *what* to do and *how* to do it; (2) identifying steps needed to meet the standards (such as refresher training in safe injection practices or acquiring more equipment and supplies); (3) measuring progress; and (4) motivating the providers to achieve objectives by offering incentives and recognizing achievements. Supervisors can use the "Checklist for Giving Intramuscular Contraceptive Injections" to ensure that providers are following the appropriate steps (see the companion issue of *INFO Reports*, "Injectable Contraceptives: Tools for Providers," p. 2).

Ongoing supportive supervision is particularly important when programs increase the number of providers giving injections.

With Training, a Range of Providers Can Give Contraceptive Injections

Service delivery guidelines in some countries restrict who can give injections. They limit provision to doctors and nurses. Studies show, however, that many types of health care providers can give injections if they are appropriately trained (36, 66, *183, 200*). Such providers include pharmacists, auxiliary nurses, midwives, medical assistants, community health workers, and others who have been specifically trained to provide family planning, as well as those who have general medical education. Training a wider range of providers to give injections safely can expand access to injectables, reduce unsafe unauthorized injections, and save programs money.

In some cases, particularly when scaling up pilot programs, allowing certain groups of providers to give injectables may require changes in national policy. For example, in Honduras service delivery guidelines did not authorize auxiliary nurses to provide DMPA until 1999. Because an auxiliary nurse is often the only provider at a rural health center, women in rural areas who wanted injectables could not obtain the method easily. When a 1997–98 study demonstrated that auxiliary nurses could provide these services safely and cost-effectively, the Ministry of Health changed the service delivery guidelines (*200*). As a result, use of injectables increased 19% after three months in clinics where auxiliary nurses began offering injectables, and 35% in clinics where the auxiliary nurses offered injectables and also promoted the new services to clients and the community (112).

Formally training those who may be giving unregulated injections is another way to increase safe access to injectables. For example, a 2003 study in Egypt found that women frequently seek injections, both contraceptive and therapeutic, from informal providers, or "health barbers" (187). Because they often charge less than the cost of a new needle and syringe, it is likely that these providers reuse injection equipment. In this situation, changing guidelines to allow such providers to provide injections, training them appropriately, and supplying them with single-use injection equipment could reduce the potential for unsafe injections (86).

Checklist for Good-Quality Injectables Services

Family planning program managers can use this checklist to help ensure that programs are providing good-quality injectables services.

Clinics have adequate supplies

- ❑ Sufficient single-dose vials are available.
- ❑ Sufficient sterile syringes and needles are available. Use disposable syringes, ideally auto-disable (AD) syringes, if possible. If only reusable equipment is available, sterilize according to WHO recommendations (heating to 121°C (250°F) in high-pressure steam for at least 20 minutes).
- ❑ Sufficient sharps containers are available for disposal of used needles and syringes.
- ❑ Injectables are properly stored, upright and away from direct sunlight at 20–25°C (68–77°F).
- ❑ The oldest stock of injectables is used first.
  Tip: Establish a First-to-Expire/First-Out (FEFO) policy (see *Pocket Guide to Managing Contraceptive Supplies**).
- ❑ Timely supply orders are submitted.
  Tip: Use *PipeLine Software* to assist with forecasting, pipeline management, and procurement planning.*
- ❑ A clean space is designated for preparing and giving injections, with a sharps container nearby.

Providers safely give injections and manage waste properly

- ❑ Providers screen clients for medical eligibility.
  Tip: For screening, use the *Checklist for Screening Clients Who Want to Initiate DMPA (or NET-EN)* in the companion issue of *INFO Reports*.
- ❑ Providers counsel clients, with particular emphasis on side effects and how to manage them.
- ❑ Job descriptions define who:
  - Oversees logistics, equipment, and supplies
  - Counsels clients
  - Provides injections
  - Manages waste
- ❑ Providers and staff receive ongoing, supportive supervision.
  Tip: Use the *Standards-Based Management and Recognition* (SBM-R) approach.*
- ❑ Pre-service and in-service trainings are offered regularly for all staff involved in giving injections and managing waste.
  Tip: For developing training tools and job aids, use *Do No Harm: Injection Safety in the Context of Infection Prevention and Control: Training Tools and Job Aids.**
- ❑ Guidelines are established for management of injection waste.
  Tip: Use *Management of Waste from Injection Activities at the District Level: Guidelines for District Health Managers.**
- ❑ All staff members follow waste management guidelines.
- ❑ The disposal area (for example, burial pit) is in a convenient location and secure from intruders.

Injectables services are organized efficiently

- ❑ Injectables users receive routine repeat injections without a long wait.
  Tip: Set up an "express line" for repeat injections.

Clients and the community are well informed about injectables

- ❑ Mass media campaigns for family planning mention injectables, if possible.
- ❑ Providers are knowledgeable about injectables and can respond accurately and helpfully to rumors and misperceptions.
- ❑ Printed materials about injectables are available to clients.

*For more information, see Table 3, p. 22.

Providing injectables in the community gives women the choice of injectables in rural areas of Ethiopia, Ghana, Papua New Guinea, Thailand, and parts of other countries where clinics are hard to reach (8, *44*, 61, 101, 124, *139*, 147). In Bangladesh community programs serve both urban and rural areas (*164*). Community programs offer injectables from mobile clinics, village clinics, periodic temporary outreach clinics, or at the homes of clients or community health workers. Injectables services have been added to community provision of oral contraceptives and condoms and offered along with immunizations, other maternal and child health services, and some curative services (*44*, 183, *186*).

In most countries these efforts have consisted of pilot studies. Two exceptions are Bangladesh, which used elements of the Matlab Project in the government family planning program, and Ghana, which is scaling up the Navrongo Initiative in the nationwide Community-Based Health Planning and Services (CHPS) Initiative (138, *164*).

Community provision has dramatically increased use of injectables. In the Navrongo Initiative, for example, contraceptive prevalence rose from 3.4% to 8.2% between 1993 and 1999, when 92% of contraceptive users were using injectables (*44*, 138). In this and other projects, many women chose injectables as their first modern method of contraception (*44*, 54, 138, *139)*. In some areas of Bangladesh, however, community provision had less of an effect on overall prevalence because women switched to injectables from other modern methods (66).

Community Provision and Clinic Provision Prove Comparable in Quality

A study in Uganda compared the quality of the provision of injectables in the community and in the clinic. The study—carried out by Family Health International and Save the Children/USA in collaboration with the Ministry of Health (MOH) and Nakasongola local government—enrolled 449 community clients and 328 clinic clients and followed them up 13 weeks after their first injection of DMPA. Clinic providers were MOH nurses, and the community providers were local volunteers, who were affiliated with a clinic and had been providing free oral contraceptives and condoms in the community.

The community providers received classroom and clinical training, and they learned to screen clients with the help of a checklist (see *Checklist for Screening Clients Who Want to Initiate DMPA (or NET-EN)*, p. 5 in the companion issue of *INFO Reports*).

They gave injections in their homes or at the homes of their clients and were supervised by program and clinic staff and district health officers (183).

© Kingston Namun/Mark Munguas, Courtesy of Photoshare

A community nurse gives a contraceptive injection to a woman in Papua New Guinea. Small community programs in several countries and large-scale programs in a few have given women in rural areas the choice of injectables.

Community provision has dramatically increased use of injectables in some areas.

The study compared several factors that contribute to quality:

- ***Screening for medical eligibility:*** There were no reported screening mistakes made by community providers or clinic providers (182).
- ***Counseling:*** At follow-up the clients were asked about side effects and about specific points made by their providers. Levels of clients' knowledge of bleeding changes, sexually transmitted infections, and reasons to return to the clinic were the same for community and clinic groups, and both needed improvement. For example, 20% or less of community and clinic clients knew that no monthly bleeding was a common side effect of DMPA. One difference reported by clients was that in initial counseling community providers mentioned other contraceptive choices less often than did clinic providers.
- ***Injection safety:*** None of the 777 clients reported infections at the injection site, and no providers reported needlestick injuries. Overall, 24 of the 449 community clients (5%) reported problems, compared with 8 of the 328 clinic clients (2%). Most of the problems were minor, such as temporary numbness or mild pain at the injection site. Four of the eight community clients reported severe pain. Three had received their injection from the same provider, who was then given more training. In the Matlab Project in Bangladesh, an assessment reported four abscesses in over 14,000 DMPA injections (3).

- ***Disposal of waste:*** In Uganda community providers were instructed to place used needles and syringes into sharps containers and carry the boxes to a clinic, where they would be burned and buried. Also, they could throw used needles and syringes into pit latrines. The community providers handled syringes safely, but disposal of used syringes from both clinic and community providers needed improvement at some clinics (182). Disposal has also needed improvement in the Navrongo and CHPS initiatives in Ghana (1, 225).
- ***Continuation rates:*** The percentages who had second injections in Uganda were similar—88% among community clients and 85% among clinic clients. Few other studies have compared continuation rates in community and clinic programs. In one, a Mexican study of the combined injectable *Cyclofem*, the one-year continuation rate was 37% among the 640 community clients and 22% among 2,817 clinic clients (60).

  In Bangladesh continuation rates were lower in some areas of the scaled-up government program than in the Matlab Project. The one-year continuation rate was 69% in the Matlab Project, in which each provider was responsible for a population of 1,200 and visited clients every two weeks. In eight scale-up areas where each provider was responsible for a population of 6,800 and visited clients every three months or more, one-year continuation rates in two areas were 35% and 46% (*139*).
- ***On-time repeat injections:*** In Uganda almost all continuing clinic and community clients received their second injections on time, 94% in both groups. A little more than half of community clients had their second injection at the community provider's home, and about one-third had the injection in their own home. The rest had the injection either at a clinic or an unrecorded location (183).

Many women had injections at clinics or the homes of community providers rather than in their own homes, most likely to maintain privacy.

In trials in Bolivia and Guatemala also, many women had injections at clinics or the homes of community providers rather than in their own homes, most likely to maintain privacy (*109*).

In the Navrongo Initiative some women choose to visit the community provider on market days, and they count on her to know if they need an injection or can wait for the next visit (1).

Morale and Costs Are Concerns of Scaled-Up Programs

The benefits of training last only as long as providers remain on the job. Turnover among community nurses has been high in the CHPS Initiative in Ghana. Community nurses work in difficult conditions, and some are stationed away from their families. To improve morale, the Ghana Health Service is increasing incentives for nurses to stay on the job and encouraging communities to select candidates and pay for their training. After training, the nurses return and work in their home areas (1,138, 225).

Photo: Courtesy of Uganda Ministry of Health

Community providers in Uganda practice safe injection techniques. With appropriate training, a range of health care providers can learn to give injections safely.

The cost of offering injectables and other health services in clients' homes has been a concern in Bangladesh. The government stopped household services in the late 1990s and set up community clinics to save money and increase efficiency by offering more services at each client visit (*113, 164*). The change in policy did not affect use of injectables or oral contraceptives in general, but it may have reduced access to health services for some poor and uneducated women (5, *113, 164*). In a survey, over 80% of women said they valued home visits because the community provider gave them helpful information and their housework was not interrupted. A new government elected in 2002 resumed household services (*113*).

Today, as pilot projects are scaled-up, community provision of injectables challenges programs to ensure quality of care. Hiring and retaining enough providers, screening for medical eligibility, counseling, and waste disposal need attention in training and supervision (1, *66*, 182, 225). Tomorrow, as more countries test and improve community provision of injectables, more women in isolated areas will have another contraceptive choice.

Meeting Rising Demand Efficiently

Faced with limited resources, family planning programs need to serve more users of injectables without greatly increasing costs. Programs can increase efficiency by:

- Organizing work to save time,
- Getting supplies and equipment at the lowest available prices,
- Adding outlets without building clinics,
- Encouraging providers to decrease unproductive time while on the job, and
- Enabling a range of providers to give injections, as noted (see p. 10).

Also, programs can recover some costs by asking users to pay for injectables if they can.

Organizing Work Better Can Save Time

Improving the flow of clients through clinics allows programs to care for more clients without lowering quality, hiring more providers, or increasing staff hours. For example, in Guatemala a clinic providing maternal and child health services improved client flow after a self-assessment by staff and a survey of clients. Clients used to wait, have a pre-visit discussion, return to the waiting room, see the provider, return to the waiting room, and then have a post-visit discussion. In the improved flow clients wait once and receive all services in one visit with one provider. This change enabled staff to see 33% more clients and reduced the wait for clients (28). For injectables users returning for routine repeat injections, clinics can set up an "express" line to save time for both clients and staff (*172*), while giving returning clients the option of more time with a provider if they have questions, problems, or something to discuss.

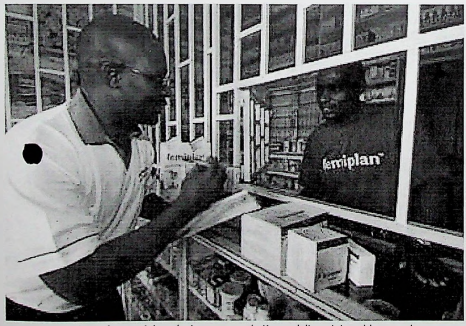
Recording clients' waiting time and providers' time spent with clients can help programs identify problems with organization of work. The *COPE*® (Client Oriented, Provider Efficient) process developed by EngenderHealth can help to organize work more efficiently. *COPE* tools include software to track the cost of staff time and supplies (52). The NGO (Non-Governmental Organization) Service Delivery Program (NSDP) in Bangladesh uses the CORE (Cost and Revenue Analysis) computer program developed by Management Sciences for Health to model the effects on efficiency and cost recovery of changes in client flow, prices, and staff time (133) (see Table 3, p. 22).

Programs Can Hold Down Costs of Supplies and Facilities

DMPA and monthly injectables currently cost US$0.78 to $0.84 per dose from UNFPA. NET-EN costs 30%–50% more (*91, 197*). The cost of supplies for DMPA, for example, for one woman for one year (four injections) would be US$3.36 to $3.60, including four auto-disable syringes costing $0.06 each. By comparison, 12 cycles of oral contraceptives at US$0.16 to $0.63 per cycle from UNFPA would cost $1.92 to $7.56 (*197*). The total cost of providing injectables, of course, includes the time of the provider to counsel and give the injection and the overhead cost of the facility and equipment (see Table 3, p. 22, for resources to estimate total costs).

To keep costs down programs can buy supplies in bulk, set up services in existing buildings, and share facilities with other health services.

Procure good-quality injectables, injectable equipment, and other contraceptives at the lowest available price. Programs that buy their own commodities can get low prices by asking for competitive bids from some of the more than two dozen manufacturers of injectables (*83*). To ensure the quality of supplies, programs should ask for bids only from manufacturers that have been assessed for quality. WHO will prequalify injectables and manufacturers by mid-2007 and will provide this information on its Web site (http://mednet3.who.int/prequal/default.htm) (104).



Population Services International

A distributor for a social marketing program in Kenya delivers injectables to a pharmacy. Clients buy the injectable and take it to a health care provider for the injection. The availability of injectables in the public and private sector is increasing in Kenya. A projected shortfall in supplies persuaded the government to allocate funds for injectables and seek help from donors. Many women are willing to pay for injectables, and sales in the private sector have increased.

Programs can also work with the UNFPA, which helps countries procure injectables and other contraceptives at low prices. Also, a number of procurement agents consolidate orders from several clients to qualify for volume discounts from manufacturers, and they ensure the quality of the products that they order (38, 127).

Adjust procurement to match demand. As users switch to injectables from other methods, demand for other methods may rise more slowly or even decrease. If so, programs can place larger orders for injectables and smaller orders for other methods. Monitoring use with a logistics management system will indicate changes in demand and in the method mix and will help programs avoid overstocking some contraceptives if demand for them decreases.

Set up more outlets for injectables without building more clinics. Injections have been given in existing community clinics, mobile clinics, and the homes of clients or community providers (8, 61, *139, 183*). Facilities for giving injections need not be elaborate: a private examination area, a waiting area for clients, space to store supplies and client records, and, if possible, a place for providers to wash hands (204, 227).

Share cost of outreach services with other services. Outreach services can follow the example of clinic-based integrated family planning and maternal and child health services. In Thailand mobile clinics offered STI services, Pap smears, and other services as well as contraceptives (8). In rural Ethiopia teams offering DMPA, immunizations, and antenatal care set up monthly outreach sites in a project managed by Save the Children/USA (61). Offering multiple services can save on fixed costs and is likely to be more convenient for clients who need several types of health care.

Some Providers Can Increase Productivity

Family planning providers in many programs are overworked. If they are providing other services, especially curative services, clients typically form long lines at the clinic, and providers are fully occupied.

In some programs, however, there may be opportunities to increase providers' productivity and serve more clients without increasing costs. Studies in several countries report that providers in some public or NGO clinics do not work a full day, and they spend less than half their time with clients. Many spend considerable time performing administrative duties or waiting for clients (76, 88, 89, 133). For example, from observations of nurses and doctors in 82 Mexican Ministry of Health (MOH) facilities in 1996, a study concluded that, with small changes in providers' schedules, the MOH could meet demand for family planning through the year 2010 without increasing costs or hiring more providers. If providers increased their work time from six to seven hours a day and increased the time spent with clients from about 3 to 4½ hours a day, the cost per client

Checklist for Improving Access to Injectables

To meet the rising demand for injectables, program managers need to make it easier for women to get to services—and without a long wait. The items in this checklist can help to remove barriers and improve access to injectables.

Women can get to services easily

- ☐ Services in cities and towns are conveniently located. They are within walking distance or close to public transportation.
- ☐ Injectables are available five or more days a week.
- ☐ Clinic hours allow women to visit without taking time off from work.
- ☐ Most clients wait no more than one hour for service.
- ☐ Users of injectables receive routine repeat injections without a long wait—for example, in an express line.

Services are offered in rural areas through community programs

- ☐ Services are available to women who cannot leave their homes or villages.
- ☐ Outreach clinics are set up at least once a month.
- ☐ Community health workers provide injectables or refer women to accessible clinics.

Injectables are available from:

- ☐ Hospitals
- ☐ Family planning clinics
- ☐ Maternity clinics
- ☐ Clinics providing postabortion care
- ☐ Private doctors and nurse-midwives (Is there a network of private providers offering injectables?)
- ☐ Pharmacies, including those working with social marketing programs

Location of service outlets and their hours are well known to women and their partners

Outlets are well marked. Location and hours are:

- ☐ Publicized at public events set up to provide information about family planning
- ☐ Included in counseling at clinics providing maternity and postabortion care
- ☐ Broadcast on radio and television, if possible
- ☐ Publicized regularly in newspapers and magazines
- ☐ Posted on billboards

Injectables Tomorrow:
Subcutaneous DMPA and Home Injection

A new lower-dose formulation of DMPA, *depo-subQ provera 104* (also called DMPA-SC), is injected under the skin rather than in the muscle. It contains 104 mg of DMPA rather than the 150 mg in the intramuscular formulation. Like the intramuscular formulation, DMPA-SC is given at 3-month intervals.

Approved first in the United States and the United Kingdom, subcutaneous injection of DMPA may be available in some developing countries by 2008. DMPA-SC is available only in prefilled, single-use syringes. In developing countries it will be available only in prefilled *Uniject*™ devices designed for subcutaneous injection (102, 103).

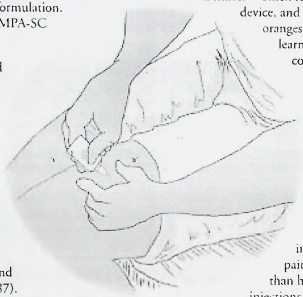
DMPA-SC is just as effective as the formulation injected into the muscle, and the patterns of bleeding changes and amount of weight gain are similar (7, 87). One-year continuation rates in clinical trials were high, 68% on average at sites in North and South America and 80% in Europe and Asia. Despite the lower dose, DMPA-SC is effective for overweight or obese women (41).

Injections of DMPA-SC are given in the upper thigh or abdomen. DMPA-SC should not be injected intramuscularly, and the intramuscular formulation should not be injected subcutaneously. The intramuscular formulation cannot be diluted to make the lower-dose subcutaneous formulation.

Given the choice, many women prefer self-injections or home injection. In trials of DMPA-SC, some women gave themselves injections and many said they would prefer self-injection. For example, among 1,787 women participating in trials of DMPA-SC with standard syringes, 16% gave themselves injections. Among the approximately 1,600 participants who answered a questionnaire, most would prefer to give themselves the injection either at home (50%) or in a doctor's office (21%), while 29% would prefer injections by a provider (42). Even with intramuscular injections, most women in small studies of *Cyclofem* in Brazil and the United States preferred self-injection in the clinic or at home (11, 184). Self-injection of DMPA-SC may require approval by drug regulatory agencies and ministries of health.

Self-injection will save women the time and expense of repeated visits to a health care provider and could increase continuation rates. Among 111 women who stopped using *Cyclofem* or DMPA in a study enrolling 360 women in Kenya, for example, 43% said the reason was related to problems returning to the clinic on time (165). Women could be given several *Uniject* devices at the clinic so that they could have home injections for a year or more, or they could buy the devices at a pharmacy.

Women or family members will need training to give injections. Training in Brazil to use *Uniject* for intramuscular injection of *Cyclofem* included several sessions under the supervision of a nurse. Women learned how to use the *Uniject* device, and they practiced giving injections in oranges. More than 90% of the participants learned to give themselves injections correctly (11).



Some women will not want to give themselves injections. In Brazil 102 *Cyclofem* users were invited to participate in the study of self-injection. Of these, 14 declined because they did not want to give themselves injections, 32 balked at giving themselves injections even after training, and 7 gave themselves one injection but no more, because of pain. The remaining 49—slightly less than half—gave themselves two or three injections (11).

Thus, while self-injection may become an option, it should not be required of everyone. Those who are fearful or hesitant may put off giving themselves an injection and thus increase the chances of pregnancy. Among people with diabetes or multiple sclerosis who give themselves daily or weekly therapeutic injections, anxiety reduces adherence to injection schedules (116, 117).

Self-service offers possible savings and will need guidelines. Home injection will decrease cost per client because self-service clients need less time with health care providers. Still, community providers will need to check periodically for problems with side effects, adherence to the injection schedule, and changes in health that would make switching to another method advisable. Providers will also need to ensure that women dispose of used injection equipment safely. A study of 100 diabetic patients in Tunisia reported that 94% threw used equipment in the household garbage (39). Family planning programs may want to develop guidance, including information on storage of injectable contraceptives and safe disposal of *Uniject* for women who choose self-injection and for the providers who serve them.

Illustration: *A new lower-dose formulation of DMPA is injected under the skin rather than in the muscle. In developing countries it will be available in prefilled* Uniject *devices, possibly by 2008. Many women may choose to give themselves the subcutaneous injection or have family members give the injection.* *Illustration: Rafael Avila/CCP*

using combined injectables for a year would decrease from about US$49 to $37 (*76*).

Providers can be more productive if more clients come during times of the day when the clinic is normally not busy. Appointments can be scheduled during these times, generally after 1:00 p.m., and clients could be charged less. More research is needed, however, to assess providers' motivation and the best ways to reward them for seeing more clients (*88*). Programs may need to raise salaries or reward providers for seeing more clients, but the result can still be a net decrease in cost per client served (89).

Some Injectables Users Are Willing to Pay

Program managers can recover some costs from users of injectables. Starting to charge clients who have received free services and supplies, or increasing existing charges, does not always decrease demand substantially. In general, managers of public and private nonprofit family planning programs overestimate the effect of price increases on demand (*2, 56*). In fact, even doubling the price of contraceptives has reduced demand by no more than 15%, according to five studies in Bangladesh, Indonesia, and Nigeria (*107*). In Indonesia during the economic crisis in the late 1990s, prices rose faster than incomes. The price of injectables more than doubled on average, but demand was unchanged (*58*, 118).

In some countries, however, family planning clients are sensitive to price changes. In Malawi, for example, increases and then decreases in prices by an NGO in response to changes in donor funding led to dramatic decreases and then increases in numbers of family planning clients (*180*).

To gauge what people would pay for injectables and other contraceptives, program managers can conduct a willingness-to-pay survey. Applied to injectables, the survey starts with two questions: What do you pay for injectables? Would you be willing to pay X amount (a moderately higher price) for injectables? The third question suggests a higher price if a woman is willing to pay X, or less of an increase if she is not willing to pay X amount. Before increasing prices throughout the program, managers can raise prices in a few clinics first to check the accuracy of any predicted changes in demand (*2, 56*).

In rural Ethiopia teams offering DMPA, immunization, and antenatal care set up monthly outreach sites.

By definition, social marketing programs charge for their products. Pricing is not based on costs but rather on ability to pay. Some social marketing programs set the annual price of injectables and other contraceptives at 1% or less of median annual family income—a price that most people can afford. These programs use attractive packaging for injectables and other contraceptives to promote them and distinguish them from public-sector products (69). Sales of injectables in social marketing programs have risen dramatically. Among country programs with total annual contraceptive sales of at least 10,000 couple-years of protection, sales of injectables more than doubled from 8.4 million doses in 2000 to 20.2 million doses in 2005. By comparison, sales of oral contraceptives increased by about 50% and total couple-years of protection provided by these programs increased by 57% (46).

Cross-subsidization is another way to shift costs. Programs charge more than cost for some products or services and use the profits to subsidize services that do not cover costs or to offer free services for the poor. For example, social marketing programs in Brazil, China, El Salvador, the Philippines, and other countries have charged more than cost for some brands of injectables, oral contraceptives, and condoms (9).

Communication Helps Women Try and Use Injectables

When interest in a new product is growing, as with injectables, communication by family planning programs can address people who know about the product but are hesitating to try it. These are people who think a long time before trying something new or who are skeptical about innovations. Many need to see satisfied users among their peers or be encouraged by opinion leaders before they try something new (*162*, 227). Each of the three stages they pass through—being persuaded that the product is good, deciding to use it, and then starting to use it—can be addressed by different messages (*140*).

At the same time that programs address this main audience, they can also address other important audiences—women who are already using injectables, men, and providers. Women who are using injectables often have questions or concerns about side effects. Some men help their partners choose injectables and use them effectively (*227*). For example, a 1995 study in the Philippines found that women whose husbands supported DMPA use were more than twice as likely to continue the method as women whose husbands disapproved (143). Providers may need information that addresses their own knowledge and attitudes about

injectables (6, 54). Efforts to introduce injectables in public family planning programs should include information for private providers because women may consult them about side effects (227). Audience research—with focus groups, for example—helps programs choose messages, sources, and media that will be effective for the specific audiences they want to address.

Injectables have been controversial in some countries because of health concerns. In India, for example, injectables are not offered in the government family planning program in part because of opposition from women's groups (63, 72, 169). Programs should be ready to respond to groups that publicly oppose injectables specifically or modern contraceptives in general. Making reliable and balanced information available to the public and providers has helped programs both avoid and deal with controversy. Maintaining a good working relationship with the news media and making sure that reporters are well-informed is an important task for family planning programs (161). For example, in Indonesia, when the risk of bone loss among DMPA users was in the news in 2004 and 2005, programs contacted journalists so that stories in the mass media presented information about the benefits of using DMPA along with the risk of bone loss (105) (For information about bone loss, see p. 21).

In Various Media Trusted Sources Address Benefits and Misinformation

Potential users assess the benefits and drawbacks of a new product before deciding to use it. The important characteristics of a new product are its advantages over current products, its compatibility with a potential user's life (how familiar it seems), and ease of use. Being easy to try or to observe is an advantage for a new product (*162*).

To help potential users assess injectables, communication programs have pointed out advantages, side effects, and health concerns. Also, programs have corrected misinformation about injectables by pointing out, for example, that women can get pregnant after stopping injections (146). Women may need assurance, if monthly bleeding stops, that they are not pregnant and that blood is not building up in their bodies (*18*, 61, 79). For women ready to try injectables, programs publicize the location and hours of services (61, *183*).

Trusted sources have delivered information about injectables in media or forums that are appropriate for the audience. In sub-Saharan Africa aunts are trusted sources of information about sexuality, and in Côte d'Ivoire "Auntie Fatou" provided information about injectables and other contraceptives in television spots (146). Doctors have been portrayed discussing injectables in television spots in Egypt and radio spots broadcast in several sub-Saharan African countries (51, 82, 134). In Pakistan, where many people own cassette tape players, a social marketing program distributed a cassette recording of a simulated discussion of injectables by a provider and a couple (*34*).

When interest in a new product is growing, as with injectables, communication can address people who know about the product but are hesitating to try it.

For some people, information in the mass media or on the Internet may be enough to get them to try a new method. But for the majority who are hesitating or skeptical, a medium that offers the opportunity to interact can be helpful (*162*). For example, in social marketing projects carried out by Social Marketing for Change (SOMARC) in Kazakhstan, Turkey, and Uganda, radio and television advertising alleviated concerns about convenience, cost, or availability of injectables and oral contraceptives. To address concerns about side effects, however, women needed to interact with a credible source, such as a doctor or family planning counselor, and be able to ask questions (*18*). Interactive media and forums have included telephone hotlines, discussions with providers, and community meetings.

Telephone hotlines offer a private connection between contraceptive users and a trained, credible family planning counselor. Among callers to a hotline in Turkey were both women who were using injectables and women who were

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A billboard in Guinea promotes the progestin-only injectable Depo Provera *as "effective, reversible, private—a long-acting contraceptive." Communication programs address both women and men, who often help their partners choose and use injectables.*

interested but not using them. DMPA users typically called because they had no monthly bleeding and worried that they might be pregnant. One caller had a pregnancy test every month to make sure she was not pregnant. Some women called the hotline for more information after their doctors had told them about irregular or heavy bleeding caused by DMPA. Health care providers also called the hotline for information. For example, a pharmacist called to confirm that DMPA is given every three months rather than every month as some local doctors had said (*18*).

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A woman carries a model of a needle and syringe to publicize injectables in a family planning parade in Peru. Engaging communities and their leaders in communication activities has been an important part of efforts to increase access to injectables and other contraceptives.

Discussions with providers. Inviting women to a clinic to discuss family planning has given them a chance to interact directly with providers and let them know where injectables are available (50). In one-to-one discussions in women's homes, village health workers in Ethiopia provide information about the benefits of family planning and the availability of injectables. They refer women to health clinics for more information and services (61).

Coaching can help women talk to providers and get the information they need. In a study of family planning counseling in Indonesia, for example, a patient educator coached women about the importance of asking questions and helped them prepare questions and practice asking them. One practice question concerned injectables: "If women don't menstruate when they use injections, where does the blood go?" (for the answer, see p. 20). In taped counseling sessions, coached women asked more questions than uncoached women and they expressed more concerns about contraceptive methods. As a result, providers gave the coached women more information specific to their situation (96).

To address concerns about side effects of injectables, some women need to interact with a credible source, such as a doctor or family planning counselor.

Community meetings are an interactive and public way to improve knowledge and answer questions about injectables and other methods. They also provide information for women who are unable to travel, and for men (*18, 34*). For example, in the SOMARC project in Uganda midwives set up one-hour meetings with women interested in family planning by working with local officials, religious groups, trade schools, and factories. About 11% of the approximately 17,000 women who attended community meetings later obtained a contraceptive from a clinic. In the areas where the meetings were held, sales of injectables more than doubled from the six months before the meetings to the six months after the meetings (*18*).

Engaging community leaders has helped the introduction of injectables and other methods in Ghana and Vietnam (*44*, 227). The Navrongo initiative in Ghana, for example, encouraged support for family planning by enlisting the help of opinion leaders and using men's and women's social networks. Councils of elders formed health care action committees, and village leaders and elders convened regular community gatherings to discuss health and family planning with the men. The goal was to show that village leaders endorse family planning and to encourage couples to discuss their reproductive health. As noted, the vast majority of women starting a modern method of contraception in the Navrongo Initiative chose injectables offered by community providers (*44*, 138).

Today injectables are becoming more available and attracting more users. Tomorrow, demand for injectables will likely grow further as these methods are offered in more community programs and as subcutaneous injection of DMPA becomes available. Programs are trying to keep up with demand by keeping supplies in stock, ensuring that providers give injections safely, and informing women about injectables. The result of these efforts will be more satisfied users of this safe and effective contraceptive method.

Questions & Answers About Injectables

1 How do injectables work?

Injectables work mainly by preventing the development and release of eggs from the ovaries (ovulation). They also thicken cervical mucus, which blocks sperm from meeting the egg. Both progestin-only and combined injectables are very effective when users return on time for their next injections.

2 How are combined injectables similar to combined oral contraceptives? How do they differ?

Long-term studies of the health risks and benefits are under way, but few results are available yet. Still, combined injectable contraceptives contain the same types of hormones as combined oral contraceptives (COCs). Therefore researchers assume that most of the findings about COCs also apply to combined injectables. A difference is that monthly injectables are not processed by the liver before entering the bloodstream, as are medications taken by mouth. As a result, monthly injectables have less effect on liver function than COCs, and women can use them with some conditions, such as gall bladder disease, that would make use of COCs less safe (*212*). Also, short-term studies have found that monthly injectables have less effect than COCs do on blood pressure, blood clotting, and the breakdown of fatty substances (lipid metabolism).

Side Effects

3 Are the bleeding changes caused by injectables harmful?

In most cases, no. Heavy bleeding, however, which is uncommon, may contribute to anemia, particularly among women who are nearly anemic. Also, if there is reason to suspect that a bleeding pattern has another cause—not the injectable—then the cause should be investigated.

4 If a woman does not have monthly bleeding while using progestin-only injectables, does this mean that she is pregnant or that blood is building up in the body?

No. Lack of bleeding most likely does not mean a woman is pregnant if she was not pregnant when she started injectables and has been having injections on time. Blood does not build up inside a woman's body while she uses progestin-only injectables. Lack of bleeding while using injectables is similar to lack of bleeding while breastfeeding. During the menstrual cycle the lining of the womb thickens and a woman releases an egg (ovulates). If the egg is not fertilized, the tissue and blood from the thickened lining are shed as menstrual bleeding. When a woman uses progestin-only injectables or if she fully breastfeeds her baby for six months, the lining of the womb does not thicken, the woman usually does not ovulate, and there is no menstrual bleeding.

5 Will injectables change mood or sex drive?

Some women using injectables report mood changes and less sex drive, but the great majority do not (*65, 87, 202*). It is difficult to tell whether such changes are due to injectables or to other causes. There is no evidence that using injectables changes a woman's sexual behavior.

Safety

6 Will a woman still be able to become pregnant after she stops using an injectable?

Yes. Monthly bleeding and release of eggs from the ovaries (ovulation) return. Women of any age, whether or not they already have children or want more children, can use any injectable contraceptive, and it will have no effect on future fertility.

7 Do injectables cause cancer?

Many studies show that DMPA does not cause cancer. DMPA use helps *protect* against cancer of the lining of the uterus (endometrial cancer). Women have a slightly increased risk of being diagnosed with breast cancer while using DMPA or shortly after they stop, but this may be due to earlier detection of existing disease. If a woman has not developed breast cancer within five years of starting DMPA, then her risk of breast cancer is the same as the risk for a similar woman who never used DMPA.

A few studies suggest that there may be a slightly increased risk of cervical cancer among women who use DMPA for five years or more if they have persistent infection with certain strains of human papillomavirus (HPV) (178). Cervical cancer cannot develop because of DMPA use alone. It is caused by persistent infection with these strains of HPV. While HPV infection is common, *persistent* HPV infection with one of the cancer-causing strains is not common. Few additional cases of cervical cancer will occur because of DMPA use.

Little information is available about NET-EN. It is thought to be as safe as DMPA and other contraceptive methods containing only a progestin, such as progestin-only pills and implants.

8 Can injectables cause abortion?

No. Injectables do not disrupt an existing pregnancy. They should not be used to cause abortion. They will not do so.

9 Do injectables cause birth defects?

No. DMPA does not cause birth defects even if a woman mistakenly receives an injection when she is pregnant or even if a woman becomes pregnant while using DMPA (131). There is little evidence about NET-EN, but it is assumed to be the same as DMPA in this regard.

Combined oral contraceptives do not cause birth defects, and so it is assumed that combined injectables do not cause birth defects, either (26, 131, 155).

10 Why does DMPA affect bone density?

DMPA reduces levels of estrogen in the body. Estrogen helps to regulate the flow of minerals to and from the bones. When estrogen levels are low, more minerals are lost from bone than are reabsorbed. This leads to a decrease in bone density (137).

Whether DMPA increases the risk of broken bones requires more research. A woman's lifetime risk of broken bones is unlikely to be affected because women regain bone density after stopping DMPA. Among adults who stop using DMPA, after two to three years their bone density appears to be similar to that of women who have not used DMPA. Among adolescents, it is not clear whether the loss in bone density prevents them from reaching their potential peak bone mass. Also, more research is needed on the effect of DMPA use during the reproductive years on the risk of broken bones during menopause, and the effect of DMPA use near menopause on a woman's ability to regain lost bone density.

Because of the bone loss issue, drug regulatory agencies in the United Kingdom and United States advise women to consult providers after using DMPA for two years to decide if they want to continue DMPA or to choose another method (49, 193). An expert working group advising the World Health Organization, however, concluded that the decrease in bone density should not limit who uses DMPA, or for how long, among women ages 18 to 45. The benefits of using DMPA outweigh the theoretical concerns about bone fracture for these women and for adolescents younger than 18 and women over 45. Since there is not enough information about long-term DMPA use by adolescents and women over 45, the expert group recommended that providers and these women reconsider the benefits of DMPA and their risk of bone fracture over time. These recommendations also apply to NET-EN (*216*).

Other Uses

11 Can a single injection of a combined injectable be used to bring on regular monthly bleeding in a woman with irregular bleeding?

No. A woman may experience some bleeding (a "withdrawal bleed") about a month later as a result of the injection, but there is no evidence that giving one injection of a combined injectable to a woman with irregular bleeding will cause her monthly bleeding to become regular.

12 Can a single injection of a combined injectable be used as a pregnancy test?

Giving a woman combined injectables to see if she has bleeding when she stops taking them is not recommended as a way to tell if she is pregnant. Combined injectables should not be given to a woman as a "hormonal pregnancy test" because they do not produce accurate results.

Women With HIV/AIDS Can Use Injectables

Injectables are safe and effective for women who have HIV, including those who have AIDS and those who are taking antiretroviral (ARV) medications. Effective contraception helps women avoid the health risks of unintended pregnancy with HIV infection, including mother-to-child transmission of HIV (119, 148). Also, although there have been few studies, there is evidence that some ARV medications harm a fetus. Women should use efavirenz, for example, only if they use effective contraception (214).

There have been theoretical concerns that ARV medications could reduce the effectiveness of hormonal contraceptives because some medications speed up liver metabolism (141). One small study of women using efavirenz, nelfinavir, or nevirapine reported that after an injection of DMPA, levels of progesterone indicated that no women ovulated (33). A study of an oral contraceptive, however, reported that nevirapine had a significant effect on both estrogen and progestin levels (114). Even if an ARV medication did decrease the hormone level in the blood somewhat, users are probably still well protected against pregnancy because DMPA is nearly as effective for three months at a 100 mg dose as at the usual 150 mg dose (*203*). To date, no studies have looked at NET-EN or combined injectable contraceptives.

Because of the concerns about decreased effectiveness, it has been suggested that women using nevirapine and DMPA be especially urged to return on time for injections (*173*). Women using nevirapine or other ARV medications who return late but within two weeks of their injection date, however, should not be denied an injection. No evidence supports shortening the interval between injections for women using ARV medications.

The few studies available find that DMPA has little or no effect on the plasma concentration of ARV medications (33) or on their effectiveness as measured by the plasma concentration of lymphocytes (white blood cells) and HIV (32).

Injectable contraceptives offer no protection against transmission of HIV or other sexually transmitted infections. Used consistently and correctly, male or female condoms help prevent transmission of infection. Condoms can be used along with injectables and with other family planning methods. Also, monogamy or at least reducing the number of sexual partners can lower the risk of HIV infection.

Table 3: Key Resources for Program Managers and Providers

Resource	Availability
Ensuring Reliable Supplies	
Title: *Pocket Guide to Managing Contraceptive Supplies* **Organization:** U.S. Centers for Disease Control and Prevention **Description:** A quick reference guide for staff who manage contraceptive supplies and logistics. Includes logistics formulas and principles.	PDF available online.* To order print copies, contact: U.S. Centers for Disease Control and Prevention Division of Reproductive Health, MS K-22, 4770 Buford Hwy., NE Atlanta, GA 30341, USA E-mail: ttj2@cdc.gov
Title: *PipeLine Software Tool* **Organization:** John Snow, Inc. (JSI) **Description:** A tool to help program managers monitor stock and plan procurement through forecasting, maintaining consistent stock levels, and preventing stockouts.	Tool available online.* To request the PipeLine CD, contact: John Snow, Inc./DELIVER Project 1616 N. Fort Myer Drive, 11th Floor Arlington, VA 22209, USA E-mail: deliver_pubs@jsi.com Web site: www.jsi.com
Title: *Procuring Single-Use Injection Equipment and Safety Boxes: A Practical Guide for Pharmacists, Physicians, Procurement Staff and Programme Managers* **Organization:** World Health Organization (WHO) **Description:** A guide to help programs procure injection equipment and safety boxes and to develop a monitoring system to ensure quality and reliability.	PDF available online.* To order print copies, contact: World Health Organization Department of Essential Health Technologies 20 Avenue Appia 1211, Geneva 27, Switzerland E-mail: eht@who.int Web site: www.who.int/eht
Title: *UNFPA Procurement Services* **Organization:** United Nations Population Fund (UNFPA) **Description:** UNFPA is the largest public sector procurer of contraceptives. UNFPA accepts standard orders of US$6,000 or more, and also accepts emergency procurement orders.	For more information, contact: UNFPA Procurement Services Section Midtermolen 3, P.O. Box 2530 2100 Copenhagen, Denmark Web site: www.unfpa.org/procurement/index.htm
Safe Injections and Waste Management	
Title: *Safe Injection and Waste Management: A Reference for Logistics Advisors* **Organization:** JSI **Description:** A reference guide to help design and support programs for safe injections and waste disposal. Includes assessment tools and additional references.	PDF available online.* To order print copies, contact: John Snow, Inc./DELIVER Project 1616 N. Fort Myer Drive, 11th Floor Arlington, VA 22209, USA E-mail: deliver_pubs@jsi.com Web site: www.jsi.com
Title: *Management of Waste from Injection Activities at the District Level: Guidelines for District Health Managers* **Organization:** WHO **Description:** A guide to help develop an action plan to reduce improper disposal of injection waste.	PDF available online.* To order print copies, contact: World Health Organization Press 20 Avenue Appia 1211, Geneva 27, Switzerland E-mail: bookorders@who.int Web site: www.who.int
Title: *Do No Harm: Injection Safety in the Context of Infection Prevention and Control Training Tools and Job Aids* (forthcoming) **Organization:** JSI and WHO **Description:** A tool for implementing national injection safety training program strategies. Includes sample handouts and job aids.	For more information, contact: John Snow, Inc./DELIVER Project 1616 N. Fort Myer Drive, 11th Floor Arlington, VA 22209, USA E-mail: deliver_pubs@jsi.com Web site: www.jsi.com
Training and Supervision	
Title: *Comprehensive Family Planning and Reproductive Health Training Curriculum Module 6: DMPA Injectable Contraceptive* **Organization:** Pathfinder International **Description:** An adaptable module to train health care workers to provide injectables.	PDF available online.* To order print copies, contact: Pathfinder International 9 Galen Street, Suite 217 Watertown, MA 02472, USA E-mail: information@pathfind.org Web site: www.pathfind.org
Title: *Standards-Based Management and Recognition (SBM-R)—A Field Guide, Facilitator's Handbook, and CD-ROM* **Organization:** JHPIEGO **Description:** A guide for improving performance and the quality of health care services.	For more information, contact: JHPIEGO 1615 Thames Street Baltimore, MD 21231, USA E-mail: orders@jhpiego.net Web site: www.jhpiego.org

Resource	Availability
Training and Supervision (Continued)	
Title: *A Guide for Supervising Injections* **Organization:** WHO **Description:** A guide for supervisors to observe injection practices, provide feedback about safe and unsafe practices, and help resolve problems contributing to unsafe injections	PDF available online.* To order print copies, contact: World Health Organization Department of Essential Health Technologies 20 Avenue Appia 1211, Geneva 27, Switzerland E-mail: eht@who.int
Improving Efficiency	
Title: *CORE: A Tool for Cost and Revenue Analysis* **Organization:** Management Sciences for Health, Inc. (MSH) **Description:** CORE helps managers analyze and compare a facility's current and projected costs and revenues.	For more information, contact: Elizabeth Lewis, Management Sciences for Health, Inc. 748 Memorial Drive Cambridge, MA 02139, USA E-mail: core@msh.org Web site: www.msh.org
Title: *COPE: A Process for Improving Quality in Health Services* **Organization:** EngenderHealth **Description:** The COPE technique helps supervisors and staff assess the quality of services, identify problems, and recommend and implement solutions.	PDF available online.* To order print copies, contact: EngenderHealth 440 Ninth Avenue New York, NY 10001, USA E-mail: info@engenderhealth.org Web site: www.engenderhealth.org
Title: *Maternal and Reproductive Health Costing Model*, Version 1.1 (Millennium Project Version) **Organization:** UNFPA **Description:** A tool to help program managers estimate the personnel, drug, and supply costs associated with providing injectables and other reproductive health services.	Excel spreadsheet available online.* For more information, contact: Millennium Project One United Nations Plaza 21st floor Rm. 2160 New York, NY 10017, USA E-mail: Eva Weissman weissman@unfpa.org or Janneke Saltner saltner@unfpa.org
Title: *International Drug Price Indicator Guide* **Organization:** MSH **Description:** This guide provides prices from pharmaceutical suppliers and procurement agencies, international development organizations and government donor agencies.	PDF available online.* To order print copies, contact: Management Sciences for Health, Inc. 748 Memorial Drive Cambridge, MA 02139, USA Web site: www.msh.org
Helping Clients Make an Informed Choice	
Title: *Decision-Making Tool for Family Planning Clients and Providers* **Organization:** WHO and the INFO Project, Johns Hopkins Bloomberg School of Public Health Center for Communication Programs **Description:** An evidence-based counseling resource for providers to help clients make informed choices about family planning.	PDF available online.* To order print copies, contact: Johns Hopkins Bloomberg School of Public Health Center for Communication Programs 111 Market Place, Suite 310 Baltimore, MD 21202, USA E-mail: orders@jhuccp.org
Title: *Medical Eligibility Criteria for Contraceptive Use* **Organization:** WHO **Description:** A guide for the safe use of 19 methods for women and men with known medical conditions.	PDF available online.* To order print copies, contact: Department of Reproductive Health and Research, WHO 1211 Geneva 27, Switzerland E-mail: rhrpublications@who.int
Title: *Family Planning: A Global Handbook for Providers* (forthcoming) **Organization:** WHO and the INFO Project **Description:** A guide for providing family planning methods, including counseling and managing side effects. Also covers prevention and identification of sexually transmitted infections, including HIV, and numerous health topics related to family planning.	To order print copies, contact: Johns Hopkins Bloomberg School of Public Health Center for Communication Programs 111 Market Place, Suite 310 Baltimore, MD 21202, USA E-mail: orders@jhuccp.org Web site: www.infoforhealth.org/pubs/globalhandbook/
Communicating About Injectables	
Title: *Media/Materials Clearinghouse* (M/MC) **Organization:** Johns Hopkins Bloomberg School of Public Health Center for Communication Programs **Description:** A resource for health communication materials from around the world, with over 200 items pertaining to injectables.	For more information, contact: Media/Materials Clearinghouse Johns Hopkins Bloomberg School of Public Health Center for Communication Programs 111 Market Place, Suite 310 Baltimore, MD 21202, USA Web site: www.m-mc.org/

*See Web Table 3 for URL. Additional information at http://populationreports.org/k6/k6tables.shtml

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This bibliography includes citations to the materials most helpful in the preparation of this report. In the text, reference numbers for these citations appear in italics. The complete bibliography can be found on the internet at: http://www.populationreports.org/k6/ The links included in this report are up-to-date as of publication.

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Population Reports

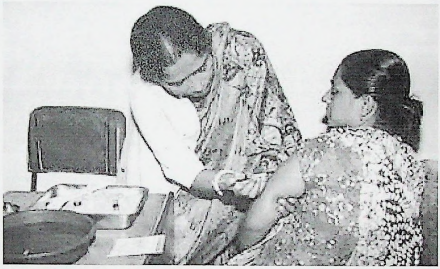
December 2006

JOHNS HOPKINS BLOOMBERG SCHOOL of PUBLIC HEALTH

INFO Project
Center for Communication Programs

How family planning programs and providers can meet clients' needs for injectable contraceptives

Expanding Services for Injectables



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Key Points

More than twice as many women are using injectable contraceptives today as a decade ago, and the numbers keep growing. Injectables appeal to the many women who seek a family planning method that is effective and long-acting and can be used privately.

Family planning services can meet the rising demand for injectables by:

- Keeping enough supplies on hand. Anticipating demand for injectables and placing accurate and timely orders helps programs maintain adequate supplies and avoid stockouts.
- Mobilizing a range of providers to offer injectables. With training, any health care worker can give contraceptive injections.
- Taking injectables into the community. Offering injectables in community programs increases access and can be as safe as clinic services.
- Organizing services efficiently. Programs can hold down cost increases by organizing work more efficiently, purchasing supplies at the lowest available prices, and encouraging staff to increase productivity.
- Informing the public. Communication programs can tailor messages to address women who know about injectables but hesitate to try them.

As services expand, maintaining good quality remains an obligation to clients for all family planning methods. For injectables, attention to quality includes:

- Giving injections safely. Applying safe injection technique and the universal precautions, including disposing of used syringes and needles properly, helps prevent infection.
- Helping clients decide about injectables. Good counseling helps women decide if an injectable contraceptive suits their preferences and their situation. Providers must tell women that injectables change bleeding patterns.
- **Helping clients use injectables successfully.** Women who choose injectables keep using them longer when they know that bleeding changes are normal and understand the importance of returning for injections on time.

See companion *INFO Reports*, "Injectable Contraceptives: Tools for Providers"

Series K, Number 6
Injectables and Implants

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CONTENTS

Tools for Providers are in the companion *INFO Reports*. See also *Population Reports*, "When Contraceptives Change Monthly Bleeding," Series J, No. 54, August 2006.

Coming Soon: "Injectables Toolkit" Web site. Go to http://www.injectablestoolkit.org for job aids and information about injectable contraceptives.

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Cover Photo: A provider gives a client an injection in Bangladesh, where use of injectables has doubled over the last decade. As more women choose injectable contraceptives, programs will need to offer more good-quality services.

Injectables Today and Tomorrow

More and more women are using injectable contraceptives today, and very likely even more will use this method in the future as it becomes increasingly available. Women choose injectables because they are effective, long-lasting, and private. For family planning programs, meeting increasing demand while maintaining good quality will be the key to success with injectables.

Between 1995 and 2005 the number of women worldwide using injectable contraceptives more than doubled. About 12 million married women used injectables in 1995. In 2005 over 32 million were using injectables (*108, 163, 194*). Injectables are the fourth most popular method worldwide, after female sterilization, the intrauterine device (IUD), and oral contraceptives. In sub-Saharan Africa, injectables are the most popular method, chosen by 38% of women using modern methods (see Table 1). By 2015 worldwide use is projected to reach nearly 40 million—more than triple the 1995 level (*163*).

Greater access largely explains this rapid growth in use. Approval of the progestin-only injectable DMPA (depot medroxyprogesterone acetate) in the United States in 1992 removed a constraint to access and a source of controversy in many countries over providing a drug that was not approved for contraception in the United States. Also, approval in the United States enabled the U.S. Agency for International Development (USAID) to supply DMPA to developing countries. As of 2006 DMPA was registered in 179 countries, an increase from 106 countries in 1995 (*83, 99*). Several countries, including Ghana, Vietnam, and Zambia are introducing or scaling up DMPA services as part of a package of reproductive or primary health care services (138, 224, 226).

In the next 10 years more family planning programs will offer injectables, and they will offer clients more choices of injectables. Most can be expected to offer a progestin-only injectable—DMPA injected every three months or NET-EN (norethisterone enanthate) injected every two months. Many will offer a combined injectable, probably either medroxyprogesterone acetate (MPA) combined with the estrogen estradiol cypionate (E_2C) or NET-EN combined with the estrogen estradiol valerate (E_2V). Both are injected monthly. Other combined injectables are available in some countries and regions (see Table 2, p. 5).

Women will be able to have injections in more convenient locations (see Checklist, p. 15). More private clinics and providers will offer injectables (144, 152). More pharmacists will provide injectables in many countries, often as a part of social marketing programs (35, 36, 145). More programs will offer injectables in community services, and some women will choose home injection with the new DMPA formulation for subcutaneous injection (under the skin rather than in the muscle) (see box, p. 16).

Table 1. Estimated Worldwide Use of Injectables Among Married Women Ages 15–49, 2006

QUICK LOOK

Region & Selected Countries	% Currently Using: Any Method	Any Modern Method	Injectables	% of Modern Method Users Using Injectables
DEVELOPING AREAS	**58**	**52**	**3**	**7**
Sub-Saharan Africa	21	15	6	38
Kenya 2003	38	31	14	46
Lesotho 2004	36	35	15	42
Malawi 2004	31	28	18	64
Namibia 2000	44	43	19	44
South Africa 2003	60	60	28	47
Near East & North Africa	52	40	2	4
Egypt 2005	62	57	7	12
Asia	63	59	3	5
Bangladesh 2004	53	47	10	21
Cambodia 2005	40	27	8	29
Indonesia 2002–03	60	57	28	49
Nepal 2006	48	44	10	23
Latin America & Caribbean	71	62	4	6
Haiti 2005–06	30	24	11	47
El Salvador 2002–03[a]	67	61	18	30
Nicaragua 2001	67	66	14	22
DEVELOPED AREAS	**68**	**57**	**1**	**1**
Europe	74	64	0	0
Eastern Europe & Central Asia	63	42	0	1
North America	75	71	3	4
Other developed[b]	59	64	0	0
WORLD	**59**	**53**	**3**	**6**

[a]Data for women 15–44.
[b]Includes Australia, Israel, Japan, and New Zealand.

Methodology and data sources: Data for the number of married women ages 15–49 for each country were obtained from population projections for 2005 by the World Bank (201). Percentages are weighted by population size—that is, they reflect differences in population among the countries. Usage rates come from the most recent data from the Demographic and Health Surveys and Reproductive Health Surveys and, for countries without these surveys, data from the United Nations, 2005 (*194*), the U.S. Census Bureau's International Database (191), and other nationally representative surveys, including the U.S. National Surveys of Family Growth (122).

How to Use This Report

This report can help family planning program managers develop strategies to:

- Meet the increasing demand for injectables with good-quality services.
- Address women who:
  - Would like to use injectables but lack access.
  - Hesitate to use injectables because they need more information about side effects or safety.

Providers can use the companion issue of *INFO Reports*, "Injectable Contraceptives: Tools for Providers," to review the important elements of good-quality services. The tables and checklists in the INFO Report are aids for counseling women, giving safe injections, and helping women be satisfied users of injectables.

Demand Accelerates and Suppliers Respond

Since 1995 the percentage of married women who rely on injectables has increased in 40 of 44 developing countries with multiple surveys (see Web Table 1[1]). Use increased particularly in Indonesia among married women ages 15–49 from 15% in 1994 to 28% in 2002, after the method was vigorously promoted and more widely distributed. Nearly half of all married Indonesian women using contraception now rely on injectables. Use also has increased sharply in Haiti, Malawi, and Namibia. Between 2005 and 2015 the largest increases in number of users are expected in Indonesia (almost 2 million additional users), Nigeria (almost 1 million more), and Pakistan (over 200,000 more) (*163*).

Popular in some countries but little used in others. Overall, awareness and use of injectables are increasing, but levels of use vary widely within regions. In sub-Saharan Africa, Asia, and Latin America and the Caribbean, over 40% of married contraceptive users rely on injectables in some countries, while 5%–7% use them in other countries (see Web Table 2[1]). Variations within regions can be attributed to a variety of factors, including access to injectables, norms related to contraceptive use, government policies, women's tolerance for side effects, and communication about injectables.

Governments, donors, and manufacturers respond. Where demand is increasing rapidly, governments have responded by placing larger procurement orders for injectables (see p. 6). Major donor agencies have steadily increased shipments of progestin-only injectables to developing countries (see Web Figure[2]). Between 2003 and 2005 shipments by the United Nations Population Fund (UNFPA), USAID, and the International Planned Parenthood Federation (IPPF) more than doubled, rising from 23 to 48 million doses per year. These donors contribute almost 60% of the total donated contraceptives worldwide. UNFPA, currently the largest supplier of injectables, shipped 27 million doses in 2005, a 35% increase over 2004. Shipments by USAID doubled between 2000 and 2005, rising from 9.3 million to 18.6 million doses, and they are expected to increase to 20 million in 2006 (21, 159). Sales of injectables by social marketing programs more than doubled between 2000 and 2005 (see p. 17). One manufacturer of DMPA projects annual demand for 150 million doses (enough for 37.5 million users) by 2010 (103).

Effectiveness, Convenience, and Side Effects Influence Use

Many women have chosen injectables as their first modern method, and others have switched to injectables from oral contraceptives or other methods (*44, 139*). Women are choosing injectables because they offer a variety of advantages:

- **Highly effective.** Used correctly, injectables are more effective than female sterilization. If women return on time for injections, in the first year on average 3 among every 1,000 women using progestin-only injectables will become pregnant, and 5 among every 10,000 women using combined injectables (*190*). As injectables are commonly used in the United States, 3 in every 100 women become pregnant in the first year of use. This pregnancy rate is higher than that for IUDs, implants, and male and female sterilization but lower than that for oral contraceptives.
- **Long-acting.** Users need to remember only to have an injection every two or three months for progestin-only injectables or once a month for combined injectables. Users do not have to remember to do something every day or when about to have sex (*20, 54*).
- **Reversible.** Fertility returns after a woman stops using an injectable.

Population Services International

Workers package DMPA in the warehouse of ProSalud, a nonprofit organization in Bolivia. Manufacturers, donors, and family planning programs in many countries are increasing the supply of injectables to meet demand.

Web Tables are available for download and printing at http://www.populationreports.org/k6/k6tables.shtml
The Web Figure is available for download and printing at http://www.populationreports.org/k6/k6figures.shtml

Table 2. Formulations, Injection Schedules, and Availability of Injectable Contraceptives

Common Trade Names	Formulation	Injection Type and Schedule	Registration/ Availability in 2006
Progestin-Only Injectables			
Depo-Provera[A], *Megestron*[C], *Contracep*[D], *Depo-Prodasone*[R]	Depot medroxyprogesterone acetate (DMPA) 150 mg	One intramuscular (IM) injection every 3 months	Registered in 179 countries
depo-subQ provera 104[D] *(DMPA-SC)*	DMPA 104 mg	One subcutaneous injection every 3 months	Approved in United States and United Kingdom; approval expected soon in other European countries; expected to be available in some developing countries by 2008
Noristerat[K], *Norigest*[C], *Doryxas*[C]	Norethisterone enanthate (NET-EN) 200 mg	One IM injection every 2 months	Registered in 91 countries
Combined Injectables (progestin + estrogen)[1]			
Cyclofem[C], *Ciclofemina*[B], *Lunelle*[N]	Medroxyprogesterone acetate 25 mg + Estradiol cypionate 5 mg (MPA/E_2C)	One IM injection every month	Registered in 12 countries[2]
Mesigyna[K], *Norigynon*[D]	NET-EN 50 mg + Estradiol valerate 5 mg ($NET\text{-}EN/E_2V$)	One IM injection every month	Registered in 33 countries
Deladroxate[D], *Perlutal*[B], *Topasel*[K], *Patectro*[S], *Deproxone*[B], *Nomagest*[C]	Dihydroxyprogesterone (algestone) acetophenide 150 mg + Estradiol enanthate 10 mg	One IM injection every month	Registered in 14 Latin American countries and Spain
Anafertin[S], *Yectames*[S]	Dihydroxyprogesterone (algestone) acetophenide 75 mg + Estradiol enanthate 5 mg	One IM injection every month	Registered in 7 Latin American countries
Chinese Injectable No. 1[SE]	17 α-hydroxyprogesterone caproate 250 mg + Estradiol valerate 5 mg	One IM injection every month, except 2 injections in first month	Registered in China

Sources: IPPF 2005 (*83*), Lande 1995 (*99*), Liggeri 2006 (103), WHO 1990 (*204*), WHO 1993 (*205*)

[1] Also called monthly injectables.

[2] The U.S. Food and Drug Administration has approved *Lunelle*, but it is currently not available in the United States.

Women stopping DMPA to become pregnant, however, take several months longer to conceive on average than women who used other methods (130, 171).

- **Private.** Women can use injectables without anyone else knowing (*20, 109,* 126, 138, *186*)—particularly if a partner or in-laws object to contraception (*19, 31*).

Progestin-only injectables offer additional advantages for some women:

- They can be used during breastfeeding starting six weeks after giving birth (*212*).
- Monthly bleeding stops after a time for many users. Some women see this as an advantage of the method (62).
- Weight gain, common with use of injectables, is welcome for some women (4, 78, *109,* 166).

Side effects deter many, but counseling helps. At the same time, many women do not choose injectables or they stop using them mainly because of side effects—particularly bleeding changes, no monthly bleeding, and weight gain (13, 70, 135, 168). In a large multinational World Health Organization (WHO) trial, on average half of women stopped using DMPA and NET-EN within 12 months (*202*). In the United States more women stop using injectables within 12 months than stop oral contraceptives or the copper IUD (*190*).

Good counseling can be the difference between successful and unsuccessful efforts to expand access to injectables.

Good counseling, especially about changes in monthly bleeding and other side effects, helps women decide whether injectable contraception will suit them and it helps women continue using injectables (30, 59, *75, 100,* 227). Good counseling can be the difference between successful and unsuccessful efforts to expand access to injectables (77, 78, 224). Introducing injectables or any new method is an opportunity to improve counseling and quality of care for all available methods (224).

: Contraception. 1997 Dec;56(6):353-9. Related Articles, Links

ELSEVIER SCIENCE
FULL-TEXT ARTICLE

Introductory study of the once-a-month, injectable contraceptive Cyclofem in Brazil, Chile, Colombia, and Peru.

Hall P, Bahamondes L, Diaz J, Petta C.

Special Programme of Research, Development and Research Training in Human Reproduction, World Health Organization, Geneva, Switzerland.

An introductory trial with the injectable contraceptive Cyclofem was carried out in Brazil, Chile, Colombia, and Peru, with participation by 3,183 women. Women were followed-up for up to 2 years of use and the data were evaluated by life table analysis. A total of 29,676 women-months were accumulated for up to 2 years. No pregnancies were observed in the 2 years. The discontinuation rates for amenorrhea in the first year ranged from 3.4 in Brazil to 8.1 in Colombia, and for menstrual disturbances from 5.1 in Chile to 9.2 in Brazil. The discontinuation rates for other medical reasons ranged from 7.8 in Brazil to 26.3 in Colombia, and for personal reasons from 17.2 in Chile to 23.5 in Brazil. Continuation rates ranged from 42.3 in Colombia to 52 in Chile. In the second year of observation the rates of discontinuation were lower than those observed in the first year, with the exception of personal reasons in Brazil, which were the same as those observed in the first year. Continuation rates ranged from 19.4 in Brazil to 36.8 in Chile. The comparison of reasons for discontinuation in selected clinics showed that the rate for amenorrhea in one clinic in Chile was more than three times that in others and in Peru was seven times more in one clinic than in another. Regarding menstrual disturbances, in Peru one clinic presented a rate three times higher than the others. The main reasons for discontinuation due to other medical reasons were headache and weight gain. In conclusion, Cyclofem presented a high contraceptive efficacy and an acceptable rate of continuation and discontinuation for up to 2 years in the four countries.

PIP: The performance of the monthly injectable contraceptive, Cyclofem, was evaluated in an introductory trial involving 3183 women recruited from family planning centers in Brazil, Chile, Colombia, and Peru. A total of 29,676 women-months of use were accumulated during up to 2 years of follow-up. No pregnancies occurred during the study period. Discontinuation rates per 100 women in the first year ranged from 3.4 in Brazil to 8.1 in Colombia for amenorrhea and from 5.1 in Chile to 9.2 in Brazil for menstrual disturbances. The discontinuation rate for other medical reasons (primarily headache, weight gain, and acne) ranged from 7.8 in Brazil to 26.3 in Colombia and for personal reasons from 17.2 in Chile to 23.5 in Brazil. First-year continuation rates ranged from 42.3 in Colombia to 52.0 in Chile. In the second year of use, continuation rates ranged from 19.4 in Brazil to 36.8 in Chile. Upon receiving these results, national regulatory authorities in the 4 participating countries approved Cyclofem registration. Acceptance of injectable contraception, which currently entails

administration of the method by a service provider and travel to a clinic, could be improved in developing countries by training in self-administration.

: Contraception. 1994 Apr;49(4):387-98. Related Articles, Links

Once-a-month injectable contraceptives: efficacy and reasons for discontinuation.

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Siriraj Family Planning Health Research Centre, Department of Obstetrics and Gynaecology, Mahidol University, Bangkok, Thailand.

Reports of the phase III clinical trials on four combined progestogen-estrogen once-a-month injectable contraceptives, Deladroxate, Cyclofem, Mesigyna and Chinese Injectable No. 1, are reviewed focussing on efficacy and reasons for discontinuation. Deladroxate, currently used in many Latin American countries has proved to be highly effective and well accepted. However, this combination was withdrawn by the original manufacturer because the progestogen component of this drug induced a high number of breast cancers in dogs and very curious pituitary hyperplasia in rats. Cyclofem and Mesigyna were found to be highly effective and highly acceptable drugs. Side-effects were minimal and were of minor importance. The Chinese Injectable No. 1 had unacceptably high failure rates with a monthly injection schedule. After doubling the dose in the first month of use, the efficacy was satisfactory. It was found that all monthly injectable contraceptives provided better cycle control than the every 3 months depot-medroxyprogesterone acetate, although abnormal bleeding was still the main drug-related complaint and reason for discontinuation. Missed appointment is another reason for discontinuation which might reflect the problem of frequent injection schedule, thus indicating the need for proper selection of the users and good counselling.

PIP: This literature review examines the efficacy and reasons for discontinuation of 4 combined progestogen-estrogen, once-a-month injectable contraceptives: Deladroxate, Cyclofem, Mesigyna, and Chinese injectable No. 1. Deladroxate is used mainly in Latin America, while the Chinese injectable No. 1 is largely limited to China. Among 18 studies, no pregnancies occurred in the 3017 women using Deladroxate (32,857 woman-months). It was well accepted, but the manufacturer withdrew it from the market after studies showed that the progestogen (dihydroxyprogesterone acetophenide) caused dogs to develop breast cancer and rats to develop an odd pituitary hyperplasia. Of the 4 once-a-month injectables, Cyclofem and Mesigyna provide the most promise. They are very effective at preventing pregnancy (0-0.23/100 women-years of use and 0.08-0.48/100 women-years of use, respectively). Acceptance of Cyclofem and

Mesigyna was high. Side effects were limited and had minimal importance. An advantage of Cyclofem and Mesigyna is their much better cycle control than the once-every-3 months injectable Depo-Provera. The failure rate of the Chinese Injectable No. 1 on the once-a-month injection schedule was too high (10.35/100 women-years of use). When researchers doubled the dose in the 1st month of use, however, efficacy was satisfactory (0.8/100 women-years of use). The main drug-related complaint and reason for discontinuation of all once-a-month injectables was abnormal bleeding. Another key reason for discontinuation was missed appointment, suggesting that a frequent injection schedule poses a problem. Good planning and health workers properly selecting users and providing them good counseling may overcome this problem. Frequent visits would increase the staff work load.

CONTENTS

Combined Injectable Contraceptives

The name of combined injectable contraceptives, or CICs, is given to a group of hormonal contraceptives administered by intramuscular injection. The term "combined" indicates that these injectables contain both a progestin and an estrogen. At present there are three main types of CICs on the market:

Progestin	Natural Estrogen	Brand Name
Depomedroxy-progesterone acetate (DMPA) 25 mg	Estradiol cypionate 5 mg	*Cyclofem*
Norethisterone enanthate (NET EN) 50 mg	Estradiol valerate 5 mg	*Mesigyna*
Dihydroxy-progesterone acetophenide 150 mg	Estradiol enanthate 10 mg	*Deladroxate*

The first two are new products becoming more widely used throughout the world; the third is mostly used in some Latin American countries. The three formulations provide very effective pregnancy protection for a 30-day period. Therefore they are also referred to as "monthly injectables."

CICs have some similarities with progestin-only injectables:

- WHO Medical Eligibility Criteria
- Bibliography

- POPLINE
- Other Issues
- To Order
- CCP Home Page

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the two new CICs contain precisely the same progestin as the two most widely used progestin-only injectables (*Depo-Provera* and *Noristerat*); however, the progestin dose received over time is much lower with the new CICs. Although a basic difference from the progestin-only injectables is the presence of estrogen in the CICs, the estrogen was incorporated mostly to improve the control of the menstrual cycle.

Both CICs and combined oral contraceptives (COCs) are combined hormonal contraceptives. Besides the different route of administration, from a safety point of view the most important difference is the presence of a "natural" estrogen in the CICs versus a "synthetic" estrogen in the COCs. It is now recognized that natural estrogens have very favorable effects on lipid metabolism and cardiovascular function. The use of natural estrogens in postmenopausal women has actually shown a protective effect against cardiovascular disease, including both cerebrovascular and cardiac problems. Estradiol has direct effects on the arterial wall and on various stages of atherosclerotic plaque formation, resulting in an increase of tissue blood flow and in an anti-atherosclerotic effect. No significant changes in these effects have been found attributable to the addition of a progestin.

Based on the above evidence, CICs might actually be considered safer than COCs. However, due to the recent introduction of the two new CICs, no long-term safety information on CIC use is available yet. Therefore, the medical criteria for CIC use are mostly derived from the information existing on COC use.

Q.1. When is the best time to start CICs?

In general?

Recommendation: CICs can be started any time you can be reasonably sure the woman is not pregnant (see [illegible]).

If given within the first 7 days of the menstrual cycle, it becomes effective immediately. However, if CICs are started after the first 7 days of a cycle or the woman is not menstruating, a back-up method is recommended to be used for 7 days. Some providers recommend a back-up method be used for 7 days if *Cyclofem* or *Mesigyna* are begun after the fifth day of the cycle.

Hypothetically, all CICs are effective when begun within the first 7 days

of the menstrual cycle.

Rationale: *Deladroxate* is effective immediately when given within the first 7 days of the menstrual cycle and possibly later. Most clinical trials of *Cyclofem* and *Mesigyna* (two newer, lower-dose formulations of CICs) have used the first 5 days of the cycle as the period for initiation. However, a recent study has demonstrated high contraceptive efficacy for a CIC similar to *Cyclofem* and *Mesigyna* when initiated between days 7 and 10 of the menstrual cycle.

Some experts believe that the lower-dose CICs are effective at least as promptly as COCs. These CICs have slightly less estrogen effect and more progestin effect than COCs, and it is presumed that their effect on cervical mucus is at least as prompt as the effect of COCs (46, 152).

Postpartum for breastfeeding women?

Recommendation: Because they contain estrogen, CICs should not be considered the first option for breastfeeding women. The WHO considers the risks from using estrogen-containing methods during breastfeeding before 6 weeks postpartum to generally outweigh the benefits (Category 3), unless other methods are not available or acceptable.

Rationale: There are no data on the effects of combined injectables used during lactation. The following rationale is based on what is known about combined oral contraceptives.

Even low-dose (30 micrograms) COCs decrease breastmilk production; it may be that estrogen-containing injectables, although they have a lower estrogen dose than COCs, will have a similar effect, but this has not been studied (310, 311).

Postpartum for nonbreastfeeding women?

Recommendation: CICs can be started from the second to the third week postpartum or at the first postpartum menstruation.

Rationale: Blood coagulation and fibrinolysis are essentially normalized by 3 weeks postpartum (and are close to normal at 2 weeks postpartum). CICs have minor effects on blood coagulation (51, 98).

Postabortion?

Recommendation: CICs can be initiated any time within the first-week after an abortion.

Rationale: CICs may be initiated any time after a first- or second-trimester abortion or postseptic abortion (310).

Q.2. When can the next injection be provided?

Recommendation: The best time to provide the next injection is on the same date each month (or a 4-week schedule may be practical for some programs). This should be emphasized when training personnel and counseling clients.

The grace period of combined injectable contraceptives is officially 3 days. If a client comes in after the grace period (27 to 33 days after the previous injection), advise her that delays in obtaining injections increase the risk of pregnancy. Offering re-injection for women who come in after the grace period is reasonable for women who state that, once beyond the grace period, they have been abstaining or consistently using a back-up method and/or the provider can be reasonably sure that the woman is not pregnant.

Rationale: Clinical trials have studied the efficacy of CICs given 27 to 33 days after the previous injection and found the efficacy to be very high. Some studies have found that the risk of ovulation is low up to 60 days after the previous *Cyclofem* or *Mesigyna* injection (1, 18, 235).

Recommendation: There is a risk of *in utero* exposure to the injectable if she is pregnant when she receives the next injection. However, there is no evidence that fetal exposure to CICs will be harmful.

Rationale: Although the estrogens and progestins in CICs have no known teratogenic effects, avoiding the risk of fetal exposure is preferable on general principles (28, 251).

Recommendation: It is acceptable to give the injection if you can be reasonably sure she is not pregnant (see How to Be Reasonably Sure the Woman Is Not Pregnant). Some programs will advise women to use a back-up method for the rest of the cycle.

Q.3. If a woman complains of heavier menses and/or prolonged bleeding, is there a medical basis for discontinuing CICs?

Recommendation: Not usually. Heavy bleeding (greater than normal menstrual bleeding) is common in the first 3 months of use and usually does not require discontinuation.

Rationale: Approximately 20% of CIC users experience frequent or prolonged menstrual bleeding within the first 3 months. However, these variations from normal bleeding patterns tend to decrease with time (300).

Recommendation: If bleeding has stopped and the woman wants to continue using CICs, reassure her first. The woman should be reassured by informing her that these effects usually pose no threat to health and tend to improve over time.

Rationale: Compared with women not using any contraceptive method, CIC users experience a significantly increased incidence of frequent, irregular, and prolonged bleeding (300).

Recommendation: If a woman is experiencing more days of bleeding than she was prior to starting CICs, the first approach should be

counseling to provide information and reassurance.

If the bleeding is intolerable to the woman but she wishes to continue CICs, then administration of supplementary short-term estrogen (or COCs) or prostaglandin inhibitors may be tried.

Rationale: Little research has been done on the management of heavy bleeding in CIC users. Prolonged or heavy bleeding in users of COCs or progestin-only injectables may be managed by stabilizing the endometrium with increased doses of estrogen or by ibuprofen (or related nonsteriodal anti-inflammatory drugs), which blocks prostaglandin synthesis and thus decreases uterine bleeding (261, 303).

Recommendation: Some women may not be able to tolerate heavy or prolonged bleeding and will discontinue CICs and need another method. Evaluate and address anemia if appropriate.

Do not perform uterine evacuation unless another medical condition is suspected. (Vacuum aspiration is always the preferred method of uterine evacuation.)

Q.4. Who can safely initiate and resupply CICs?

Recommendation: CICs (including immediate postpartum and postabortion injections) can be safely administered by appropriately trained service providers (e.g., nurses, midwives, pharmacists, CBD workers, and others), provided that infection-prevention measures can be assured.

Rationale: Nurses, midwives, and other community health workers can be appropriately trained to initiate and resupply injectables (303).

Recommendation: Under certain circumstances, clients may be provided with the supplies for self-administration or administration by another individual, provided that appropriate storage and infection-prevention procedures can be assured and that the woman knows where she can receive supportive services, should she have any problems.

Q.5. What is the recommendation for the once-a-month injectable contraceptive with 10 mg of estradiol enanthate and 150 mg of dihydroxyprogesterone acetophenide?

Recommendation: Use of the older injectable (10 mg of estradiol enanthate and 150 mg of dihydroxyprogesterone acetophenide) is not encouraged due to the availability of newer, lower-dose injectables (*Mesigyna* and *Cyclofem*). The newer CICs have theoretical advantages (lower estrogen dose) and more clinical trial data demonstrating their safety and efficacy.

However, some women may prefer the more reliable menstrual periods produced by the CIC with 10 mg of estradiol enanthate and 150 mg of

dihydroxyprogesterone acetophenide (this "menstrual signal" can serve as a reminder for reinjection) or may otherwise have a personal preference. The older CIC may be made available since it may be an appropriate choice for some women.

Rationale: Both the older and newer CICs have very high efficacy. However, there is a theoretical concern of using 10 mg of estrogen monthly, because of the possible negative effects on blood coagulation. Newer CICs, such as *Cyclofem* and *Mesigyna*, have half the estrogen dosage of the older CICs. The lower-dose CICs have, at least theoretically, less risk.

In the first year of use, the CICs with 10 mg of estradiol enanthate and 150 mg of dihydroxyprogesterone acetophenide cause menstrual irregularities in an average 22.4% of users, with a range of 7.5% to 24.4%. However, 30% of users of *Cyclofem* and *Mesigyna* experienced menstrual irregularities within the first year. The incidence of menstrual irregularities decreased with duration of use (152, 300).

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Phone: (410) 659.6300/Fax: (410) 659.6266/E-mail: Poprepts@jhuccp.org

1: Contraception. 2005 Aug;72(2):138-45. ELSEVIER FULL TEXT ARTICLE Links

Comparative acceptability of combined and progestin-only injectable contraceptives in Kenya.

Ruminjo JK, Sekadde-Kigondu CB, Karanja JG, Rivera R, Nasution M, Nutley T.

Department of Obstetrics and Gynecology, University of Nairobi, Nairobi, Kenya.

OBJECTIVE: We compared 12-month continuation rates, menstrual bleeding patterns and other aspects of acceptability between users of Cyclofem and users of Depo-Provera. METHODS: The life-table method was used to calculate quarterly continuation rates. In all, 360 Kenyan women were randomly assigned to one of the two contraceptives. User-satisfaction questionnaires were administered at 6 and 12 months or at discontinuation, whichever occurred first. RESULTS: The 1-year continuation rate was 75.4% for Depo-Provera users versus 56.5% for Cyclofem users ($p<.001$). Main reasons for discontinuation included difficulty making clinic visits (45.1% for Cyclofem vs. 40% for Depo-Provera), menstrual changes (14.1% vs. 12.5%) and nonmenstrual problems (15.5% vs. 12.5%). None of the Depo-Provera users and 8.5% of the Cyclofem users claimed frequency of visits as the main reason for discontinuation. In all, 70.6% of the Depo-Provera users were amenorrheic after 12 months, as were 20.8% of the Cyclofem users. CONCLUSIONS: The 1-year continuation rate was higher for Depo-Provera than for Cyclofem. There was no important difference in discontinuation rates because of menstrual problems; the difference mainly reflected the frequency of visits required.

1: Contraception. 2004 Feb;69(2):115-9. ELSEVIER FULL TEXT ARTICLE Links

Menstrual pattern and lipid profiles during use of medroxyprogesterone acetate and estradiol cypionate and NET-EN (200 mg) as contraceptive injections.

Canto de Cetina TE, Luna MO, Cetina Canto JA, Bassol S.

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The objectives of this study were to compare effects of medroxyprogesterone acetate 25 mg + estradiol cypionate 5 mg (Cyclofem) and norethisterone enanthate (NET-EN) upon the menstrual pattern and determine changes in lipoprotein parameters after 12 months of use. One-hundred females were included and 87 (45 with Cyclofem and 42 with NET-EN) women completing 12

months were evaluated. Menstrual changes were the leading complaint among users. At the end of 12 months, 20/45 (44.4%) and 18/41 (43.9%) Cyclofem and NET-EN users, respectively, had normal menstrual pattern. Irregular and infrequent bleeding were the two most important changes that occurred. The discontinuation rate at 12 months due to menstrual disturbances did not show any significant differences between the two preparations, but showed lower incidence compared to other studies. Total cholesterol, high-density, low-density and very low-density lipoprotein cholesterol and triglyceride levels decreased at 12 months in both groups and these changes were statistically significant.

1: Contraception. 2003 Sep;68(3):159-76 ELSEVIER FULL-TEXT ARTICLE Links

Comparative study of the effects of two once-a-month injectable contraceptives (Cyclofem and Mesigyna) and one oral contraceptive (Ortho-Novum 1/35) on coagulation and fibrinolysis.

United Nations Development Programme/United Nations Population Fund/World Health Organization/World Bank Special Programme of Research, Development and Research Training in Human Reproduction, Task Force on Long-acting Systemic Agents for Fertility Regulaion.

A randomized controlled multicenter study was undertaken to monitor the effects on hemostasis of two once-a-month injectable contraceptive preparations, Mesigyna (50 mg norethisterone enanthate and 5 mg estradiol valerate) and Cyclofem (25 mg medroxyprogesterone acetate and 5 mg estradiol cypionate) in comparison with a well-known oral contraceptive (OC) Ortho-Novum 1/35 (norethisterone 1 mg and ethinyl estradiol 35 microg). A total of 378 volunteers from four centers (Bangkok, Hangzhou, Santiago and Singapore) were monitored. Blood sampling took place in one pretreatment cycle, the third and ninth injection intervals and one posttreatment cycle. In each of the three treatment groups, a rise in hemoglobin, and increases in platelet count and in prothrombin time were observed. With treatment there was a significant increase in activated partial thromboplastin time among Mesigyna users, no change among Cyclofem users and a significant decrease among OC users. OC use led to increases in plasma levels of fibrinogen, factor VII, factor X, plasminogen, protein C and decreases in plasma levels of t-PAI and antithrombin. Use of combined injectables induced no change (Cyclofem) or decreases (Mesigyna) in plasma levels of fibrinogen, factor VII, factor X and antithrombin. Use of both combined injectables led to decreases in protein C, slight decreases in plasminogen and increases in plasminogen and fibrinogen. Overall, the injectable preparations may be more beneficial than the oral preparation in not enhancing a hypercoagulable state because of the reduced synthesis of fibrinogen, factors VII and X; however, decreases in antithrombin and protein C, which are potent coagulation inhibitors, may raise some concern.

Whether these changes can lead to modifications in the risk of arterial or venous disease can only be ascertained by conducting epidemiological studies.

1: Contracept Technol Update. 1998 Jan;19(1):3-4. Links

New year, new option: Cyclo-Provera awaits word.

[No authors listed]

PIP: This article discusses the potential availability of Cyclo-Provera, a monthly injectable similar to Depo-Provera that is being considered for approval by the US Food and Drug Administration (FDA). A new drug application was filed by its marketing company, Pharmacia and Upjohn of Kalamazoo, Michigan, in September 1997. The company wants mutual recognition by the FDA in US and European markets. The Jones Institute for Reproductive Medicine at the Eastern Virginia Medical School in Norfolk recently completed a company-sponsored clinical trial of the drug. This Institute is 1 of 44 sites conducting nationwide clinical trials among a total sample of 1200 women over 5 years. Cyclo-Provera is comprised of depomedroxyprogesterone acetate (DMPA), which is the same ingredient in Depo-Provera. Cyclo-Provera has a lower dose of DMPA (25 mg) combined with 5 mg of estradiol cypionate. The ingredients are expected to provide improved monthly menstrual cycle control. Cyclo-Provera is marketed outside the US under the name Cyclofem. Cyclofem is mainly used in China and Latin America. Germany produces a similar drug. The World Health Organization (WHO) has conducted multinational studies on both drugs. WHO recommends Cyclofem for most women who desire effective, reversible contraception and who are not at risk for most cardiovascular complications. The estrogen in Cyclofem is less potent and has a shorter life span than the estrogen in combined contraceptives. WHO guidelines suggest that Cyclofem has advantages that outweigh disadvantages for smokers under 35 years old, light smokers older than 35, women with mild hypertension (160/100), women with current or medically treated gall bladder disease, or women with mild cirrhosis. Cyclofem is not recommended for heavy smokers over 35 years old, women with a history of hypertension, and women with severe cirrhosis.

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1: Contraception. 1997 Dec;56(6):353-9. ELSEVIER FULL TEXT ARTICLE Links

Introductory study of the once-a-month, injectable contraceptive Cyclofem in Brazil, Chile, Colombia, and Peru.

Hall P, Bahamondes L, Diaz J, Petta C.

Special Programme of Research, Development and Research Training in Human Reproduction, World Health Organization, Geneva, Switzerland.

An introductory trial with the injectable contraceptive Cyclofem was carried out in Brazil, Chile, Colombia, and Peru, with participation by 3,183 women. Women were followed-up for up to 2 years of use and the data were evaluated by life table analysis. A total of 29,676 women-months were accumulated for up to 2 years. No pregnancies were observed in the 2 years. The discontinuation rates for amenorrhea in the first year ranged from 3.4 in Brazil to 8.1 in Colombia, and for menstrual disturbances from 5.1 in Chile to 9.2 in Brazil. The discontinuation rates for other medical reasons ranged from 7.8 in Brazil to 26.3 in Colombia, and for personal reasons from 17.2 in Chile to 23.5 in Brazil. Continuation rates ranged from 42.3 in Colombia to 52 in Chile. In the second year of observation the rates of discontinuation were lower than those observed in the first year, with the exception of personal reasons in Brazil, which were the same as those

observed in the first year. Continuation rates ranged from 19.4 in Brazil to 36.8 in Chile. The comparison of reasons for discontinuation in selected clinics showed that the rate for amenorrhea in one clinic in Chile was more than three times that in others and in Peru was seven times more in one clinic than in another. Regarding menstrual disturbances, in Peru one clinic presented a rate three times higher than the others. The main reasons for discontinuation due to other medical reasons were headache and weight gain. In conclusion, Cyclofem presented a high contraceptive efficacy and an acceptable rate of continuation and discontinuation for up to 2 years in the four countries.

PIP: The performance of the monthly injectable contraceptive, Cyclofem, was evaluated in an introductory trial involving 3183 women recruited from family planning centers in Brazil, Chile, Colombia, and Peru. A total of 29,676 women-months of use were accumulated during up to 2 years of follow-up. No pregnancies occurred during the study period. Discontinuation rates per 100 women in the first year ranged from 3.4 in Brazil to 8.1 in Colombia for amenorrhea and from 5.1 in Chile to 9.2 in Brazil for menstrual disturbances. The discontinuation rate for other medical reasons (primarily headache, weight gain, and acne) ranged from 7.8 in Brazil to 26.3 in Colombia and for personal reasons from 17.2 in Chile to 23.5 in Brazil. First-year continuation rates ranged from 42.3 in Colombia to 52.0 in Chile. In the second year of use, continuation rates ranged from 19.4 in Brazil to 36.8 in Chile. Upon receiving these results, national regulatory authorities in the 4 participating countries approved Cyclofem registration. Acceptance of injectable contraception, which currently entails administration of the method by a service provider and travel to a clinic, could be improved in developing countries by training in self-administration.

Population Reports

New Era for Injectables

In the next few years millions of couples throughout the world will be offered the choice of injectable contraceptives. Reassuring research findings, approval of the 3-month injectable in the US, and the introduction of new monthly injectables promise wider access. Whether expanding services or offering injectables for the first time, programs have a new opportunity and challenge to provide good care that responds to their clients' needs.

About 12 million couples throughout the world now use injectable contraceptives. Progestin-only injectables are the most widely used: DMPA (depot medroxyprogesterone acetate), known by the brand name *Depo-Provera*, provides three months of protection, and NET EN (norethindrone enanthate), known as *Noristerat*, two months. One-month injectables combine estrogen with progestin. The new monthly injectables *Cyclofem* and *Mesigyna* are well-tested alternatives to older monthlies.

Although the first injectables were developed soon after oral contraceptives, limited availability has constrained use in all but a few countries, such as Indonesia and Thailand. More than 100 countries have approved DMPA since the early 1960s, but political controversy and scientific uncertainty have held back injectables in some programs.

Now, research by the World Health Organization (WHO) and US regulatory approval of DMPA may mark the start of a new era for injectables. The WHO research reduced fears

HIGHLIGHTS

CONTENTS

Published with this issue:
"DMPA at a Glance" fact sheet
"Counseling Guide"

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about DMPA causing cancer. Approval of DMPA by the United States Food and Drug Administration in 1992 made this injectable available in the US and allows the United States Agency for International Development (USAID) to offer DMPA to developing-country family planning programs.

The User's Perspective

Throughout the world many women value injectables because they are highly effective, long-acting, reversible, and convenient, and they can be used privately. Also, breastfeeding women who want to use a hormonal contraceptive can use progestin-only DMPA or NET EN.

Women experience a variety of side effects with injectables, however. Disruption of menstrual bleeding is common, and some women find it troublesome. Counseling helps women understand that the frequent or irregular bleeding and amenorrhea are not dangerous, and many continue to use injectables despite these bleeding changes. *Cyclofem* and *Mesigyna* disrupt menstrual bleeding less than DMPA and NET EN. Also, some women using injectables report weight gain, headaches, and dizziness.

Introducing or Expanding Services

Experience with injectables for more than 20 years suggests that the most successful programs:

- **Provide accurate and balanced information** and dispel unwarranted fears about injectables through mass-media communication for the public, testimony from satisfied users, client education, and counseling.
- **Counsel to ensure informed choice and use.** With information and encouragement from providers, women make their own choices among family planning methods. They also learn what to expect and how to use their method. Having chosen injectables, women need to know when they can get injections and to expect bleeding changes.
- **Expand provision of injectables through pilot projects.** Seminars can inform providers and policymakers. Pilot studies can gauge clients' responses and identify key communication and counseling issues.
- **Ensure reliable supply.** Order injectables six months to a year in advance, making accurate forecasts of demand. To avoid logistical problems, offer only one progestin-only injectable and, if there is a demand, one monthly injectable.
- **Avoid unnecessary barriers** to use of injectables, such as age and parity requirements or restricting the first injection to the first seven days of the menstrual cycle.
- **Use needles and syringes safely.** Used disposable equipment should be destroyed. Reusable equipment should be sterilized or high-level disinfected.
- **Consider community-based distribution or social marketing** of injectables. These approaches increase availability but require good training and attention to quality.

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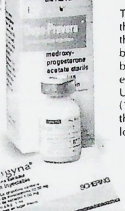
Research and Regulatory Approval

Three events signal a new era for injectable contraceptives:

- A multinational epidemiological study by the World Health Organization (WHO) produced largely reassuring findings about the 3-month injectable depot medroxyprogesterone acetate (DMPA) and cancer. Previous controversy about DMPA had arisen from animal studies.
- The United States Food and Drug Administration (US FDA) approved DMPA as a contraceptive in 1992, 25 years after the manufacturer, the Upjohn Company, first applied. As a result, the United States Agency for International Development (USAID) has begun providing DMPA to developing countries; and
- Two new monthly injectables, *Cyclofem*™ and *Mesigyna*®, are being introduced after thorough clinical studies by WHO (see pp. 4–5).

Together, these events may clear away some of the constraints that have limited widespread use of this 30-year-old method to a few countries.



Development of Injectables

Research on injectable contraceptives began shortly after the development of oral contraceptives. Karl Junkmann and colleagues at the German pharmaceutical firm Schering AG synthesized the first injectable progestins in 1953 (64, 149) and in 1957 developed norethindrone enanthate (NET EN, or *Noristerat*®), the first injectable contraceptive, which is injected every two months (150). The US pharmaceutical firm the Upjohn Company synthesized medroxyprogesterone acetate (*Provera*®) in the late 1950s (17). Upjohn conducted the first clinical trials of *Provera* in its depot, or injectable, form—*Depo-Provera*®—in 1963 (313, 321). Researchers developed the first monthly injectables and conducted clinical trials in the 1960s. The combination of progestin and estrogen that became *Cyclofem* was first tested in 1968, and the combination that became *Mesigyna* was first tested in 1974 (223).

US Regulatory History of DMPA

DMPA has always been the most widely used injectable, but the long wait for approval in the US has made it controversial. Upjohn applied for US FDA approval in 1967. At the time progestin-only methods seemed promising because the estrogen in combined oral contraceptives (OCs) caused nausea and vomiting in some women. Researchers suspected as well that estrogen caused blood clots (thromboembolic disease) in some users of combined OCs. These suspicions were later confirmed. Also, progestin-only contraceptive injections fulfilled many of the goals of researchers and family planning providers who wanted to be able to offer a method that was effective, reversible, did not interfere with lactation or require action at the time of sexual relations, and could be easily delivered by rural health care providers.

Nevertheless, the US FDA denied approval of DMPA in 1978, saying that it lacked sufficient evidence demonstrating safety, particularly with regard to breast and cervical cancer (35). A 3-member expert review panel, convened in 1983 at Upjohn's request, upheld the US FDA decision (322).

DMPA Research

Tests of DMPA in beagle dogs and monkeys in the early 1970s raised questions about cancer that delayed US regulatory approval and held back use in many countries. Beagles developed breast tumors and some monkeys developed endometrial tumors in tests then required by the US FDA of any new hormonal contraceptive (148). These studies were influential because at the time there was little information on the long-term effects of DMPA use among women (322). Many experts questioned the relevance to humans of the beagle and monkey studies, however (3, 10, 136, 313, 330, 346).

The WHO Collaborative Study of Neoplasia and Steroid Contraceptives examined the risk of cancer among users of hormonal contraceptives and reached the following conclusions, published largely in 1991, about DMPA and cancer:

- **Breast cancer:** No increased risk overall, but the study found that DMPA users had an increased risk for several years after starting DMPA—perhaps due to accelerated growth of existing tumors. Some of the apparent increase in risk may be explained by detection bias (see p. 14).
- **Cervical cancer:** No increased risk of invasive cancer.
- **Endometrial cancer:** Protective effect.
- **Ovarian cancer:** No increased risk.
- **Liver cancer:** No increased risk.

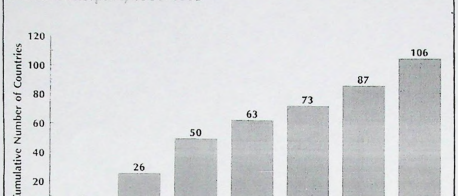
The findings about breast and endometrial cancer were the most crucial because they answered the long-standing questions raised by animal studies.

The WHO study provided epidemiologic evidence that humans differ from these animals in their response to hormones. The US FDA no longer requires testing contraceptive hormones for carcinogenicity in beagles (148).

The WHO study led the US FDA to change its position in 1992 and approve DMPA. US FDA approval removed a source of controversy in the history of DMPA use in developing countries of a drug that was not approved for contraceptive use in the US.

The US had been one of the few countries to withhold approval of DMPA. Over 90 countries had approved DMPA

Figure 1. Cumulative Number of Countries Registering DMPA as a Contraceptive, 1961–1995



before the US (see Figure 1). Following US approval, India, the Philippines, and several other countries also approved DMPA. By comparision, NET EN is registered in over 60 countries. Registration does not necessarily mean, however, that a product is readily available.

Monthly Injectables

Monthly injectables have been most widely used in China and Latin America. Chinese *Injectable Number 1* consists of hydroxyprogesterone caproate and estradiol valerate and has been used by about 1 million women (271). In Latin America at least one million women use dihydroxyprogesterone aceto-

Table 1. Formulation, Injection Schedule, and Availability of Injectable Contraceptives

Formulation	Developer	Brand Name/Manufacturer	Injection Schedule	Availability
Progestin only: 150 mg depot medroxyprogesterone acetate (DMPA)	The Upjohn Company	*Depo-Provera*/Upjohn *Megestron*/Organon	Every 3 months, 12 weeks, or 90 days	Registered in over 100 countries; available in both public and private sectors.
Progestin only: 200 mg norethindrone (norethisterone) enanthate (NET EN)	Schering AG	*Noristerat*[a]/Schering AG *Doryxus*/Richter Gedeon Ltd.	Every 2 months[b]	Registered in over 60 countries; available in both public and private sectors.
Progestin + estrogen: 25 mg DMPA + 5 mg estradiol cypionate	Upjohn, WHO	*Cyclofem*/Aplicaciónes Farmaceuticas (Mexico), Upjohn (US) *Cyclo Gestor*/PT Tunggal, PT Triyasa Nagamas Farma (Indonesia)	Every month	Registered in Guatemala, Indonesia, Mexico, Peru, and Thailand
Progestin + estrogen: 50 mg NET EN + 5 mg estradiol valerate	WHO	*Mesigyna*/Schering AG	Every month	Registered in Argentina, Brazil, and Mexico
Progestin + estrogen: 150 mg dihydroxy-progesterone acetophenide + 10 mg estradiol enanthate	Squibb Pharma-ceutical Company	*Perlutan, Topasel, Agurin, Horprotal, Uno-Ciclo*/ Various manufacturers in Latin America	Every month	Available in pharmacies in many Latin American countries and Spain; generally not available in public family planning programs.
Half-dose: 75 mg dihydroxyprogesterone acetophenide + 5 mg estradiol enanthate		*Anafertin, Yectames*/Various manufacturers in Latin America	Every month	
Progestin + estrogen: 250 mg 17α-hydroxy-progesterone caproate + 5 mg estradiol valerate	Chinese researchers; Squibb Pharmaceutical Company	Chinese *Injectable No. 1*	Every month; 2 injections in first month	China

[a]Called Norigest in Pakistan. [b]Alternative schedule: every 2 months for 6 months and then every 3 months
Sources: Warner-Rowe (318), WHO 1990 (333), WHO 1993 (331)
Population Reports

phenide and estradiol enanthate, which was originally developed by Squibb Pharmaceutical Company in the 1960s and marketed under the brand name *Deladroxate*. Within a few years Squibb withdrew *Deladroxate*, but the same formulation, manufactured by others, is now marketed in Latin America and Spain under a variety of other brand names (see Table 1). It has not been thoroughly studied (223, 331).

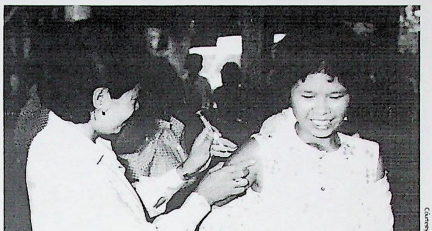
Two new monthly injectables, *Cyclofem* and *Mesigyna*, have completed multinational clinical trials conducted by WHO. They are being introduced in a number of countries.

- *Cyclofem*, previously known as *Cycloprovera*, combines DMPA and the estrogen estradiol cypionate. The Upjohn Company developed *Cycloprovera* and turned it over to WHO in 1984.
- *Mesigyna*, developed by WHO, combines NET-EN and the estrogen estradiol valerate.

Introductory trials of *Cyclofem* have been conducted in Chile, Indonesia, Jamaica, Mexico, Thailand, and Tunisia, and the new injectable has been registered in Guatemala, Indonesia, Mexico, Peru, and Thailand. The Concept Foundation, a private nonprofit organization set up by the Program for Appropriate Technology in Health (PATH) and given rights to *Cyclofem* by WHO, has licensed manufacturers in Indonesia and Mexico to produce *Cyclofem* and has identified distributors in other countries, primarily in Latin America. The Upjohn Company has obtained rights to *Cyclofem* in the US and in several other developed and developing countries. Upjohn plans to submit an application for *Cyclofem* to the US FDA by August 1996 (318).

Schering AG is handling registration, distribution, and marketing of *Mesigyna*. Schering AG plans to begin marketing *Mesigyna* in Latin America. *Mesigyna* is manufactured in Mexico and has been registered in Argentina and Brazil as well as Mexico (74).

With new opportunities to offer injectables, policymakers, program managers, and providers need to reacquaint themselves with these contraceptives: their effectiveness and reversibility, side effects, and noncontraceptive benefits, why women use injectables, and how users respond to side effects. This knowledge can help program staff make decisions concerning communication and service delivery issues posed by injectables (see "Lessons Learned" on back of "DMPA at a Glance").



A Thai woman receives an injection of DMPA from a provider who traveled to her village in a mobile clinic. The McCormick Family Planning Program began the mobile clinic in 1969 to reach women in rural areas of northern Thailand. In 1970 it was one of the first programs to offer DMPA, which became its most popular method.

Use of Injectables

Except in a handful of countries, few women use injectable contraceptives compared with other methods. Statistics from donor agencies, however, suggest that use is increasing.

About 12 million women in developing countries use injectable contraceptives, 1.5% of married women of reproductive age and about 3% of married contraceptive users. By comparison, 36% of married contraceptive users rely on voluntary female sterilization, 25% on IUDs, 12% on oral contraceptives, 9% on vasectomy, and 6% on condoms. In most countries levels of use of injectables are too low to detect any trends over time (83, 195).

Regulatory delay in the US and the controversy surrounding injectables have limited availability and thus use around the world. Many clinics do not offer injectables, or they often run short of supplies (4, 19, 134, 144, 262, 281, 297, 366). In Bangladesh, for example, even though injectables are widely available, 58% of providers and program managers surveyed in 1992 said that lack of supply had forced them to turn away would-be users; 11% of women said that they had stopped using injectables or had switched to another method because they could not get an injection (4). In 1994, 5% of married women of reproductive age in Bangladesh were using injectables (218).

Knowledge of injectables is not as widespread as knowledge of some other methods. For example, in 31 of 53 countries covered by Demographic and Health Surveys or similar surveys, one-quarter or more of married women of reproductive age did not know about injectables (268) (see Table 2). (By comparison, in 16 countries one-quarter or more did not know about OCs.) Women who know of injectables often do not know where to obtain them.

A few countries offer a contrast to the world pattern. In the countries with the greatest use of injectables—Indonesia, at 15% of married women of reproductive age and Thailand, at 12%—injectables have been widely available for more than 15 years. Thailand registered DMPA in 1970 and began to offer it in the national family planning program in 1975, becoming one of the first countries to do so (20, 34). Between 1987 and 1991 use in Thailand increased from 9% to 12% of married women of reproductive age. Indonesia registered DMPA in 1976, and it is manufactured locally (187). Between 1987 and 1994 use increased from 10% to

Table 2

Knowledge and Current Use of Injectable Contraceptives Among Married Women of Reproductive Age, Survey Findings, 1984–1994

Region, Country, & Year of Survey	% Aware of: Any Modern Method	% Aware of: Injectables	% Currently Using: Any Modern Method	% Currently Using: Injectables	% of Contraceptive Users Who Use Injectables
AFRICA					
Botswana 1988	96	91	33	6	18
Burkina Faso 1993	63	41	4	<1	<25
Burundi 1987	65	58	1	1	100
Cameroon 1991	63	40	4	0	0
Ghana 1988	77	48	4	0	0
Kenya1993	97	93	27	7	26
Liberia 1986	68	43	5	0	0
Madagascar 1992	62	48	5	2	40
Malawi 1992	92	68	7	2	29
Mali 1987	30	18	1	0	0
Mauritius1991	100	94	49	4	8
Namibia 1992	90	85	26	8	31
Niger 1992	58	39	2	1	50
Nigeria 1990	42	34	4	1	25
Senegal 1992–93	70	34	5	<1*	<20
South Africa 1987–89	NA	NA	56	23	41
Black	NA	NA	49	27	55
White	NA	NA	79	3	4
Sudan 1989–90	71	46	6	0	0
Swaziland 1988	NA	75	17	4	24
Tanzania 1991–92	72	40	7	0	0
Togo 1988	82	61	3	0	0
Uganda 1988–89	79	41	3	0	0
Zambia 1992	87	38	9	0	0
Zimbabwe 1994	99	87	42	3	7
ASIA & PACIFIC					
Bangladesh 1993–94	100	97	36	5	14
China 1988	NA	NA	71	<1	<1
India 1992–93	96	19	36	0	0
Indonesia 1994	96	91	52	15	29
Nepal 1991	93	65	24	2	8
Pakistan 1990–91	77	62	9	1	11
Philippines 1993	97	54	25	<1	<4
Sri Lanka 1987	99	85	41	3	7
Thailand 1991	NA	NA	69	12	18
Vietnam 1994	NA	NA	65	<1	<1
LATIN AMERICA & CARIBBEAN					
Belize 1991	NA	86	42	4	10
Bolivia 1989	69	44	13	1	8
Brazil 1986	100	58	57	1	2
Northeast 1991	100	85	54	<1	<2
Colombia 1990	100	92	55	2	4
Costa Rica 1986	NA	90	58	1	2
Dominican Rep. 1991	100	57	52	0	0
Ecuador 1989	92	72	42	0	0
El Salvador 1988	NA	81	44	1	2
Guatemala 1987	72	46	19	1	5
Haiti 1989	NA	61	9	2	20
Jamaica 1993	NA	NA	58	6	10
Mexico 1987	93	87	46	3	7
Panama 1984	NA	86	53	1	2
Paraguay 1990	98	89	35	5	14
Peru 1991–92	95	82	33	2	6
Trinidad & Tobago 1987	99	80	46	1	2
NEAR EAST & NORTH AFRICA					
Egypt 1992	100	82	45	<1	<2
Jordan 1990	99	51	27	0	0
Morocco 1992	99	63	36	0	0
Tunisia 1988	99	60	41	1	2
Turkey 1993	99	39	35	<1	<1
Yemen 1991–92	53	32	6	1	17

*Includes Norplant

Sources: Robey et al. 1992 (268) except: El-Zanaty et al. 1993 (73) (Egypt); Ferraz et al. 1992 (82) (Brazil); IIPS 1994 (135) (India); Kenya & DHS 1994 (156); Indonesia et al. 1994 (131); Katjiuanjo et al. 1993 (153) (Namibia); Knodel 1995 (163) (Thailand, Vietnam); Konaté et al. 1994 (170) (Burkina Faso); McFarlane et al. 1994 (202) (Jamaica); Malawi & DHS 1994 (191); Mostert 1990 (213) (South Africa); Ndhaye et al. 1994 (219) (Senegal); Nipon et al. 1994 (218) (Bangladesh); NIV 1992 (220) (Nepal); Philippines & DHS 1994 (249); Reteno et al. 1994 (266) (Madagascar); Turkey & DHS 1994 (310); Zimbabwe CSO & DHS 1995 (358)

15% of married women of reproductive age. Injectables are well liked in these countries, where women value the convenience of injectables and are not discouraged by irregular menstrual bleeding or amenorrhea (see pp. 9–12).

Among developed countries the highest prevalence of injectables use is in South Africa (see Table 2) and New Zealand. In 1993–94, 4% of visits to the Family Planning Association of New Zealand were for initial or repeat injections of DMPA (206). Surveys in other developed countries do not mention injectables or else include them among "other" methods (228, 289, 319). In the US the latest national survey was done before DMPA was approved (247). The Planned Parenthood Federation of America supplied DMPA to about 141,000 women in 1994, about 7% of their family planning clients (363).

Shipments by Donors Increase

Donor agencies report increasing orders for injectables in the 1990s. The United Nations Population Fund (UNFPA), the largest supplier of injectables, provided about 12 million doses in 1992 and 20 million doses in 1994, including shipments for the World Bank. DMPA makes up three-quarters of UNFPA shipments of injectables, and NET EN, one-quarter (118). Thus in 1994 UNFPA shipped enough injectables for about 4.6 million woman-years of use. Deliveries of DMPA by the International Planned Parenthood Federation (IPPF) increased from 336,000 doses in 1991 to 735,000 in 1994. Deliveries of NET EN increased from 305,000 in 1991 to 438,000 in 1994 (145).

USAID plans to deliver at least 2.6 million doses of DMPA in 1995—enough for 650,000 women for one year. The agency delivered 1 million doses in 1994 between August, when shipments began, and December. The largest shipments for 1995 are planned for Nepal (311,200 doses), Mozambique (248,000), Peru (215,600), Tanzania (206,400), and Nigeria (200,000) (45).

Effectiveness and Reversibility

Injectable contraceptives combine almost complete effectiveness with reliable reversibility. Most clinical trials report less than 1 pregnancy per 100 women in the first year of use (39, 41, 271, 277, 336, 338, 340, 342). Thus injectables are comparable in effectiveness to Norplant® implants, the TCu-380A IUD, and voluntary sterilization.

Women who have used DMPA or NET EN and stop to have a baby may have to wait several months longer on average for pregnancy than former IUD or OC users. Thus rumors persist that some women who use injectables become sterile. In fact, after two years pregnancy rates among former DMPA, IUD, and OC users are the same. Providers may need to reassure clients and the public that injectables do not cause infertility but to note that women should expect a wait of some months after stopping injectables to become pregnant. Service policies based on a fear of infertility—in particular, age and parity restrictions—can be dropped (see p. 24).

Effectiveness

Injectables work mainly by preventing ovulation. They suppress the surge in hormones from the pituitary gland that is necessary for ovulation (70). They also thicken cervical mucus, making it a barrier to sperm (357).

DMPA has been tested in a variety of doses and injection schedules. The 150 mg dose every three months (or 12 weeks or 90 days) is the most widely used regimen. The first-year failure rate in the US for the 150 mg dose is 0.3% compared with 0.4% for voluntary female sterilization, 0.4% for *Norplant* implants, 0.8% for the TCu-380A IUD, and 3.0% for oral contraceptives (370).

The 200 mg dose of NET EN is mostly used on a 2-month schedule. Some programs use a 2-month schedule for the first six months and then give injections every three months (107, 193, 200, 209, 342). In a WHO trial the one-year pregnancy rates for the two schedules were not significantly different: 0.4 per 100 women on the 2-month schedule and 0.6 on the 2- and then 3-month schedule. IPPF and WHO recommend the 2-month schedule, however (333, 365).

Monthly injectables also are highly effective (157, 166, 271, 331, 336). In a WHO trial there were two pregnancies among 1,152 *Mesigyna* users (0.2 per 100 women) and none among 1,168 *Cyclofem* users after one year (336). Women using *Deladroxate*, the precursor of many monthly injectables currently available through pharmacies in Latin America, had no pregnancies in 10 studies conducted in the 1960s and 1970s and covering more than 1,500 woman-years of use (166).

The effectiveness of injectables depends on the timing of the first injection, adherence to the injection schedule, and the injection technique (see box, this page). In a Thai study the timing of the first injection made a significant difference in the accidental pregnancy rate. The 3-month pregnancy rate was 0.16 per 100 women receiving their first injection in the first eight days of the menstrual cycle but 0.62 per 100 women receiving their first injection after the eighth day (102). Thus the first injection is usually given during the first seven days of the menstrual cycle but can be given at other times (see Table 3).

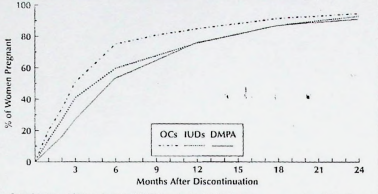
The dosages and injection schedules ensure that users can come a little late for the next injection without risking pregnancy. As a guideline for programs, DMPA users can come at least two weeks late; NET EN users, at least one week late; and users of monthly injectables, up to three days late. If users come any later, the provider must be reasonably sure that they are not pregnant before giving the next injection. Clients also may return early (see Table 3).

Injection Technique Important

Careful injection technique ensures that the full dose is absorbed at the right rate and thus is fully effective.

- With DMPA, providers need to shake vials to dissolve any sediment at the bottom, but they should not shake so vigorously that the liquid becomes frothy and difficult to draw into the syringe.
- With NET EN, warming vials to body temperature thins the viscous solution and makes it easier to draw completely into the syringe (333).
- With all injectables, the injection should be given in muscle because absorption may be too slow if the provider injects into fat (85). In contrast, massaging the injection site accelerates absorption and thus also should be avoided (333).

Figure 2. Cumulative Conception Rates for Women Discontinuing DMPA, OCs, and IUDs to Become Pregnant



Note: Researchers assumed that users discontinued DMPA 15 weeks after their last injection.
Source: Pardthaisong 1984 (236)

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Return to Fertility

Most former users of injectables can expect to become pregnant within a year after their last injection if they do not use another contraceptive. The largest study of return to fertility among users of DMPA, conducted in Thailand, found that women conceived nine months on average after the last injection, or 5.5 months after discontinuing, which the researchers assumed to be 15 weeks after the last injection (236). Other studies report similar findings (24, 277). By comparison, OC users in the Thai study conceived on average three months after discontinuing, and IUD users, 4.5 months after discontinuing (233, 235, 236) (see Figure 2). An Indian study found that 69 former NET EN users on the 2- and then 3-month schedule conceived on average 11 months after the last injection, or 8 months

Table 3. Progestin-Only Injectables: When to Give the Injection

Question	*Recommendation*
When can the first injection be given?	Any time the provider can be reasonably sure that a woman is not pregnant[a]—for example, during any of the 7 days that begin with the onset of menses (days 1 through 7 of the menstrual cycle). **Use of backup methods:** For a woman having menstrual cycles, no backup method is needed if she is in the first 7 days of her menstrual cycle and is still menstruating. If she is in the first 7 days of her cycle but is not menstruating, some programs may recommend use of a backup method for 1 week. If injections are started after day 7 of a regular cycle, a backup method (or abstinence) for up to 1 week may be recommended.
Postpartum: When can the first injection be given?	**For breastfeeding women:** If she does not rely on the Lactational Amenorrhea Method (LAM) or another nonhormonal method, ideally wait until 6 weeks postpartum. If the woman relies on LAM, she can start DMPA or NET EN when her menses return, or when she is no longer fully or nearly fully breastfeeding, or at 6 months postpartum, whichever comes first. **For women who are not breastfeeding:** The first DMPA or NET EN injection can be given immediately postpartum or whenever the provider can be reasonably sure that the woman is not pregnant.[a]
After spontaneous or induced abortion: When can the first injection be given?	Within the next 7 days, because fertility returns almost immediately.
Where should the injection be given?	Into the muscle of the arm or the buttock. The choice is best left to the client.
Grace period: How late or early can users come for subsequent injections?	DMPA: Up to 2 weeks late and possibly up to 4 weeks late depending on the population. Up to 4 weeks early although not ideal. **NET EN[b]:** Up to 1 week late and possibly up to 2 weeks late depending on the population. Up to 2 weeks early although not ideal. **Monthly injectables:** Up to 3 days late and up to 3 days early. If a woman returns after the grace period, she can receive the injection if the provider is reasonably sure that she is not pregnant.[a] If she may be pregnant, she should use a barrier method until it is clear whether or not she is pregnant.
Cumulative effect? Does a woman have to stop using injectables at any point to give her body a rest?	No. There is no cumulative effect of injectables, and extended amenorrhea is not a medical problem. It may be an advantage in areas where anemia is common. Counseling can reassure the user who is worried about amenorrhea.

[a] *A provider can be reasonably sure that a woman is not pregnant if she has no symptoms or signs of pregnancy and she:*
- *has not had intercourse since her last normal menses; or*
- *has been correctly and consistently using a reliable contraceptive; or*
- *is within the first 7 days after normal menses; or*
- *is within 4 weeks postpartum (for nonlactating women); or*
- *is within the first 7 days postabortion, or*
- *is fully breastfeeding, amenorrheic, and less than 6 months postpartum.*

If available, a pregnancy test may be helpful, but it is not required.

[b] *2-month schedule.*

Source: *Technical Guidance Working Group 1994 (299)* *Population Reports*

after they would have received their next injection. By comparison, 110 former IUD users in the study conceived on average about 3.5 months after discontinuing (21). With monthly injectables, studies of ovarian function indicate that most former users first ovulate three to four months after the last injection, or two to three months after the next injection would have been given (26, 27, 339).

Women have to wait to conceive partly because injectables remain in the bloodstream for several months after the next injection would have been given. DMPA, for example, is detectable in the bloodstream for eight months on average after one injection (277).

There is no evidence that injectables cause infertility. In the Thai study 91% of former DMPA users had conceived within two years after discontinuing compared with 93% of former IUD users and 95% of former OC users. These differences are not statistically significant (236). By comparison, among US couples stopping contraception of all types, about 90% have conceived in 18 months, and about 10% of couples are infertile (351, 367). Amenorrhea may persist for several months after women discontinue injectables. Providers should warn women of this and reassure them that their regular cycles will return eventually.

Long-term users of injectables need not fear any cumulative impairment of fertility. There is no difference in the time to return of fertility between long-term and short-term users of DMPA (24, 87, 92, 235, 236, 277).

Despite this evidence, to avoid any possible blame for subsequent infertility, some programs have required women to have been pregnant at least once before allowing them to use DMPA. Such a policy restricts use unnecessarily. The McCormick Family Planning Program in Thailand followed this policy at first but removed it because of demand from women without children; indeed, some women lied about a previous pregnancy to be able to use DMPA. Following up these women after they stopped using DMPA, the program found no difference between their fertility and that of DMPA users who had had previous pregnancies (199).

Side Effects and Complications

Disruption of regular menstrual bleeding and amenorrhea are the most common side effects of injectables and the main reasons that women stop using them. Also, most women report weight gain. Far fewer women report a variety of other side effects, for example, headaches, dizziness, abdominal discomfort, acne, and moodiness. These side effects are bothersome for some women, but they are generally not dangerous. Some of these less common side effects are plausible reactions to hormones, while others occur at rates typical of the general population and cannot be clearly attributed to injectables.

Because bleeding changes and weight gain are so common, during counseling all women who choose injectables should be told of these likely changes. Program managers need to decide what other side effects to mention based in part on the side effects most often reported by clients. These decisions should be made with the goal of helping clients to make a fully informed choice and to use the method effectively and confidently (see pp.18–19).

A Colombian poster by Profamilia offers 1-month and 3-month injectables along with other family planning methods. Injectables add to the choice of methods a very effective hormonal contraceptive that is private and requires no daily pill-taking

Researchers have investigated whether use of injectables might increase the risk of certain serious conditions. In general, studies of the cardiovascular system, carbohydrate metabolism, liver function, and lactation have been reassuring (see Table 4). Some recommended restrictions on use of DMPA and NET EN, however, are based on their effect on cholesterol metabolism (see p. 12). Conflicting findings on bone density and the outcome of pregnancy are being debated (see pp. 13–14).

Bleeding Changes

The most reliable information on bleeding patterns among women using injectables and other hormonal contraceptives comes from WHO-coordinated multicenter clinical trials in which women keep menstrual diaries. These records document the diversity of bleeding patterns as well as the averages (see Table 5 for definitions) (30, 31, 331). Data on menstrual bleeding among women not using hormonal contraceptives, used for comparison, were collected from 2,700 US women between 1935 and 1962 by Alan Treloar and colleagues (308, 331).

Only about 10% of DMPA users have normal cycles in the first year of use. DMPA users can expect to have irregular bleeding in the first six months and then infrequent bleeding or amenorrhea in the next six months and beyond. By comparison, in a WHO trial of six OCs, 59% to 87% of women had normal bleeding patterns after one year (349).

NET EN has somewhat less effect on bleeding patterns than DMPA. In a comparative trial bleeding episodes in the first six months were significantly shorter among NET EN users than among DMPA users. Bleeding patterns after six months were similar, however. Amenorrhea lasting more than 90 days was significantly less common among NET EN users (342).

With monthly injectables, about half of women have regular bleeding during the first year of use (see Table 5). Users tend to have irregular or prolonged bleeding in the first three months and then increasingly regular patterns by the end of the first year (272, 331). In particular, the first bleeding interval may be shorter than usual (157). With monthly

Table 4. Investigating Injectables: Study Findings

	DMPA and NET EN		Monthly Injectables	
	Findings	*Ref. Nos.*	*Findings*	*Ref. Nos.*
Blood pressure	Most studies find no effect.	75, 122, 129, 276, 338	No significant effects	108, 271, 336
Blood coagulation	Most studies find no effect.	77, 122, 123, 124, 201, 208, 209, 309	No significant effects	86, 94, 208, 331
Cholesterol	Most studies find higher levels of low-density lipoprotein (LDL) cholesterol and lower levels of high-density lipoprotein (HDL) cholesterol.[a]	6, 75, 77, 78, 122, 158, 200, 334	Most studies find no significant effects on total, LDL, or HDL cholesterol.	86, 94, 108, 331
Carbohydrate metabolism	Do not induce diabetes in normal women but may significantly increase glucose and insulin levels.	7, 47, 76, 105, 122, 184	No significant effects	86, 94, 108, 331
Liver function	Most studies find no effect.[b]	7, 47, 276, 280	No significant effects	108
Lactation	Increase or no effect on milk volume	126, 165, 197, 329	Not studied. (With combined oral contraceptives, the estrogen component decreases the quantity and quality of breast milk (329).)	
	No effect or possibly beneficial effect on quality of breast milk.[c]	52, 56, 72, 197, 329		
	Lengthening or no effect on duration of lactation[d]	42, 143, 279, 347, 354, 356		
	No effect on nursing infants[e]	61, 126, 143, 152, 168, 237, 279, 347, 348		

[a] *Three studies find no changes in LDL or HDL cholesterol (93, 122, 300).*
[b] *One study of DMPA reported a possible enhancing effect through induction of liver enzymes (79).*
[c] *Measured by fat concentration, calories, minerals, protein, lactose, and immunoglobulin.*
[d] *One review concluded that DMPA and Norplant implants had little effect on women whose breastfeeding was partial or taken but shortened the duration of breastfeeding among women who practiced full breastfeeding (175).*
[e] *Nursing infants ingest a small amount of hormone if their mothers use injectables—up to 10 mg of DMPA or 2 mg of NET EN per day (56). Studies have examined children's weight, height, movement, skills, and general health from ages 1 to 15 years.*

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injectables, most women have bleeding 10 to 15 days after the first injection and then every 30 days after that. Thus women have regular bleeding 10 to 15 days after each injection (336).

Bleeding patterns may differ among ethnic groups. Southeast Asian women using DMPA, for example, report more days of bleeding and spotting than women in the Caribbean, Europe, South Asia, or North Africa. North African women report amenorrhea more often than European women. The full reasons for these differences are not known. Some of the variation may be due to regional differences in the nutritional status of users, sensitivity to menstrual changes and thus reporting, and accuracy of menstrual diaries (32).

Individual differences may also affect bleeding patterns. For example, among DMPA users in a WHO trial, heavy women tended to have more amenorrhea and less bleeding than lighter women. Among women using NET EN, however, there was no relationship between weight and amenorrhea (341). Bleeding patterns of individuals cannot be predicted.

Discontinuation of use because of menstrual bleeding changes or amenorrhea in WHO trials reflected their differing effects on bleeding patterns. After one year 15% of DMPA users had discontinued use because of bleeding changes, and about another 12%, because of amenorrhea. NET EN users discontinued for bleeding problems at about the same rate as DMPA users, but only 7% discontinued because of amenorrhea. About 7% of users of monthly injectables discontinued for bleeding problems, and only about 2% discontinued because of amenorrhea (89, 157, 331, 338, 340, 342). Frequent bleeding or a worsening pattern—a change from a regular pattern to amenorrhea or infrequent bleeding, for example—was especially likely to lead to discontinuation (103, 337).

Discontinuation rates vary widely among regions. In a one-year study of DMPA, for example, Thai women had a median of 4.7 months without bleeding or spotting, but none discontinued because of amenorrhea. Egyptian women, in contrast, had a median of 5.0 months without bleeding or spotting, and 27% discontinued because of amenorrhea (338). Counseling may have influenced these discontinuation rates.

The reasons that women give for stopping a method, however, may not always be the real reasons. Some may want to stop for a personal reason, but, afraid the provider will not accept it, they give medical reasons instead. Others may have been troubled by a number of side effects but tell providers only about the one that made the most difference. For example, in a clinical trial of DMPA, almost two-thirds of women who discontinued citing other medical or non-medical reasons or who were lost to follow-up after several injections had severely disrupted bleeding patterns (339).

Clinical implications. Since bleeding patterns vary among injectables, programs may offer clients a choice. In Namibia, for example, providers recommend NET EN over DMPA for younger clients partly because, providers say, it causes less

Table 5. Menstrual Patterns Among Users of Injectable Contraceptives, WHO Multicenter Studies, 1983–1988

Type of Injectable or Untreated	Months	Number of Diaries	% Experiencing Bleeding Patterns						Total Variations from Regular Pattern[a]
			Regular Patterns	Amenorrhea	Infrequent Bleeding	Irregular Bleeding	Frequent Bleeding	Prolonged Bleeding	
DMPA	0-3	509	9.0	10.6	15.7	46.0	17.7	43.4	91.0
	4-6	406	6.9	23.9	25.8	35.7	10.5	27.7	93.1
	7-9	311	6.4	37.0	24.8	27.7	8.3	17.3	93.6
	10-12	241	8.3	38.6	27.8	17.9	6.6	16.5	91.7
Cyclofem.....	0-3	1,001	43.0	0.1	0.1	39.6	22.3	20.8	57.0
	4-6	885	63.2	0.2	3.4	23.5	3.3	13.3	36.8
	7-9	802	61.3	1.1	5.4	25.4	2.8	9.4	38.7
	10-12	730	70.0	2.3	3.7	13.6	6.5	10.1	30.0
Mesigyna.....	0-3	1,000	47.2	0.2	0.1	34.6	29.6	16.2	52.8
	4-6	860	62.8	0.6	2.2	25.2	5.5	11.1	37.2
	7-9	766	63.3	1.3	2.9	24.8	4.9	12.6	36.7
	10-12	713	68.4	2.0	5.0	14.6	6.2	12.7	31.6
Untreated[b] ...	0-3	3,893	90.3	1.3	3.4	4.5	0.2	2.6	9.7
	4-6	3,893	90.8	1.5	2.9	4.8	0.3	2.3	9.2
	7-9	3,893	90.1	1.3	2.8	5.4	0.1	2.6	9.9
	10-12	3,893	85.1	1.6	3.1	8.6	0.3	4.3	14.9

Note: Patterns are defined for 90-day observation periods:
Regular patterns—Three episodes of bleeding or spotting each lasting about five days.
Amenorrhea—No bleeding.
Infrequent bleeding—Fewer than two bleeding or spotting episodes.
Frequent bleeding—More than four bleeding or spotting episodes.
Irregular bleeding—A pattern in which the difference between the longest and shortest bleeding-free intervals is more than 17 days.
Prolonged bleeding—At least one bleeding or spotting episode lasting 10 days or more (30, 31, 331).

A bleeding episode is defined as requiring the use of a pad or other protection. A spotting episode does not require protection. No comparable data for NET EN are available.
[a] *Some subjects appear in more than one category.*
[b] *From Treloar et al. 1967 (308).*

Source: WHO 1993 (331).

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menstrual disruption (186). In introductory trials of *Cyclofem* in Indonesia, Jamaica, and Thailand, 36% to 45% of women had switched from DMPA mainly because of bleeding problems (110). Offering several injectables may pose logistical problems, however (see p. 22). Counseling can help women deal with menstrual bleeding changes or amenorrhea (see p. 18 and Counseling Guide).

Some women using progestin-only injectables cannot accept frequent bleeding despite counseling. They have no choice but to continue for several months, until the injectable wears off. Providers have used several approaches to decrease bleeding.

If estrogens are not contraindicated, providers have given one to three weeks of combined oral contraceptives or of estrogen, which temporarily reduce or stop most episodes of bleeding. For example, in a WHO study among women with bleeding lasting seven days or more during the first six months of DMPA use, 93% of women given ethinyl estradiol stopped bleeding while under treatment compared with about three-quarters of women given a placebo, a significant difference (60). Women also have used OCs for a few months to get over initial irregular bleeding caused by DMPA.

Over the long term, however, estrogen may be no more helpful than counseling. After treatment in the WHO study, women given ethinyl estradiol had fewer bleeding days but more varied patterns than women given the placebo, and after one year rates of discontinuation for bleeding were the same for both groups (60).

Anti-inflammatory drugs (except aspirin) also have helped to control bleeding. Ibuprofen and other nonsteroidal anti-inflammatory drugs block the synthesis of prostaglandins, which induce bleeding (299).

Giving the next injection of DMPA or NET EN early can temporarily reduce bleeding among women who want to continue despite bleeding problems. Injections generally should not be given sooner than four weeks after the previous injection, however (299).

Women with heavy or prolonged bleeding—twice as much or twice as long as usual for them—require special care. Such bleeding is unusual and rarely requires treatment. A survey of 35 researchers in 20 countries found that 1% to 2% of users have heavy bleeding (88). Only 6 of 1,200 women participating in a WHO multicenter trial required treatment for heavy bleeding, and in the first 10 years of the McCormick Family Planning Program in Thailand, only two of more than 70,000 DMPA users had very heavy bleeding that was considered a medical complication (20, 346). Nevertheless, programs must ensure that women using injectables can be treated for heavy bleeding.

Before treating heavy bleeding, providers should consider other causes of bleeding, such as pregnancy, cancer, or sexually transmitted disease, and should check for anemia. If estrogen is not contraindicated, providers may give

high or low blood pressure, or low blood sugar could cause dizziness. Lack of exercise or pregnancy could cause weight gain. In some instances providers can encourage women concerned about weight gain to diet and exercise more.

If other causes are unlikely, these side effects often can be handled through counseling. Clients may need reassurance that these side effects are not dangerous and are not symptoms of more serious problems. If, after counseling, a client insists that side effects are unacceptable, providers should recommend that she choose another method and help her to do so without expressing criticism or disapproval (259).

To provide support and reassurance, providers emphasize that clients should return for help whenever they have problems or questions. If possible, clients who receive injections at a clinic should return there for help because those providers are trained to handle side effects of injectables. Inexperienced providers at other clinics may respond inappropriately—for example, treating bleeding by dilation and curettage (23).

Because of the effect of progestin-only injectables on cholesterol levels, a group of experts assembled by WHO recommends that women with severe vascular diseases (such as severe hypertension, a history of stroke, or ischemic heart disease) or with diabetes involving vascular complications should not use these injectables unless other methods are not available, or, in a provider's careful clinical judgment, other methods would not be acceptable. Women who develop these conditions while using progestin-only injectables or who develop recurrent severe headaches with focal neurologic symptoms should see a doctor or nurse and switch to a nonhormonal contraceptive method because there is some concern that such headaches sometimes progress to stroke (332) (see p. 24).

Bone Density

DMPA may have both an enhancing and depleting effect on bone. Estrogen maintains bone density by slowing bone resorption (36). In premenopausal women medroxyprogesterone acetate (MPA) suppresses estrogen production, which increases loss of bone density (58, 287). In contrast, in postmenopausal women, whose natural estrogen levels are already low, MPA slows loss of bone density (367).

Three studies have examined osteoporosis (reduction in the quantity of bone) among DMPA users. A Thai study reported no difference in bone density between 75 women who had been using DMPA for at least three years and 147 women who had not used DMPA (316). A 6-month Swedish study found no change in bone density among 9 DMPA users (215). A study in New Zealand, however, found a difference of about 7% in the density of the lumbar spine and femoral neck between women 25 to 51 years old who had been using DMPA for at least five years, on one hand, and other premenopausal women, on the other (58). The longer duration of DMPA use in the New Zealand study may explain the different results. A 7% bone loss would not increase the risk of fracture immediately but might increase the risk of a fracture at some time in a woman's life by 10% to 15% (207). The loss appeared to reverse, however, when women stopped using DMPA (57). In general, genetic inheritance and family history have the most influence on bone development, explaining 10% to 50% of the variation in bone mass among premenopausal women. Exercise, diet, and smoking also affect bone density (287).

The New Zealand study has been criticized. It was retrospective and thus could not measure bone densities of the women before they started DMPA (296). Also, the study did not control for smoking (369). Two prospective studies are under way in the US (34, 38). There are no published studies of the effects of NET EN on bone density.

Clinical implications. Findings on bone density to date do not warrant denying DMPA to any group of women. Providers may give special consideration to women under age 16, however. Loss of bone mass at this age may increase the risk of osteoporosis after menopause. Pregnancy at this age, however, also can affect bone mass (287). Thus the benefits of an effective, reversible method such as DMPA to sexually active young women probably outweigh the risks (332).

Fetal and Child Development

A fetus could be exposed to contraceptive hormones in the rare cases that injectables fail to prevent pregnancy, if a woman receives an injection while pregnant, or if a woman becomes pregnant after discontinuing the method but hormones are still in her bloodstream.

The great majority of studies assessing fetal exposure to oral contraceptives or other progestins or estrogens at contraceptive doses find no effects on development of the heart, limbs, spinal chord, brain, or genitalia (40, 49, 59, 155, 265, 276, 282, 326, 328). Clinical findings with DMPA have been mixed but largely reassuring. Early clinical studies of DMPA in Bangladesh, Sri Lanka, and Thailand found no evidence of developmental defects after fetal exposure (25, 169, 240, 276). A Thai cohort study, however, involving about 4,000 women not using contraception, 3,300 OC users, and 1,200 DMPA users, reported that children of DMPA users were more likely to have extra or missing fingers (polydactyly and syndactyly) and chromosomal defects. The researchers doubt that DMPA caused the defects because (1) limb defects and chromosomal defects generally have different causes; (2) other studies have not found such defects among DMPA users; and (3) 9 of the 15 children with defects were conceived more than nine months after the last injection, when DMPA would no longer be in the bloodstream; only 4 were definitely exposed to DMPA (234).

Another Thai study, which reported on more than 1,400 pregnancies of women who had used DMPA, found a link between DMPA exposure during gestation and the outcome of pregnancy. The study reported that exposure to DMPA within one month before or after conception almost doubled the risk of low birthweight and, perhaps partly as a result, more than doubled the risk of neonatal death. Risks declined with increasing time between exposure to DMPA and conception in the study, a dose-response relationship that strengthens the link to DMPA (100, 101, 232). If there is an increased risk, however, the resulting attributable risk would be very low because accidental pregnancies among DMPA users are rare. The mechanism of the effect is unknown. Followed to age 17, children exposed to DMPA during pregnancy have grown and developed normally (237).

The studies of pregnancy outcome have been criticized because of the difficulty of controlling other related factors and of estimating gestational age because of DMPA-induced amenorrhea. Both difficulties could bias the finding of a

dose-response relationship in the Thai study (106). Further, the study compared unplanned pregnancies among DMPA users with planned pregnancies. Unplanned pregnancies have a higher risk of poor outcome than planned pregnancies (120).

There is little information on possible fetal effects of NET EN. Small clinical studies have found no abnormalities in babies who had been exposed to NET EN during gestation or whose mothers had used NET EN before becoming pregnant (87, 122). No cases of fetal anomalies have been reported to Schering AG (15). There have been no studies of the effect of monthly injectables on fetal development.

Clinical implications. Providers need to be reasonably sure that women are not pregnant when they are given injectables. This can be done by giving the injection in the first seven days after menstruation starts or by asking questions to determine whether a woman has been exposed to the risk of pregnancy since her last menstrual period (see Table 3). If a woman mistakenly receives an injection while pregnant or becomes pregnant while using an injectable, providers can reassure her that contraceptive hormones have no harmful effect on the fetus in the vast majority of cases.

More Evidence in the Cancer Debate

In the 1980s several epidemiologic studies assessed the risk of cancer among women using injectables. As noted (see p. 3), the largest and most carefully controlled of these studies was the WHO Collaborative Study of Neoplasia and Steroid Contraceptives, conducted from 1979 to 1988 in 10 countries. It examined the risk of cancer of the breast, cervix, endometrium, ovary, and liver among users of various hormonal contraceptives. The study investigated DMPA in Kenya, Mexico, and Thailand and reported generally reassuring findings (see Table 6). Little information is available on NET EN or monthly injectables. Inferences about monthly injectables cannot be made from findings on oral contraceptives because they use different hormones, and the daily levels of hormones in the bloodstream differ (283).

Breast Cancer

After skin cancer, breast cancer is the most common cancer among women worldwide. In 1985, the last year for which global estimates are available, there were an estimated 719,000 cases of breast cancer worldwide compared with 437,000 cases of cervical cancer, which has the next highest incidence (239) (see Table 6).

DMPA. The WHO study found no overall increased risk of breast cancer among women using DMPA. A similar finding was reported by a well-controlled study in New Zealand. Both studies, however, found that young women faced an increased risk, as did women in the first few years after they started to use DMPA (243, 301). An analysis of combined data from the two studies found that the increased risk was mainly among women in the first five years after they started DMPA (relative risk of 2.0, statistically significant). Most of these recent users were young women. If women had not developed breast cancer within five years after starting DMPA, they faced no increased risk (284). The few earlier studies of DMPA and breast cancer, smaller and less reliable than the WHO and New Zealand studies, reported conflicting results (104, 180, 183).

The pattern of increased risk in recent users but not in users in the distant past suggests that DMPA may speed up the growth of existing tumors rather than turn normal cells into cancerous cells (243, 284, 301). If DMPA initiated breast cancer, women exposed to the largest amounts of DMPA—that is, women who used DMPA the longest—would have the highest risk of breast cancer. Among all users, however, duration of use makes little difference to risk.

Better detection of breast cancer among DMPA users may explain part of the apparently increased risk. If contraceptive users age 20 to 34 detected breast cancer one year earlier than nonusers, their relative risk would be 1.2 (284). The relative size of the tumors in users and nonusers suggests little or no detection bias, however; the tumors in DMPA users were as large as or larger than the tumors in nonusers (301). Another possible explanation involves benign breast disease, which can mask breast cancer. DMPA suppresses benign breast disease and thus could reveal cancerous tumors that remain hidden in women not using DMPA (98).

DMPA users and users of combined OCs may face similar risks of breast cancer. Most studies find no overall increase in risk of breast cancer among OC users, but young users or recent users may be at slightly increased risk (192, 314).

Pregnancy has a similar effect on the risk of breast cancer. Several studies report that after a full-term pregnancy women have a greater risk of breast cancer than women with no children (44, 141, 178, 325). After 15 years, however, women with one child may have less risk of breast cancer than women with no children (141, 178). This pattern, too, suggests that higher than usual levels of reproductive hormones accelerate the development of existing tumors.

If DMPA does increase the risk of breast cancer, the additional cases attributable to DMPA would be slight. Most users are young women whose risk of breast cancer is low; only about 15% of breast cancers occur in women under age 40 (69). According to the WHO study, in Chiang Mai, Thailand, an estimated additional 1 or 2 women per 100,000 might be diagnosed with breast cancer each year because they used DMPA. This estimate applies to women 20 to 35 years of age, whose relative risk of breast cancer in the study was 1.4 if they used DMPA. The incidence of breast cancer among women in this age group who had never used DMPA would be 3.2 per 100,000 per year, according to the study, while, for women who had ever used DMPA, it would be 4.5 per 100,000 per year—a difference of 1.3 cases per 100,000 per year (301). The findings concerning breast cancer do not justify restrictions on the availability of DMPA.

Monthly injectables. The only study of breast cancer among users of monthly injectables found a relative risk of 0.8 (a slight protective effect), not statistically significant. The report used data collected by the WHO study in Chile and Mexico and involved 267 women with breast cancer and 1,520 women in the control group (13).

Cervical Cancer

DMPA. The WHO study found no increased risk of invasive cervical cancer (see Table 6). There were no trends in risk of invasive cancer by duration of use or time since first or last

Table 6. Risk of Various Cancers and Use of DMPA
WHO Collaborative Study of Neoplasia and Steroid Contraceptives, 1979–1988

Site of Cancer[a]	*Ref. No.*	*No. of Cases Who Used DMPA/All Cases*	*No. of Controls Who Used DMPA/All Controls*	*Relative Risk for Women Who Ever Used DMPA (95% Confidence Intervals)*[b]	*Worldwide Incidence Among Women, 1985*[c]
Breast					719,000
WHO Study	301	109/869 (13%)	1,452/11,890 (12%)	1.2 (0.96-1.52)	
WHO + New Zealand[d]	284	219/1,788 (12%)	1,725/13,905 (12%)	1.1 (0.97-1.4)	
Cervix					
Invasive	303	338/2,009 (17%)	1,415/9,583 (15%)	1.1 (0.96-1.29)	437,000
In situ	304	168/757 (22%)[e]	1,375/8,942 (15%)	1.25 (1.02-1.52)[e]	
Endometrium	302	3/122 (2%)	84/919 (9%)	0.2 (0.1-0.8)	140,000
Ovary	291	22/224 (10%)	229/1,781 (13%)	1.1 (0.6-1.8)	162,000
Liver[f]					101,000
Kenya	269	4/22 (18%)	12/142 (9%)	1.64 (0.4-6.6)	
Thailand	269	4/49 (8%)	65/388 (17%)	0.33 (0.1-1.0)	

[a]WHO study data for breast and invasive cervical cancer come from Kenya, Mexico, and Thailand; for cervical carcinoma in situ and ovarian cancer, from Mexico and Thailand; for endometrial cancer, from Thailand.

[b]Relative risk is statistically significant if range of 95% confidence interval does not include 1.0. Among relative risks reported here, relative risk of cervical carcinoma in situ is significantly increased, while risk of endometrial cancer is significantly decreased (protective effect). All others are not significant. Source: Parkin et al. 1993 (239)

[c]Pooled data from WHO and New Zealand studies (243)

[d]Women with symptoms only. Relative risk statistically significant at p<.05.

[e]Results for Kenya and Thailand are presented separately because risk of liver cancer among DMPA users differed significantly between the two countries.

use. Researchers controlled for the sexual behavior of the women and their husbands and for a history of sexually transmitted diseases, among other variables (303).

The study reported a slightly increased risk of cervical cancer *in situ* (cancer confined to the epithelium, the surface layer of the cervix)—1.25 among women with symptoms (statistically significant). To avoid screening bias—more detection of cancer *in situ* without symptoms among DMPA users because they were seeing providers more regularly than nonusers—the researchers emphasize the findings for women who had symptoms at diagnosis. The researchers conclude from these findings—increased risk of *in situ* but not invasive cancer—that the *in situ* lesions induced by DMPA may be reversible or that they do not lead to invasive cancer (304). Other studies of cervical cancer among DMPA users have found no significant increased risk of cervical dysplasia (precancerous lesions) (221, 222), cancer *in situ*, or invasive cancer (227).

Monthly injectables. The only published study devoted exclusively to monthly injectables concluded that users may have a slightly increased risk of cervical cancer (relative risk of 1.3). The report, which analyzed data collected in the WHO study, involved women in Chile and Mexico who had used a monthly injectable containing dihydroxyprogesterone acetophenide and an estrogen, usually estradiol enanthate (300).

Endometrial Cancer

Women who use DMPA reduce their risk of endometrial cancer, according to the WHO study. Thai women using DMPA had a relative risk of 0.2 compared with nonusers (see Table 6). The protective effect lasted for more than 12 years after first use and 8 years after last use. Since only three women with endometrial cancer had used DMPA, the study could not tell whether risk declined with duration of use.

The protective effect of DMPA may be even stronger than the WHO study suggests. All three DMPA users who had endometrial cancer had also taken estrogen to regulate bleeding. Estrogen increases risk of endometrial cancer (317).

Epithelial Ovarian Cancer

The WHO study found no association between use of DMPA and epithelial ovarian cancer (291), which accounts for more than 90% of ovarian cancers (67). The overall relative risk among DMPA users was 1.1, not statistically significant. The study found no pattern of risk related to duration of use, time since first or last use, or age at first use (291).

The failure to find a protective effect is surprising. Like OCs, DMPA prevents ovulation, which reduces the risk of ovarian cancer. Thus the injectable should offer similar protection against ovarian cancer. Women who have ever used OCs have about two-thirds the risk of ovarian cancer of nonusers, and use for five years or more cuts the risk of ovarian cancer in half (290).

Liver Cancer

The two studies of liver cancer and injectable contraceptives, the WHO study and a South African study, report no increased risk. The WHO study reported results for Kenya and Thailand, the only countries where DMPA use is high enough to assess the risk of liver cancer. The relative risk of liver cancer among Kenyan DMPA users was 1.6, and among Thai users, 0.3. The researchers have more confidence in the Thai data because most of the cases of liver cancer were confirmed histologically in Thailand, but only about one-third were confirmed histologically in Kenya (269). The South African study found that users of progestin-only injectables had a relative risk of liver cancer of 0.4, not statistically significant but, like the Thai data, suggesting a protective effect (159).

The User's Perspective on

Women's attitudes toward progestin-only injectables largely reflect their feelings about the privacy and convenience of injections and menstrual bleeding disruptions. These feelings in turn reflect not only the attributes and physiological effects of the method but also women's knowledge and understanding of the method, personal needs, contraceptive experience, partners' attitudes, and cultural norms. Family planning providers can better counsel and advise clients if they are aware of these differing attitudes and physiological responses. Similarly, communication programs must understand people's attitudes and reactions in order to devise effective messages.

The New User

Women choose injectables because:

- They want a highly effective, reversible contraceptive.
- They want a long-acting method but not one that lasts for years. They do not want to take a pill every day.
- They have faith in the effectiveness of injectable medication because of the well-known efficacy of injectable antibiotics and the success of campaigns with injected penicillin, such as yaws eradication.
- They may like amenorrhea, especially if they usually have heavy menstrual flows and cramping.
- They want a contraceptive that can be used privately, a method that can be obtained quickly at the clinic and requires no supplies around the house.
- They want a method that does not require action at the time of sexual relations.
- They want a reliable and safe method that can be used during breastfeeding.
- They have talked with friends or relatives who are using injectables satisfactorily (14, 20, 23, 46, 54, 62, 95, 146, 160, 162, 198, 217, 350).

In interviews women in places as different as Bangladesh and the US mention many of these advantages (14, 62):

Bangladesh

...with pills you have to have a dose every day, and there's a chance of your forgetting. With injectables, you don't have such worries. The field worker keeps track of when I'm supposed to take my shots and comes and gives them to me herself. And since it's a woman who's giving me the shots, my family doesn't object.

One of my husband's relatives once said to me, 'Injectables are good. I've been using them for three years. Come with me and you'll be able to get an injection, too. There won't be any trouble.' So I talked to my husband and after he agreed, I began using injectables. Many others have followed me. Even my sister-in-law uses injectables now.

I started using injectables after I had two children in quick succession.

United States

I got pregnant when I was 13 and had my baby when I was 14. I did not use any birth control when I got pregnant. Depo is much easier than taking the Pill every day. I'm not good at remembering to take pills.

I decided to use the Depo shot because it was very easy. You just come back every three months. I didn't decide to take the Pill because I am on medication for seizures. I thought I would forget to take the pills.

I was a poor pill taker. I thought barrier methods were inconvenient and messy.

The Continuing User

Users' attitudes toward injectables are reflected in discontinuation rates. The most common reason for stopping injectables is side effects. In a WHO trial of DMPA, for example, half of users discontinued after one year: about one-third stopped because of side effects—for example, menstrual disruption, headaches, dizziness, or weight gain—and the rest stopped for personal reasons or were lost to follow-up (342).

Women's attitudes toward side effects, particularly menstrual disruption, are varied and complex (111, 115, 278, 324, 327). Irregular bleeding is inconvenient for many women who do not have sexual relations while menstruating (327). Muslim women often discontinue injectables because their religion forbids them to pray, fast, read from

Noncontraceptive Health Benefits

Injectables have several health benefits in addition to preventing unintended pregnancy. They help to prevent endometrial and possibly ovarian cancer (see p. 15). They also may help women with anemia and sickle-cell disease. Also, like other contraceptive methods that prevent ovulation, such as combined oral contraceptives and, to a lesser extent, *Norplant* implants, injectables protect women against ectopic pregnancy, which can kill from sudden and severe internal bleeding if a fallopian tube ruptures. A few studies suggest other benefits of injectables, such as prevention of pelvic inflammatory disease (PID).

Reduced Anemia

A contraceptive that increases hemoglobin levels is especially valuable in developing countries, where 20% to 40% of women suffer from iron-deficiency anemia (343). Several studies find that blood hemoglobin levels in DMPA or NET EN users increase (65, 121, 122, 201), although other studies find no change (1, 129). Progestin-only injectables may increase hemoglobin levels by reducing menstrual blood loss and by accelerating the formation of red blood cells and lengthening their survival (65, 121). Two studies of monthly injectables have found no change in hemoglobin levels (86,

Injectables

the Koran, or have sexual relations during vaginal bleeding. Amenorrhea may make some women think that they are pregnant or that a drug powerful enough to take away monthly bleeding is unhealthy in other ways. Many people have the false idea that, if a woman does not menstruate, poisonous blood collects in her body (327).

Such attitudes are not universal. Many users in Jamaica, Indonesia, and Thailand, for example, accept menstrual disruption (115). For many users the benefits of effective contraception clearly outweigh the disadvantages of side effects. A Bangladeshi woman commented:

> *We are very poor. So we won't be able to survive if we have too many children. That's why I use Depo, even though it does give me a little trouble (62).*

For some women amenorrhea and weight gain are advantages of injectables. A US woman using DMPA commented:

> *I became amenorrheic after one month of use. I love that. I haven't had periods for five years and it has been great. I worried the first month that I might be pregnant. I talked with my doctor about it and was reassured. Before Depo I had dysmenorrhea [painful menstruation] and now it has disappeared—no bloating, cramps, or weight gain (275).*

Women in Egypt, Nepal, the Philippines, Sierra Leone, and Thailand have reported that they like weight gain experienced with progestin-only injectables (11, 117, 241, 270, 298).

Counseling can help women who choose injectables to adapt to the side effects (see p. 18). Counseling may be so important to clients, in fact, that they are willing to pay for it. In the 1970s the McCormick Family Planning Program, which pioneered use of DMPA in Thailand, offered the injectable for a small fee, while the public family planning program in the same area offered free services. Program staff observed that many DMPA users preferred to pay the small fee because of the good counseling that they received with each injection in the McCormick program (20).

Survey of Service Providers

Service providers in 10 countries responded to a **Population Reports** questionnaire asking about their perception of injectables, their clients' perceptions, difficulties and benefits of providing injectable services, medical eligibility requirements for the use of injectables, and lessons learned. Their answers have been used extensively in this report, particularly in "The User's Perspective."

Bangladesh:	Sabera Rahman, Mohammadpur Fertility Services and Training Centre
Guatemala:	Roberto Santiso Galvez, Asociación Pro Bienestar de la Familia de Guatemala (APROFAM)
Hong Kong:	Margaret Kwan, Family Planning Association of Hong Kong
Kenya:	C.N. Kamau and Margaret N. Thuo, Family Planning Association of Kenya
Madagascar:	Manitra Andriamasinoro, Fianakaviana Sambatra
Philippines:	Jovencia B. Quintong, Family Planning Service, Department of Health
Sierra Leone:	Willie E. Taylor, Planned Parenthood Association of Sierra Leone
Sri Lanka:	Sriani Basnayake, Family Planning Association of Sri Lanka
Sudan:	Ahmed M. Youssif, Sudan Family Planning Association
Thailand:	Sombhong Pattawichaiporn, Planned Parenthood Association of Thailand

Interviews with users of injectables in Bangladesh were conducted by Achintya Das Gupta, Yasmin Khan, Marufa Khanam, Khadija Bilkis, Rashida Sultana, and Tawfique N. Hamid, all staff members of the Bangladesh office of Johns Hopkins Population Communication Services.

108), while a one-year study of the monthly *Mesigyna* found a significant increase after the third injection (208).

Fewer Sickle-Cell Crises

Sickle-cell disease is caused by a defect in the structure of hemoglobin that leads to deformation of red blood cells into a sickle shape when deprived of oxygen. These cells block blood flow, causing painful sickle-cell crises. Sickle-cell disease is most common among blacks and causes at least 80,000 deaths worldwide every year (231).

Testosterone, progesterone, and progestins such as DMPA prevent sickle-cell crises, probably by stabilizing the membrane of red blood cells (139). In the only study of DMPA and sickle-cell disease, women using DMPA in a 2-year trial had significantly fewer crises than women given a placebo. Hematological tests found significant increases in total hemoglobin and red cell counts among DMPA users and significant decreases in the level of irreversibly sickled cells (65).

Possible Additional Benefits

Progestin-only injectables may help women with reproductive tract infections, epilepsy, or endometriosis. Evidence is slight, however, and further studies are needed.

Progestin-only injectables may help to prevent pelvic inflammatory disease. A WHO multinational study of 319 women with PID and 638 matched controls found that the

risk of acute PID among DMPA or NET EN users was half that among nonusers, although the difference in risk was not significant because of the small sample (99). Injectables may protect against PID by thickening cervical mucus, preventing STD organisms from passing through the cervix.

Progestins have decreased the frequency of seizures in women with epilepsy (194, 359). Several studies have reported that the frequency of seizures in women decreases when progesterone levels are high during the menstrual cycle and increases when estrogen levels are high. In one study of 14 women who added oral and injected medroxyprogeterone acetate to their antiepileptic drugs for an average of 12 months, the frequency of seizures among 11 women who developed amenorrhea declined by 30%, from eight seizures per month before the addition to five after, a significant change (194).

Endometriosis causes painful menstruation and prolonged bleeding. Oral medroxyprogesterone at 20 to 30 mg a day is used to treat endometriosis (214). Clinical observation suggests that DMPA at the contraceptive dose decreases symptoms as well (154).

Counseling Issues

Good counseling helps clients choose and use contraceptives. What do clients need to know to make an informed choice of injectables and to use them successfully? Programs answer this question in counseling guidelines appropriate for their clients. The counseling guide accompanying this issue of **Population Reports** is designed to help programs set counseling guidelines for injectables, to train providers, and as a reference on the job.

Counseling for injectables and other contraceptive methods is crucial. Women are more likely to continue a method when they have received good counseling and know what to expect. Also, if informed about other methods, clients are more likely to switch to another method rather than stop using contraception if they are unhappy with their first choice (9, 256). Of course, counseling cannot be the only way that people obtain information about injectables and other family planning methods. A wide range of channels, from community meetings to broadcast media, supports and enhances face-to-face communication between providers and the public (see p. 19).

In a clinic an overview of family planning methods may be presented during education sessions for groups of clients. In individual counseling, providers can make sure that clients understand the information given to the group, help the client choose a method, and provide information that helps clients use the method—for example, the date of the next injection and likely side effects. In fact, many women come to the clinic knowing what method they want. If they obtain that method, they tend to use it longer than women given methods that they did not want (238).

Injectables pose a number of difficult counseling issues, some of which are posed by other contraceptives as well. Providers may need help in deciding what to say about:

- The range of side effects of injectables,
- Bleeding changes,
- Breast cancer,
- Delay in return of fertility, and
- Returning late or early for injections.

Counseling About Side Effects

Program managers may consider a number of factors, some of which conflict, in deciding what providers should tell clients about side effects or should be prepared to discuss with clients. For example:

- **Time.** Providers may have just a few minutes to talk with each client and dispense a method. A few extra minutes in initial counseling, however, could save more time later when women return because of unexpected side effects.
- **Clients' reactions to unexpected side effects.** People often tolerate side effects that they expect but may discontinue a method if they are surprised by a side effect. Unless clients are told, they have no way to know whether the side effect is minor or serious, or whether it will get worse and threaten their health or instead eventually will diminish or disappear.
- **Clients' reaction to a long list of side effects.** Some providers fear that mentioning side effects may discourage clients from using a method (188). Descriptions of serious but rare side effects may be especially frightening to clients. Also, providers should avoid giving clients more information than they can absorb in a short counseling session. Studies in developed countries, however, find that patients, including OC users, generally want detailed information about side effects, while doctors and pharmacists prefer to discuss only serious side effects and the most common minor effects (196, 226). Providers might ask clients if they want to know all the side effects of a drug or procedure or just the ones that are most common (250).
- **Clients' understanding of risk.** How can providers make the concept of probability understandable? Describing a slight risk of a serious side effect may be especially difficult. How risks are presented can influence a client's choice. In a study of treatment for lung cancer, for example, both doctors and patients preferred a treatment described as having a 90% survival rate after one year to an identical treatment described as having a 10% mortality rate after one year (203). Thus, family planning providers may point out that, while 5% of users experience a side effect, 95% do not.
- **Cultural or religious customs.** These may limit discussion between client and provider. For example, in some cultures clients may not expect to ask questions or to have long discussions with providers, who have higher social status than they do (281). Women may not want to discuss intimate matters with male providers (292). Where possible, managers may arrange for female providers to counsel female clients.
- **Clients' concerns.** Providers should be able to reassure clients if they raise concerns about reports in the mass media or rumors from friends or relatives. During education sessions in the McCormick Family Planning Program, for example, providers asked groups of 5 to 15 clients about the rumors that they had heard about DMPA and then provided accurate information (199).

Bleeding Changes

Women considering injectables must know that injectables probably will affect their menstrual patterns and in what ways. Women who have been counseled in advance about bleeding changes tend to continue using injectables despite

the changes (33, 41, 88, 115, 281, 331). In a WHO study of bleeding disturbance and discontinuation among women using a variety of hormonal methods, OC users, who generally did not receive counseling about bleeding, tended to discontinue for mild bleeding changes. In contrast, DMPA users, who had been counseled, continued to have injections despite major disruption of their menstrual cycles (33). In a study of monthly injectables, women who received no counseling were twice as likely to discontinue as women who were counseled (115). Women may need extra help to get through the first months of frequent or irregular bleeding (14, 212). Also important is reassurance that amenorrhea is not harmful: Lack of menstrual bleeding does not mean that women are pregnant or that blood is building up in their bodies (see Counseling Guide). Providers can reassure clients that bleeding returns to normal after stopping progestin-only injectables but may take six months or more to do so.

Breast Cancer

Telling potential users of injectables about bleeding changes is clearly necessary, but what to say about other matters is often unclear. The findings of breast cancer studies present a particular problem. According to the WHO-New Zealand combined analysis, women face an increased risk of breast cancer for five years from the time that they start using DMPA, but very few women will be diagnosed with breast cancer because they use DMPA (see p. 14). Some programs may decide that the risk of breast cancer is so small that it is not necessary to mention it. Others may decide that clients have a right to know. The WHO and New Zealand researchers suggest telling clients that DMPA may speed up the growth of tumors that already exist (284).

Return to Fertility

No woman should use DMPA or NET EN without knowing that she may have to wait to become pregnant after stopping. Providers may simply say that pregnancy may be delayed for several months. If women want to know how long they may have to wait, providers have several options for describing the typical delay:

- **Time from last injection:** Half of DMPA users become pregnant in the first nine months after the last injection, and half wait longer.
- **Time from when the next injection would have been given**—six months, on average, for DMPA.
- **Compared with other methods:** DMPA users may have to wait two to three months longer on average than former OC users.

In any case, providers need to make clear that time to conception cannot be predicted for any woman.

Returning Late or Early

Programs in Guatemala, Indonesia, Jamaica, Kenya, and other countries report that the vast majority of clients return on time for their injections (48, 127, 188). Many programs help clients return on time by giving them an appointment card. In Indonesia, for example, providers write the date of the next injection on a family planning identification card that the client keeps, and providers are encouraged to remind clients twice during counseling of the specific day to return (188).

Courtesy of David B. DeVoe, M.D.

A nurse in Thailand counsels new family planning clients about DMPA. Counseling helps women to understand that the common side effects of menstrual changes and weight gain are not harmful.

To ensure informed choice, providers should tell clients that they may return late or early for an injection and still be protected against pregnancy. Without this information, clients may assume that they have no choice but to return on a specific day. If they miss an appointment, they may assume that they cannot get another injection, and they may discontinue use (167). Providers may tell women, however, that if they have not returned by the end of the grace period and it is not reasonably certain that they are not pregnant, they may need a pregnancy test or to wait for their next menstrual period before they can get another injection. They should use condoms or another barrier method until then. In areas with reliable telephone service, some providers do not tell users about the grace period unless users call to say that they cannot come on the scheduled day.

Providers should not tell clients that the grace period is shorter than it actually is. Once users find out the truth, they may distrust providers. Studies are needed to assess the effect of information about the grace period on clients' adherence to the injection schedule.

Clients who are often late can be given appointments earlier than usual—for example, after 2 months and three weeks for DMPA rather than the full 3-month interval. Providers should try to determine why clients are late—for example, they may fear getting an injection or they may have trouble getting to the clinic—and help them to overcome any problems (116).

Communicating with the Public

injectable contraceptives have great potential, but they also have been controversial. People need to know what is true or scientifically proven about injectables and what is incorrect or unproven. Also, they need to know the advantages and disadvantages of injectables and be able to compare them with those of other methods. By creating an accurate impression of injectables at the start, programs can avoid the more difficult task of correcting a wrong impression later

The wider availability of injectables is an opportunity to reach more people with more information through a variety of media. With a few exceptions, most programs have limited experience communicating about injectables. Typically, programs have gone no further than to produce informational print materials for clients and providers—for example, posters, brochures, or flip-charts—that describe injectables along with the other contraceptive methods. As access to injectables increases, so does the need for complete and readily accessible information about injectables.

Effective communication efforts start with research. Needs assessments or situation analyses identify audiences, their interests and concerns, and how they can be reached. A particular issue with injectables is women's responses to menstrual disruption—responses that differ from country to country and even within countries (see p. 10).

Research methods include surveys, interviews, focus-group discussions, observation of providers, and evaluation of communication channels and facilities. For example, Demographic and Health Surveys and other national surveys can help programs identify audiences. Such surveys may report a high percentage of women intending to use family planning, and many of these women may say that they plan to use injectables. In Kenya, for example, 58% of currently married women not using contraception said that they intend to use family planning at some time, and 44% said that they intend to use family planning in the next year.

This Indonesian poster explains that the injectable Cyclofem *is given monthly, does not interfere with work, and affects menstrual bleeding only in the first month. Informative posters such as this one can reach many women and tell them about family planning methods even before they meet a provider. Indonesia was one of five countries that participated in introductory trials of* Cyclofem.

Among women intending to use family planning at some time, 41% said they planned to use injectables (156).

Well-planned communication programs can help these women carry out their intentions. Messages may need to address public attitudes towards family planning in general, public knowledge of injectables, and the history of controversy about DMPA.

Public attitudes toward family planning. What characteristics of injectables can communication programs emphasize? The convenience of injectables is one of their most attractive characteristics. Surveys in places as different as Egypt and the Philippines find that "easy to use" is a major asset for any contraceptive (140, 161). Research on injectables confirms this finding. For example, in focus-group discussions conducted by the Social Marketing for Change (SOMARC) project in Nepal, women suggested the brand-name for DMPA of "Easy 3-month injection" (307).

The reversibility of injectables also can be an appealing feature. In Nepal surveys find that people associate contraception with sterilization, and many are unaware of the possibility of birth spacing. In the 1991 Fertility, Family Planning and Health Survey, 14% of women said that they would like to space children, but only 1% were using contraception. Thus the Contraceptive Retail Sales project, which sells DMPA, plans to emphasize reversibility in its social marketing promotion of the injectable (117, 307).

In Zimbabwe programs have informed the public about injectables while encouraging men to share responsibility for family planning. In the mid-1980s research found that men often made the decisions about family planning and family size and that men wanted more information about family planning. Therefore, in programs conducted from 1987 to 1994 by the Zimbabwe National Family Planning Council with assistance from Johns Hopkins Population Communication Services, weekly radio dramas addressed men; posters and newspaper and magazine articles informed the public about long-acting methods; costumed performers portraying injectables and other contraceptives clowned on the football field during a tournament; and providers offered family planning counseling at community events. Surveys before and after a campaign in 1993–94 found significant increases in the percentage of men who approved of injectables, from 55% to 67%, and in the percentage of women who said their partners approve of injectables, from 46% to 60% (160, 174).

Of course, some women use injectables because they do not want their husbands to know that they are using contraception. Communication programs generally do not publicly emphasize this attribute of injectables. Rather, they encourage partners to talk and reach agreement about family planning. Women use injectables longer when they have the support of their husbands (267). Using injectables secretly is best discussed informally by providers in one-to-one counseling. While encouraging couples to discuss family planning, programs should take care not to alienate women who cannot talk with their partners about family planning.

Public knowledge. The broadcast media, widespread distribution of brochures and posters, and promotion of professional providers have helped to increase knowledge and use of injectables. Most of these programs cover injectables along with other available methods. In Tanzania, for example, a multimedia campaign conducted from 1991 to 1994 by the Ministry of Health produced posters, radio spots, and

method-specific leaflets describing injectables and other long-term methods. A national introduction and introductions in several regions attracted press and public attention. After the campaign a survey in three regions found that the percentage of men and women ages 15 to 44 who mentioned injectables without prompting had risen from 18% to 49%, and use of injectables had risen from 1% to 3% (142). Overall, in 1991–92, 0.4% of married women in Tanzania used injectables (224). In Pakistan an estimated 20 million people saw the 13-part television drama, *Nijaat (Deliverance)*, one episode of which showed a couple considering their contraceptive options and choosing an injectable (119, 147). In Indonesia the Blue Circle campaign promotes the family planning services of private doctors and midwives who provide injectables and other methods (295). The campaign distributed a leaflet on injectables for clients that asks, "Mothers, do you know enough about the injectable contraceptives?"

A full-fledged communication program may not always be necessary. The McCormick Family Planning Program in Thailand depended mainly on word of mouth. In its first four years the program attracted 60,000 clients, two-thirds of whom chose DMPA. Women in the program area had a strong desire for family planning and trusted the McCormick Christian Hospital, which ran the program (20).

Communication programs also can help to make sure injections are safe. Programs can portray providers using safe injection technique and encourage women to insist that their injections are safe (see p. 25).

The history of controversy about DMPA. Communication programs need to address providers and the public, who may ask how a drug that was once suspected of being dangerous can now be thought safe. Programs can point out that the fears were based on studies in animals and that more reliable epidemiological studies in women have now been completed.

Information about the latest research on DMPA can be presented in special seminars, as has been done in Ecuador, Peru, and the Philippines, to educate policymakers and providers. In Ecuador and Peru injectables are well known, but many providers consider them dangerous. Seminars in both countries have paved the way for limited introduction or expansion of services (51, 84, 255). In the Philippines the Department of Health produced an information kit for providers that stresses the extensive research underlying US FDA approval of DMPA. The kit also cites support for family planning by the Philippines president and health secretary, the popularity of DMPA in the Philippines, and the country's ability to produce DMPA (248). New service guidelines emphasize the importance of client education (125). The social marketing program in the Philippines placed an advertisement in the Manila *Bulletin* entitled "Facts about *Depo-Provera*." It cites studies of DMPA in the Philippines, describes use of the method in developed countries and approval in the US, emphasizes that DMPA is reversible, and refutes the rumor that it is an abortifacient (53). Also, the program has trained family planning providers to be interviewed on television and radio and to counter misinformation and false rumors about DMPA (18).

In India, however, such efforts have failed to reassure some groups opposed to DMPA. The Upjohn Company worked with the Indian Council of Medical Research (ICMR), which has endorsed DMPA. Upjohn also invited policymakers from Thailand to discussions with Indian scientists and policymakers (91). Some women's groups are unconvinced that DMPA is safe, however, and their challenges have delayed the introduction of DMPA into the national family planning program.

Working with groups opposed to DMPA, government agencies can address some of their concerns. US FDA officials, for example, have met with representatives of the National Women's Health Network to discuss establishing a national registry of DMPA users that would track side effects (244).

Maximizing Access and Quality

The potential increase in the availability of injectables offers family planning programs the opportunity to set up accessible, good-quality services. Some programs have offered injectables for many years and now are strengthening services. Others—for example, in Turkey and the US—are offering injectables for the first time. If a program decides to offer injectables or expand services, it needs to ensure that the choice of an injectable—and of every other program method—is continuously and widely available, provided safely, and offered without unnecessary restrictions on who can provide it or use it.

Program managers face a number of issues specific to injectables. These include:

- Setting up services;
- Ensuring reliable supplies;
- Establishing appropriate eligibility criteria;
- Establishing appropriate screening and counseling;
- Switching clients from one injectable to another;
- Preventing infection by properly handling used injection equipment;
- Training providers, especially in counseling and safe injection technique, and
- Offering injectables outside the clinic through community-based or social marketing programs.

Setting Up Services

Introducing a new contraceptive and expanding services are formidable tasks. Programs need to train providers, deliver supplies to clinics and other outlets, and start communication campaigns. Training and communication each can take 18 months or more to set up. Getting injectables and other contraceptives to clinics can take six months to a year or more from the time that they are ordered. Realistic estimates of the time required to prepare each component are essential for a well-coordinated introduction (311).

Many programs conduct pilot studies or operations research to gauge potential users' response to injectables. In Ecuador operations research is assessing users' attitudes toward DMPA compared with other methods, the characteristics of users, and the effectiveness and cost-effectiveness of clinic and community-based distribution (254). In Peru operations research is studying community-based distribution of DMPA and users' responses to menstrual disruption. In one part of the study, mystery clients—program staff posing as DMPA users—visited 26 community health workers and evaluated their knowledge of DMPA and their counseling skills. They

The Shelf-Life of Injectables

Confusion arises over a difference in the labeled shelf-life of DMPA: DMPA made by Upjohn's Belgian subsidiary is labeled with a shelf-life of five years; DMPA made by Upjohn in the US is currently labeled for three years of shelf-life.

The US and Belgian products are identical, however. When the US FDA first approved DMPA in 1992, the stability of DMPA manufactured in the US had been tested for just two years. Upjohn since then has continued to test DMPA, and the US FDA is gradually extending the labeled shelf-life of the US product every six months. It will reach five years in April 1997 (55). The labeled shelf-life of NET EN and *Mesigyna* is five years. The labeled shelf-life of *Cyclofem* is being extended to four years in Indonesia and to three years in Mexico (173).

All injectables should be stored at room temperature, away from excessive heat and moisture. DMPA may be stored at temperatures from 15° to 30°C (60° to 86°F) (223, 312).

found that about three-quarters offered a choice of methods including DMPA, but only about one-quarter gave users enough information about side effects (181, 255). WHO conducted introductory trials of *Cyclofem* in national family planning programs in Indonesia, Jamaica, Mexico, Thailand, and Tunisia. Such trials, a transition between clinical trials and full-scale introduction, allow program managers to assess the effectiveness and popularity of a new method and its impact on overall service delivery (110, 288). Other initiatives need not wait for the results of such pilot studies. Work on postpartum programs or social marketing programs can start at the same time.

Pilot programs are especially important where injectables are little known or have been controversial. In Turkey, for example, where few women have used injectables, the Ministry of Health introduced DMPA in a one-year pilot study in 15 urban clinics to assess clients' reactions (352). Communication programs await the completion of the pilot study. In the Philippines injectables were available in the private sector but were controversial because of religious opposition and lack of approval of DMPA in the US. After the US FDA approved DMPA, the Philippines Department of Health began to offer DMPA in 1994 through government clinics in six provinces and four cities, where about 15% of the population lives (51). Introductory programs generally offer only one type of injectable.

The private sector is helping to introduce injectables in some government family planning programs. In Ecuador, for example, the Centro Médico de Orientación y Planificación Familiar (CEMOPLAF), a private nonprofit family planning organization, is conducting the introductory study (255). The social marketing project in the Philippines added DMPA to its line of contraceptives, sold under the brand name *Couples' Choice*, and is sharing the lessons of its experience with the Department of Health (210).

Ensuring Reliable Supplies

Programs can ensure a reliable supply of injectables, needles, and syringes by:

- Offering only one or two types of injectable,
- Accurately projecting numbers of users,
- Ordering well in advance,
- Training providers in logistics (ordering and managing supplies),
- Shortening the pipeline—the stops on the route from the manufacturer to the provider; and
- Ordering needles and syringes packed with injectables.

Logistics need to be taken into account in program planning and coordinated with events that can affect demand such as communication campaigns and provider training.

Offering only one or two types of injectable. Offering several injectables increases choice but creates logistical problems. The decision about which injectables to offer rests on several factors:

- **Source of supply.** Most programs obtain injectables from donor agencies. USAID provides only DMPA, while UNFPA and IPPF supply DMPA and NET EN. Donors supporting the same program may supply different injectables; consultation can ensure that programs offer only the appropriate number of injectables. The policy of the Department of Health in the Philippines is to refuse donors' offers of injectables and other products if they would be a burden to the logistics system (113).
- **Preference of clients.** Users may have preferences based on duration of contraceptive protection or extent of bleeding changes. For example, the Thai National Family Planning Program found that NET EN was less popular than DMPA and thus decided not to offer it (167).
- **Training providers.** Providers must be able to counsel clients about each injectable that they offer.
- **Efficiency of the logistics system.** To offer several injectables, programs must be able to supply clinics with amounts that reflect clients' preferences. This requires keeping track of the different types of injectables.
- **Cost.** The cost of commodities alone—drug, needle, syringe, and swab—is US$3.88 per couple-year of protection (CYP) for DMPA and $6.30 per year for NET EN when given every two months. This calculation uses estimated average commodity costs on the international market. $0.92 per dose of DMPA, $1.00 per dose of NET EN, and $0.05 for needle, syringe, and swab (195). *Cyclofem*, at $.45 to $.65 per dose, costs an estimated $5.40 to $7.80 per year (108). The comparable commodity cost of OCs is $3.00 per CYP (195). Costs of service delivery are not included in these amounts.
- **Ease of injection.** Providers may find DMPA easier to inject than the more viscous NET EN. DMPA injection may be less painful because the needle is smaller (167, 281).
- **Providing equipment for different injectables.** Injections of DMPA are given with a 21– to 23–gauge needle, while the wider-bore 19-gauge needle is better for NET EN. An injection of NET EN with a needle appropriate for DMPA is more difficult for the provider and more painful for the client (281). Both *Cyclofem* and *Mesigyna* may be injected with a 21–23 gauge needle (223). Logistics managers must be able to ensure that service sites receive the right needles with each order (134).
- **Keeping track of schedules in community-based distribution (CBD) programs.** Setting up work schedules may be difficult if field workers are responsible for several injectables at once (134). Program managers in Matlab, Bangladesh, decided not to introduce *Cyclofem* into the CBD program because of the potential logistical and scheduling problems (211).

Programs just starting out generally begin with one injectable. The Philippines, for example, has chosen to offer only DMPA for the first five years (51). The Mexican family planning program, which first offered NET EN in 1979, is now adding *Cyclofem* (205, 245). IPPF suggests this approach to avoid logistical problems: provide only one progestin-only injectable, and, if there is demand, one monthly injectable (138).

Accurately projecting numbers of users. Assumptions that use will always increase by 10% next year are generally inaccurate. More accurate estimates can be based on historical data indicating changes in number of users and numbers of vials dispensed, on current service statistics, or on surveys of the population served by the program, which can identify women intending to use injectables. Such surveys are especially important for DMPA, use of which may increase now that it is becoming more available. Also, programs need to anticipate changes in demand in response to communication campaigns (229, 333).

Ordering well in advance—at least three months and preferably six months (118). The Family Planning Association of Sri Lanka, for example, orders a 1-year supply of DMPA, about 100,000 vials, when they have five months of stock remaining (2). Also, advance orders should be coordinated with communication campaigns.

Training providers in logistics. In some cases clinics run out of injectables because clinic staff fail to reorder until there are no supplies left. Clinic staff can be trained to collect and use the basic information needed to decide when and how much to order: average monthly consumption, losses of stock that has been damaged or whose expiration date has passed, stock on hand (inventory), and lead time—the time between ordering and receiving supplies (37).

Shortening the pipeline. Some programs have speeded the passage of contraceptives from the manufacturer to the provider. The Philippines Department of Health has removed two levels in the distribution chain. Contraceptives and other drugs used to pass from the central warehouse through regional, provincial, and district warehouses and storerooms before reaching the local health unit. In the new chain, drugs and supplies move directly from the central warehouse to the provincial or city warehouse, saving at least six months (260). Some programs speed delivery by ordering DMPA shipped by air rather than by sea (55, 114).

Ordering needles and syringes. Packed separately from contraceptives, needles and syringes may be subject to duties that have been reduced or eliminated for injectables and other contraceptives. Delivery of needles and syringes is then delayed until duties are paid. Packed together, needles and syringes have the same status as injectables.

To make up for diversion to other uses, programs should order extra needles and syringes. Some suggest ordering twice as many needles and syringes as doses of injectable (246).

An efficient logistics system can help providers prevent transmission of infections. If providers run short of needles and syringes, they may be tempted to reuse equipment. At the same time many programs must destroy and dispose of hundreds or thousands of needles and syringes every day. The national family planning program in Bangladesh, for example, uses 250,000 disposable needles and syringes every month (177) (see p. 25).

Eligibility Criteria

Programs sometimes unnecessarily exclude women from using injectables. Programs may want to review clinical guidelines for injectables to allow the widest access consistent with good care.

Two expert groups have recently collaborated on documents that help programs set up clinical guidelines for contraceptives. To help bring eligibility criteria for contraceptives up to date, WHO established a scientific working group that first met in March 1994. This was the first attempt to develop a worldwide consensus on eligibility criteria for contraceptives (332). Also, to help programs establish appropriate procedures for providing contraceptives, USAID established a Technical Guidance Working Group made up of representatives of USAID Cooperating Agencies (299).

In updating eligibility criteria, the WHO expert group classified medical conditions into four categories:

- **Category 1:** A condition for which there is no restriction on the use of a contraceptive method;
- **Category 2:** A condition for which the advantages of using the method usually outweigh the theoretical or proven risks;
- **Category 3:** A condition for which the theoretical or proven risks usually outweigh the advantages of using a method; and
- **Category 4:** A condition that poses an unacceptable health risk associated with the use of the contraceptive method.

WHO Eligibility Criteria

Differences Between Progestin-Only Injectables and Combined Oral Contraceptives

The recommendations of eligibility criteria for progestin-only injectables and combined oral contraceptives (OCs), formulated by the WHO scientific working group on improving access to quality care in family planning, are similar for most conditions. For some, however, the estrogen in combined OCs makes a difference. Thus the working group made important distinctions between DMPA/NET EN and combined OCs for women with the following conditions:

	Category[a]	
Condition	*DMPA/NET EN*	*OCs*
Breastfeeding		
Six weeks to six months after delivery	1	3
Postpartum		
Three weeks or less and not breastfeeding	1	3
Smoking and age greater than 35		
Light (fewer than 20 cigarettes)	1	3
Heavy (20 cigarettes or more)	1	4
History of hypertension	2	3
Deep venous thrombosis/pulmonary embolism[b]	1	4
Complicated valvular heart disease	1	4
Recurrent severe headaches with focal neurologic symptoms[c]	2[d]/3[e]	4
Sickle-cell disease	1	3

[a] *For description of categories 1–4, see text, this page.*
[b] *Women with varicose veins may use either DMPA/NET EN or combined OCs.*
[c] *That is, severe headaches that cause trouble seeing, speaking, or moving.*
[d] *For initiation of method.*
[e] *For continuation of method if condition develops during use.*

alternative contraceptive method, with the aim of ensuring a certain margin of safety in the indication and of trying to eliminate the term 'contraindications' [33]. The eligibility criteria for the injectable contraceptives are reviewed extensively by Laneta Dorflinger; the acceptability of the method is discussed by Pablo Lavin; while indications in special circumstances such as adolescence, post partum and during perimenopause, are described by Mamdouh M. Shaaban.

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DISCUSSION

Injectables as a choice - evidence-based lessons

Siddhivinayak Hirve

Newer, better contraceptive methods may not result in increased reproductive choice if health systems cannot ens contraceptive services.

Though extensively researched and used by over 16 million women in 130 countries DMPA's controversial history use by national family planning programmes worldwide. Early clinical trials were abandoned due to the adverse U opposition by health advocates in India. After US FDA approval DMPA was licensed for use in 1993 in India condi marketing surveillance by its manufacturer for side-effects. Since 1994, injectables are available through commerc marketing channels but not in the public sector. In 1995, a panel favoured the use of injectables rather than Norpl of the ease of dispensing injectables and the prohibitive expense of Norplant. A recommendation was made in 19 injectables in suitably equipped centres in the public sector with appropriate screening, counseling and medical ba on good clinical practice and post-introduction surveillance for side effects and management. Women activists opp in the national family welfare programme for reasons of safety and fundamental inadequacies in providing quality ensuring informed choice and consent. The debate on injectables touches wider issues of gaps in existing popula policies, a lack of male responsibility and involvement in reproductive health, and vested interests of multinationals

Injectables have the lowest failure rates among methods of contraception. This efficacy is dependent on appropria injection, and repeat injections. The typical acceptor is a woman in her early 30s, with two or three living children, rather than space her children. Women prefer injectables to pills or IUDs. Acceptors include first-time contraceptiv the convenience, effectiveness and perceived safety. They also include women who switch to injectables after exp effects with other contraceptives. An initial high acceptance of injectables is not sustained as most women experie disturbances resulting in one-year discontinuation rates of 15 to 50%. Menstrual disturbance as a reason for disco and culture-specific, with high discontinuation rates seen amongst women in Pakistan, where women are less like amenorrhoea; in contrast, infrequent bleeding was less likely to result in discontinuation than frequent heavy bleec women. Tolerance thresholds and partner attitudes to menstrual disruption need to be studied. Protagonists of inj underplay the side-effect of menstrual disturbances as not being harmful or life-threatening. This is not to underpla perception of side-effects as a reason for discontinuation. High discontinuation rates may be due to poor selection attributes of the contraceptive or just the inability of the services to ensure continued use of the injectable. Alterna as a measure for the woman's freedom of choice to opt out of the method, if she dislikes it.

Another concern is the reversibility of injectables. The median delay to return to fertility (8-9 months after last injec higher than barrier methods, OCs, or IUDs. Large variations are seen amongst women from different populations, differences in the nutritional, metabolic and fertility status. Return to fertility is not affected by duration of injectable implying that women can safely use injectables for even delaying their first pregnancy.

How safe are injectables?

This is probably the most controversial and researched aspect. Studies of Chinese women show bone mineral los than previously projected (0.4-1% per annum) and unrelated to duration of DMPA use. Debates on DMPA-induce and its effect on pubertal skeletal growth in adolescence, or the risk of aggravation or acceleration of osteoporosis vis a vis the benefits of contraception, have been largely speculative. Though WHO recommends its use amongst lactating women, India chose to play it safe by recommending that use of injectables be avoided in adolescents.

Adverse effect on blood pressure and thrombosis has not been reported. One study has shown glucose intolerand term DMPA use. There is no link between breast cancer and long-term DMPA use. An increased risk was seen in in long-term users suggesting that DMPA may trigger the growth of existing breast tumours rather than turn norma Prolonged use of DMPA may cause in situ cervical carcinoma but not invasive cervical carcinoma; hence the nee monitoring for cervical cancer.

In utero exposure to DMPA shows equivocal findings of its effect on birth weight and birth defects. DMPA and NE breast milk in lactating women. There is no effect, or insignificant effect, on breast milk or subsequently on infant c hair development was delayed significantly in girls. Increased aggression responses in adolescents and an enhan sexuality have been seen.

Service delivery issues

Screening, counselling on mode of action, side effects and their management are crucial. Poor follow-up of clients and lack of knowledge on side effects management are programme weaknesses. Standardised protocols for coun provider skills are needed. Women attending FP clinics in the Philippines were not well informed about the range

Please start a resource file on long acting Injectable contraceptives
JM
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Studies amongst private providers in India showed that they did not promote indiscriminate use of DMPA. Howeve to develop standardised protocols for counselling and improve provider skills. Medical procedures were not explai clients reported that providers did not inform them about side-effects resulting in most women with side-effects no clinic for assistance. Many DMPA programme dropouts reported that clinic staff were not caring or courteous. Finc counselling of women by providers in terms of content and quality. Periodic orientation for providers on issues rela eligibility, side-effects management and counselling and skills to counter rumours were some strategies suggeste improve quality of care.

Preference for a female provider and supply shortage often turned away would-be DMPA acceptors or resulted in Distance and inconvenience of clinic timings sometimes resulted in clinic switching or DMPA discontinuation. Clie adversely affect DMPA use. Acceptance is highest when DMPA is offered free. However, free services cannot sus acceptance.

Though DMPA and NETEN may have similar effectiveness, continuation rates and side-effects, the service delive very different. To avoid field worker confusion, error, disruption of field worker routines, simplify managerial and su recommended to use either DMPA or NETEN (not both) in the same geographical area as there are significant dif dosage regimes, needles etc.) that affect service delivery.

The Thailand experiences highlight the need for diligent follow-up, surveillance for side-effects, and accurate reco experience illustrates the need for transparency and flexibility of the health system to respond to concerns voiced The initial uptake of injectables is usually high, sustaining it is difficult because of inadequate preparation, poor tra logistics management. This resulted in poor counselling, lack of informed choice, poor selection of women and oth Injectables were prematurely withdrawn from the national programme in the Philippines, to be re-introduced more

Ethical concerns

Whether injectables undermine or further a woman's reproductive rights needs to be examined in the context of pc injectable has to be evaluated from a rights perspective in terms of who controls it, its purpose, safety, effectivene benefits, reversibility, and equally important concerns of availability, accessibility, affordability and quality of servic inception, India's FP programme has been driven by demographic goals of population control resulting in promotic controlled contraceptives. Recently we have a policy environment which reflects a commitment to widening contra broader framework of reproductive health and reproductive rights. The National Population Policy 2000 seeks to p sensitive quality services and supplies, information and counselling and widening contraceptive choice to enable v to make informed choices and access quality health care services.

Women's groups have opposed injectables because of the potential for violation of reproductive rights as well as c autonomy and safety. Addressing resource constraints, removing informational, physical and economic barriers ar quality of reproductive health care delivery - putting a reproductive rights framework into practice - presents a chal opportunity to offer injectables and widen contraceptive choices for women. It is time to ensure a health system wl social and gender inequalities, one that respects women's dignity and autonomy.

This paper derives from a scientific literature review, by the author, on the use of long-acting, progestin-only contr South Asian context. The review was commissioned by the UNFPA. A report of the review, Progestin-only Injectal Facts File, was published by UNFPA India on October 15, 2004, and was available atwww.unfa.org.in/reports/17_ accessed on December 18, 2004.

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DISCUSSION

Research on hire

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I recollect one of the first lectures in my first year of medical college where my venerable prof the first thing that a doctor should have is confidence. If you kill a patient, kill him with confide classic expression of the necessity felt by the medical profession to maintain a veneer of cont face of relative uncertainty.

In such a setting, medical technology is often used, not as a legitimate tool for diagnosis and prop to hide inadequacies regarding knowledge about what constitutes the best course of act protect themselves from the anxieties which would otherwise accompany their relative ignora seeks succour by immersing itself in the mindless pursuit of 'advanced' technology. The use c becomes an end in itself rather than a means to relieving human suffering. The last century h ECGs, sonography, computerised scanning and much more. Yet, instead of clearing the prev medical practice, many of these tools have compounded the chaos. Not because it was inevit control over these technologies has been the driving force behind the immensely profitable he Patients are over-investigated, over diagnosed, over treated and under cared for because the has to play second fiddle to large corporate interests.

Contract research

Medical research is often organised, paid for, commissioned or subsidised by the drug indust commissioning such research are only looking for conclusions which will enable them to mark reap profits. Nowhere is this more apparent than in the manner in which medical research is c 'seat' of the pharmaceutical industry, the United States.

An estimated 2 million Americans got hooked on to Redux (dexfenfluramine), a new anti-obes the US by Wyeth-Ayerst, after it was approved by the US FDA in April 1996. At its peak popul writing 85,000 new prescriptions a week. But a little more than a year after the drug's introduc collapsed, as patients began to exhibit symptoms of damage to their hearts and lungs. Fearin FDA banned the drug in September 1997. (1) The manner in which 'scientific' evidence was c Redux is a shocking indictment of the system of medical research. In 1994, Wyeth had signec contract with a medical publishing company called Excerpta Medica that offered pharmaceuti invaluable tool: ready-made scientific articles, placed in leading medical journals, and carrying influential academic leaders. Excerpta laid out for Wyeth a schedule of nine articles, each witl message aimed at a targeted audience, from primary care physicians to cardiologists to nurse pharmacists. The articles had a 'writer' and an 'author' - but they weren't the same person. Th lancer who was paid $5,000 to actually write the articles. The 'author' was often a top univers paid $1,500 to review the work and assign his or her name to it for publication.

The Redux story clearly focuses on the growing reliance of university scientists on corporate research is now a multi-billion-dollar industry, with hundreds of testing and drug companies w thousands of private doctors. Patients have become commodities, bought and traded by testi doctors. The number of private doctors in research in the US since 1990 has almost tripled, a earn as much as $500,000 to $1 million a year. Reports of fraud in drug trials are pouring in. S weaknesses in the new system that has developed in recent years for testing experimental dr the pharmaceutical industry rely on career researchers at academic medical centres, whose p reputations are forged on the quality of their data. Rather, the industry has turned to thousanc doctors for whom testing drugs is a sideline for making money.

Research in developing countries

Medical research in the developing world suffers from the problems of underdevelopment, on superimposed the ills of a neo-colonial approach assumed by external research funding. In th research is poorly funded, monitored and prioritised. The situation is compounded by foreign research priorities. While, globally, medical research is fuelled by corporate interests; the mar technology and pharmaceuticals in the developing world is very small. The size of the Indian market, for example, is less than one-tenth of the market in the US or Japan. As a consequer research in developing countries (largely, corporate sponsored research) focuses on areas of

home countries. Tropical medicine (itself a colonial construct) has a long history of descriptive researchers but have no direct implications for participants. For example, a bibliography of re Papua New Guinea identifies 135 publications that describe Melanesian blood groups but onl treating malaria (2). Different 'styles' of foreign donor driven research are prevalent. (3). 'Post western researchers request colleagues in developing countries to courier to them biological research' - where researchers travel to developing countries for short periods and take back t The most prevalent is the practice of maintaining 'annexed sites' for field research, led and m staff. These 'annexed sites' attract promising academics away from national institutions, and t findings are infrequently translated into policy and practice. Research fellows in 'annexed site training there, but few return to national institutions. In a welcome development, India has rec 'annexed site' research and outsiders are now obliged to work through Indian institutions. Hov advantages of this move will, in all probability, be frittered away given the encouragement bei sector R&D institutions to undertake contract research for corporate entities.

Drug companies have been known to perform research in developing countries that do not cc Declaration of Helsinki and could not be conducted in the developed world. Reasons quoted f research in these countries, rather than developed countries, are lower costs, lower risk of liti ethical review, the availability of populations prepared to give unquestioning consent, anticipa of side effects because of lower consumer awareness, the desire for personal advancement t the desire to create new markets for drugs. The commercial secrecy that surrounds early clin safety and dose ranging in phase I trials in paid normal volunteers (that is, poor volunteers), r preliminary research is unpublished, particularly when adverse effects are high and further de abandoned. (3).

Medical research in India

There is, however, no denying that India (as a consequence of its size and ability to pledge g different from most developing countries. Real science and research is done mostly with publ in non-profit institutions. But such indigenous research funding is still too small and too badly address local priorities. A report published in 1997 in Current Science, a journal of the Indian Sciences, suggested that most medical research in India is unrelated to the country's major h report, based on an analysis of research publications from India indexed in the Medline datab achievements in research have 'little influence' on healthcare delivery. It lamented that resear concentrated in the fields of tertiary health care and new biology. (4)

There also exists a problem in defining local priorities. For long the two thrust areas for medic have been vaccine research and research on contraceptive technologies (and recently, repro priorities can be contested on the ground that they emanate from a view of public health that vaccines as 'quick-fix' remedies for communicable diseases and contraception to control popu the hype surrounding both these concerns, government-funded research in these areas has s standard ethical guidelines.

Unethical and dubious

The decades of the 1980s and '90s have thrown up numerous instances of unethical and dub country. Research on long acting hormonal contraceptives like Net-En, Depo Provera and No conducted without observing ethical requirements like informed consent and the need to follo

A team headed by Dr G PTalwar at the National Institute of Immunology (NII) persisted for ye develop a contraceptive vaccine despite criticisms that these trials were being run unethically passed through phase II clinical trials in the late 1980s. Only 80% of the women who receivec adequate response necessary for contraception. More importantly, according to published rep 94 out of 162 women in the trial 'volunteered' for long-term follow-up. The Indian government for phase III clinical trials of the vaccine but continued to fund the research on contraceptive v were put on 'cold storage' only when Dr GP Talwar retired from the NII. In 1998 it was reveale for Cytology and Preventive Oncology, had left cervical dysplasia (a pre-cancerous condition) women to study the progress of the disease, without warning them or taking their consent. In the lesions progressed to invasive cancer, and 62 women developed localised carcinoma of t were treated. The study had been sponsored by the Indian Council for Medical Research, wh down the ethical guidelines for medical research. The investigators said, in their defence, that

written consent because most of the women in the study were illiterate and also because writ mandatory when the study was launched! (5)

In 1997 the scandal surrounding trials on quinacrine sterilisation forced the Supreme Court of Quinacrine was used in the treatment of malaria till it was replaced by better drugs. Some tim renewed interest in its use in a method of 'chemical' sterilisation. In June 1994, the WHO Con Sterilisation Methods categorically stated that human trials with quinacrine should be stopped the outcome of toxicological studies. In India, quinacrine sterilisation was carried out in the '9(doctors involved' according to an early convert to the cause, Dr.Biral Mullick. Coordinating the equipment in the country was Dr.J.K.Jain, former MP. There were widespread protests again: Government of India denied granting approval. Finally, bowing to the public outcry, quinacrine banned by the Drug Technical Advisory Board in 1997. (6)

There is a discernible pattern in all the above instances. All of them pertain to research on co technologies, reproductive health and vaccine research. More importantly, all of them (except quinacrine sterilisation) have been conducted in public funded institutions using public money extreme laxity in existing regulatory institutions and mechanisms and also to the tendency of submit themselves to pressures when faced with so called 'national priorities'. Government sp approved) research in India, seems to have been fraught with equally potent dangers as corp research is globally.

The anarchy in medical research in the country is typified in three recent examples, only one received some publicity. The last pertains to a clinical trial conducted on human subjects in th Centre (RCC) in Kerala, with an experimental drug in advanced oral and cervical malignancie conducted in collaboration with the John Hopkins University in the US. The drug used, M4N, of 'chaparral tea' made from leaves of the creosote bush, a common American desert plant. A tea has been used over the years as an herbal remedy for cancer, it is also known for its toxic While the trial was conducted in 1999 and 2000, the application for permission to conduct the to the Drug Controller of India only in February 2001! Further, the Ministry of Health and Welf RCC was granted permission to import M4N from Johns Hopkins only in February 2, 2001. A procedural problems it now appears that the trials ignored basic norms regarding informed co preliminary enquiry indicates that subjects enrolled in the trial were given the experimental dr established treatment regimes, a clear violation of the Declaration of Helsinki on research on trials had not been approved or reviewed by any of Johns Hopkins' institutional review boards protection of human subjects, in spite of the Centre's claims that the permission for the trials basis of 'pre-clinical and other relevant data'.

Even more bizarre is the report of a trial of another 'anti-cancer' cure conducted in Calcutta in conducted on 24 patients by a team comprising a private medical practitioner and a group of scientists at the Indian Association for the Cultivation of Science, (IACS), a non-clinical organ of the clinical trial have been published, of all places, in the Indian Journal of Physics! (7). The coincidentally, is run by the IACS. The paper acknowledges that the trial was conducted throu CSIR and DST and had the approval of the Institutional Ethics Committee of the IACS. Clearl obtained from any body that is authorised to give such approval. The paper goes on to exhort sincerely hope that researchers and clinicians with open minds will immediately make a conc and to further improve the present formulation and treatment." Worse still, the main ingredien formulation is a chemical (methylglyoxal) purchased from the American warehouse supplier, Company, whose chemicals are laboratory grade, not intended to be used as drugs, i.e. not b

The third instance is the permission granted by the Ministry of Health and Family Welfare to c long-acting hormonal contraceptive, Netethisterone Enanthoate (NetEn), in 12 medical colleg the country in 2001. The Ministry has not released any other details regarding the purpose of protocols to be followed. It is being presumed that the trials are a prelude to introduction of N population control programme. Various health and women's groups have represented to the Rights Commission (NHRC) against conduct of the trials on the grounds that the introduction mass population control programme is unacceptable given the drug's potential toxicity and th monitoring mechanism.

What informs medical practice?

There is possibly an even more fundamental conundrum that faces medical research in a cou Research output is, as yet, too insignificant and too unfocused to inform the practice of medic The latter continues to be largely determined by medical research conducted in the West. Thi given a novel twist recently by Dr Samiran Nundy in a letter to the British Medical Journal. He the state of medical research in the country it made more sense to first attempt to regulate m country rather than regulate medical research (8): "That medical research in developing coun of generally poor quality is well known, and it has not improved in the past 20 years. Should c research ethics in developing countries when they barely exist? In my view the ethics of medi important. To see how the public can be safeguarded from an inefficient and often corrupt me receive comprehensive health care of a reasonable quality is paramount."

Such issues arise today because the research institutions in the country have singularly failec cogent direction to the practice of medicine. It would almost appear as though the two work in paradigms. Unless there is, at the least, an attempt to marry research with practice, public pe research will continue to range from suspicion to derision.

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medical FORUM

Gynaecology Forum

Leading Article

Injectable hormonal contraceptives: an overview

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Hormonal depot contraceptives containing only progestogen administered by injection are the result of a series of studies initiated by Karl Junkmann in Germany in 1953 [1]. Almost simultaneously, Schering synthesised the injectable depot ester of the progestogen norethindrone, called norethindrone (or norethisterone) enanthate (NET-EN), which was marketed under the name Noristerat [2]. During this period, Upjohn in the USA developed medroxyprogesterone acetate in its injectable depot form (DMPA), known under its proprietary name Depo-Provera [2].

The initial clinical studies on progestogen-only injectables that analysed the efficacy and safety of the method were mainly carried out in Latin America by Zanartu in Chile [3], Coutinho in Brazil [4] and Kesserü in Peru [5], between 1963 and 1965. As a result of the outcomes of these clinical studies, NET-EN was put on the market in Peru in 1967 [6]. At present, worldwide experience with NET-EN as a contraceptive is based on more than 200,000 woman-years [2, 7] and it has been registered as a contraceptive in more than 60 countries [8].

The efficacy and safety of DMPA have been studied extensively worldwide both as a contraceptive and as a treatment for gynaecological disorders. More than 1000 publications describe its metabolism and safety [7, 9]. Numerous international health institutions supported its licence as a contraceptive, but not until October 1992 did the United States Food and Drug Administration approve its use as a contraceptive, 25 years after Upjohn first applied for approval.

DMPA is the most widely used injectable contraceptive formulation, having been marketed in more than 130 developed and developing countries. Since its introduction as a contraceptive, it has been used by more than 30 million women, more than 100,000 of whom have done so for longer than 10 years. At present it is estimated that approximately 13 million women worldwide are using it.

Combined once-a-month injectables contain a synthetic oestrogen in addition to

progestogen. This allows them to keep the contraceptive effect of progestogen together with the added benefit of oestrogen to provide regular bleeding simulating menstrual bleeding. Different combined once-a-month injectable contraceptive formulations have been evaluated and used over the last four decades. In China and neighbouring countries, the so-called Injectable No. 1 has been developed, made up of 17a-hydroxyprogesterone caproate and estradiol valerate, and this has been used by approximately 1 million women [10]. Deladroxate, an injectable formulation made up of dihydroxyprogesterone acetophenide and estradiol enanthate, has been used for years in Latin America [11, 12]. It is known in different countries under the names of Perlutal, Unalmes or Agurin.

Table I: The two groups of injectable contraceptives.

Type	Progestogen	Oestrogen	Name
Progestogen-only	Depot medroxy-progesterone acetate 150 mg	—	DMPA Depo-Provera
	Norethisterone enanthate 200 mg	—	NET-EN Noristerat
Once-a-month combined	Medroxy-progesterone acetate 25 mg	Estradiol cipionate 5 mg	Cyclofem
	Norethisterone enanthate 50 mg	Estradiol valerate 5 mg	Mesigyna

Two new combined once-a-month injectable contraceptives have been studied by the WHO and other institutions during the last 20-30 years, namely Cyclofem (previously known as Cycloprovera) and Mesigyna (registered in some countries as Norigynon). Safety and efficacy studies for Cyclofem began in 1968 and the first clinical trials with Mesigyna started in 1974. Subsequent introductory studies of these two combined injectable contraceptives, carried out in different countries, confirmed the results of the clinical trials and supported their commercialisation. Cyclofem and Mesigyna have demonstrated benefits and advantages compared with other once-a-month injectables, as indicated by the multicentre studies carried out by the WHO, and they are currently being accepted by an ever-increasing number of countries as a good contraceptive option [2, 11, 13].

Composition and dosage

Injectable contraceptives can be divided into two main groups according to their hormonal composition (Table 1):

Progestogen-only injectables

1. Depot medroxyprogesterone acetate (DMPA or Depo-Provera): 1 ml injection containing 150 mg DMPA in a microcrystalline aqueous suspension, administered intramuscularly every 3 months.
2. Norethisterone enanthate (NET-EN or Noristerat):1 ml injection containing 200 mg NET-EN in castor oil, administered intramuscularly every 2 months.

Once-a-month combined injectables

1. Cyclofem/Cycloprovera: 25 mg medroxyproges terone acetate and 5 mg estradiol cipionate.
2. Mesigyna/Norigynon: 50 mg NET-EN and 5 mg estradiol valerate.

Both preparations are administered by deep intramuscular injection. The first dose is administered during the first 5 days of menstrual bleeding and thereafter every 30 days, plus or minus 3 days. The pharmacokinetics of the different injectables are analysed in this issue by Josué Garza Flores and Teresa Navarrete.

Mechanism of action

Progestogen-only injectables

The main contraceptive effect is exerted through changes in the cervical mucus, making it hostile to the penetration of spermatozoa. They also inhibit ovulation and cause progestogenic changes in the endometrium [2, 7, 8].

Once-a-month combined injectables

The main effect is inhibition of ovulation. They also cause changes in the cervical mucus and in endometrial morphology [2, 8].

Efficacy

Both progestogen-only injectables and once-a-month combined injectables are highly effective, with pregnancy rates between 0.1 and 0.4 after 12 months [2, 8, 14]. The efficacy of the injectable methods depends on the timing of the first injection, adherence to the schedule, and on the injection technique. A study carried out in Thailand [15] shows that delaying the first injection from the fifth to the eighth day of the cycle, increases the pregnancy rate from 0.16 to 0.62 after 3 months of use. The maximum delay for the next DMPA injection should not exceed 2 weeks, 1 week for NET-EN and 3 days for the once-a-month injectables.

Non-contraceptive benefits

In addition to preventing pregnancy, injectable contraceptives also have other reported health benefits, having been shown to decrease menstrual blood loss, increase plasma haemoglobin, and decrease dysmenorrhoea and pelvic inflammatory disease [2, 7, 8]. Edith Weisberg and Ian Fraser discuss the non-contraceptive health benefits in this issue. Progestogen-only injectables decrease the risk of endometrial cancer and possibly also the risk of ovarian cancer. The relation between cancer and injectable contraceptives is reviewed in this issue by Ramiro Molina Cartes.

Use in the post partum period

Progestogen-only injectables have not shown any adverse effects on lactation with regard to quality of the milk, duration of lactation and infant growth [16-19]. However, the progestogen is present in maternal milk in the same concentration as in maternal plasma. DMPA reaches concentrations of 10 ng/ml in the first week after its administration, decreasing to 0.5 ng/ml in the third month. The concentrations of NETEN in maternal milk are lower than those of medroxyprogesterone because the 19-nor-derivatives are less soluble in milk. The estimated daily progestogen dose ingested by the infants of mothers using progestogenonly injectable contraceptives is 0.3-10 µg DMPA and 0.5-2.4 µg NET-EN. These amounts have been estimated by taking the concentrations in maternal milk and assuming that the infant ingests 600-700 ml milk a day [20, 21]. No health problems were found in children whose mothers had used these methods,

but the possible long-term effects on neuroendocrine mechanisms regulating the reproductive process are not yet known [22, 23]. More studies and long-term follow-up are necessary to answer this question.
Oestrogen-containing once-a-month combined injectables would behave in the same way as the oral combined contraceptive pill and are therefore not recommended during this period due to their possible adverse effects on the duration of lactation and infant growth [24-26].

Side effects of injectable contraceptives

Irregular bleeding

Progestogen-only injectables
Irregular bleeding is the main side effect of progestogen-only contraceptive methods. The initial use of injectables may cause irregular, unpredictable bleeding, with or without intermittent spotting. Only 10% of women who use DMPA report normal cycles during the first year of use. Irregular bleeding is usual during the first 6 months, followed by delayed bleeding and/or amenorrhoea in the months thereafter.
Menstrual irregularities with NET-EN are similar but of a lower intensity. The rate of discontinuation after 1 year is estimated at 15% due to irregular bleeding and 12% due to amenorrhoea, but these figures vary considerably from one area to another [2, 7, 8].

Once-a-month combined injectables
There are no major differences between the bleeding patterns of Cyclofem and Mesigyna users. During 10-15 days after the first injection, most women have a bleeding pattern similar to menstrual bleeding, and then they will bleed every 30 days in a regular manner, differentiating once-a-month combined injectables from progestogen-only injectables. During the first 3-6 months of use, only 25% of women experience some form of irregular bleeding and 12% develop prolonged bleeding. The discontinuation rate due to irregular bleeding is between 5 and 12% per year [2, 27].

Other side effects

Progestogen-only injectables
Most of the side effects associated with the use of progestogen-only injectables are subjective and difficult to quantify. Some users gain weight during the first year of use and some may subsequently continue to gain weight at the same rate [7, 8]. Between 3 and 19% of users report headaches or dizziness, a percentage similar to that seen in the general population; few women discontinue this method for these reasons.

Once-a-month combined injectables
Side effects are less common than those reported with progestogen-only injectables and are similar to those reported by the users of combined pills: headaches, dizziness, mastalgia, changes in body weight, etc. [28].
In their article, Edith Weisberg and Ian Fraser analyse in detail the beneficial and

adverse effects and changes in uterine bleeding with the use of injectable contraceptives.

Metabolic effects

Progestogen-only injectables tend to cause mild changes in carbohydrate metabolism. DMPA has a slight diabetogenic effect and should therefore be used with caution in diabetic women. Both types of injectables may induce changes in lipid metabolism, reducing HDL cholesterol and decreasing the HDL:LDL cholesterol ratio [29-31]. The metabolic effects of injectable contraceptives are reviewed by Luis Bahamondes.

Return to fertility

After discontinuation of progestogen-only injectables, there is generally a delay in the return to fertility in comparison with the combined pill or with non-hormonal methods. The extent of this delay varies between different regions, communities and women. After discontinuing use of DMPA, 50% of women became pregnant in the 9 months following the last injection. After discontinuing once-a-month combined injectables, ovarian function recovers quickly: 39% of women ovulated within the first 3 months and 78% within 6 months after discontinuing the method. The return to fertility is considerably shorter with these injectables, most women becoming pregnant during the first 6 months after discontinuing treatment [2, 7, 8, 13, 32]. This subject is reviewed in this issue by Susana Bassol Mayagoitia.

Interaction with other drugs

Drugs inducing liver enzymes, especially when used for prolonged periods of time, may reduce the efficacy of hormonal contraceptives. This category of drugs includes some antibiotics (rifampicin, griseofulvin), anticonvulsants and barbiturates. To date there is insufficient knowledge with regard to the possible interactions between these drugs and injectable contraceptives, and therefore it is recommended that women who need these types of drugs for prolonged periods of time use other contraceptive alternatives.

Counselling

Counselling is an essential element for any couple visiting a family planning centre to select a contraceptive method. Women choosing an injectable contraceptive must be given clear information about the advantages and disadvantages of the method, side effects, costs and comparisons with other contraceptive methods. The differences between the two types of injectables must be explained, especially with regard to menstrual irregularity and return to fertility.

Eligibility criteria for using injectable contraceptives

The WHO has taken special care to revise and reach consent on the medical criteria concerning recommendations for use of the different contraceptives. Attempts have been made to standardise medical eligibility criteria to ensure that the suggestions made during medical counselling are adequately supported by scientific evidence. Accordingly, four categories have been established for each