# INDIAN COUNCIL OF MEDICAL RESEARCH

## *Summary 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 is highly efficacious.

The most promising once-a-month combined injectable Contraceptives at present are Lunelle/Cyclofem 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 combined injectables contraceptives and has a better menstrual cycle control.

Cycloprovera/Cyclofem, combines 25mg of progestogen (medroxy progesterone acetate) and 5 mg of estrogen (estradiol cypionate). Introductory trials of Lunelle/Cyclofem have been conducted in Chile, Indonesia, Jamaica, Mexico, Thailand and Tunisia and many other countries. Cyclofem has been licensed to Concept Foundation , Bangkok, Thailand. It is currently manufactured under licence by Aplicaciones Farmaceuticas, Sa in Mexico and P.T. Tunggal in Indonesia. It is approved by the US FDA and is presently registered and distributed in 17 countries, primarily in Latin America, Africa and a few countries in Asia.

In the WHO comparative multicentre study of Cyclofem and Mesigyna, a total of 2320 women were recruited from 17 centers from Africa, Asia and South America (1108 Cyclofem, 1152 mesigyna) and followed for 10,969 woman months for Cyclofem 10,608 women month for mesigyna for one year of use. 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. Trials with Cyclofem and Mesigyna carried out in Egypt and China indicate that both the preparations were highly effective and there was no significant difference between the two groups.

ICMR in the 90's carried out a phase III clinical trial with once a month injectable contraceptive Mesigyna (NET_EN 50 mg + estradiol valerate 5 mg) v/s two monthly injectable contraceptive NET-EN 200 mg. The result indicated that the monthly injection was found to be equally efficacious as NET-EN 200mg 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.

It is expected that the addition of a once-a-month combined injectable contraceptive to the existing cafeteria of family planning methods in the National Family Welfare Programme could possibly increase the contraceptive prevalence.

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

## OBJECTIVES

- To evaluate the contraceptive efficacy, side effects, continuation rate and the bleeding pattern of the 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 16 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/Cyclofem signed an informed "consent form". A thorough systemic and pelvic examination was performed to exclude conditions listed in subject exclusion criteria. Injection Lunelle / Cyclofem was given within five days of LMP / MTP as deep intramuscular injection in the Deltoid / Gluteal region (gluteal maximus) or anterior thigh and were instructed to come for subsequent follow-up and administration of Injection of Lunelle / Cyclofem at one monthly interval (28-30 days) $\pm$ 3 days. Women were informed that they would receive 12 injections provided they didnot discontinue the method earlier (before 12 months of use) for any other reasons . 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. 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.

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 centers obtained clearance from their local Institutional ethical committees prior to initiating the study..

## RESULTS

***Relative acceptability*:** A total of 63784 women attended family planning clinics at 16 HRRCs of the Council during the enrolment period. The relative acceptability was 42.3% for Tubectomy, 0.2% for Vasectomy, 25% for Condoms, 15.8 for Intrauterine devices (IUCD), 14.7% for Oral pills and monthly injectable Cyclofem was opted by 1330 (2.1%) of total family planning seekers who fulfilling all the stipulated study inclusion criteria (Table 1).

**Table 1 : Relative acceptability**

| | **No of Subjects** | **%** |
|---|---|---|
| Tubectomy | 26856 | 42.3 |
| Vasectomy | 116 | 0.2 |
| IUCD | 10049 | 15.8 |
| Oral Pills | 9358 | 14.7 |
| Condoms | 15865 | 25 |
| Monthly injectable (Cyclofem) | 1330 | 2.1 |
| Others | 218 | 0.3 |
| **Total acceptors** | **63784** | |

***Profile of acceptors*:** Mean age of acceptors is 25.9±4.1years and mean parity of 1.8±1.0. Mean weight and height of acceptors are 48.2±10.9 kgs and 152.3±17.7cms respectively. 87% of the acceptors are literate and 17.8% are employed (Table 3).

| **Table 3: Profile of acceptors** | |
|---|---|
| No of acceptors | 1275 |
| Mean age (yrs.) | 25.9±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 |

***Women months of use and Method failure*:** Of the 1330 women enrolled for the study, 55 women were discontinued from the study due to logistics reasons (non-availability of injections due to delay in receiving the consignment) This data was not included for computing continuation rates and use-effectiveness. All the 55 women after being discontinued accepted another method of contraception. The data analysis being presented is on 1275 women observed for 10,934 woman-months of use. A total of 791 women have completed 12 injections. The continuation rates at 6, 9 and 12 months was 74.3, 66.7 and 63.2 per 100 users respectively. ***No method failure (involuntary pregnancy) has been reported during the study period*** (Table 2).

| **Table 2 : Women months of use and Method failure** | | | |
|---|---|---|---|
| | **6 months** | **9 months** | **12 months** |
| Method failure (Involuntary pregnancy) | 0.0 ± 0.0 | 0.0 ± 0.0 | 0.0 ± 0.0 |
| Continuation rate | 74.3 | 66.7 | 63.2 |
| Woman months of use | 6638 | 9318 | 10934 |
| No. of women completed | 945 | 846 | 791 |

***Net Cummulative Discontinuation Rate*:** The cumulative discontinuation rate due to personal reasons was 6.8, 10.7 and 12.4 at 6, 9 and 12 months of use (132 out of 1275 women; reasons being transfer, due to illness of husband, objection from family members etc) and similar number of women discontinued due to menstrual irregularities giving a net cumulative discontinuation rate of 12.5 per 100 users at 12 months of use (heavy bleeding 0.5, prolonged bleeding 1.3, heavy and prolonged bleeding 2.7 amenorrhoea 2.7, irregular bleeding 2.2 per 100 users). Discontinuation rate due to other medical reasons was 3.1, 4.8 and 5.2 at 6, 9 and 12 months of use (54 out of 1275 women; reasons being nausea, giddiness/vomiting, weight gain, mastalgia, increased BP, hair loss etc.). Although the window period for the study was short ± 3days, only total 43 women discontinued due to Late-for Follow-up, reasons being illness in the family, out-of-station, etc. (Table 4).

| **Table 4 : Net Cumulative discontinuation rates per 100 users** | | | |
|---|---|---|---|
| | **6 months** | **9 months** | **12 months** |
| Pain at site of 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 | 9.9 ± 0.9 | 11.5 ± 0.9 | 12.5 ± 1.0 |
| Other medical reasons | 3.1 ± 0.5 | 4.8 ± 0.7 | 5.2 ± 0.7 |

| | | | |
|---|---|---|---|
| Planning Pregnancy | 1.2 ± 0.3 | 1.5 ± 0.4 | 2.0 ± 0.4 |
| Opting permanent method | 1.0 ± 0.3 | 1.4 ± 0.4 | 1.8 ± 0.4 |
| Opting for other FP methods | 1.1 ± 0.3 | 1.5 ± 0.4 | 2.0 ± 0.4 |
| Other personal reasons | 6.8 ± 0.7 | 10.7 ± 0.9 | 12.4 ± 1.0 |
| Late for F.U | 2.7 ± 0.5 | 3.8 ± 0.6 | 4.1 ± 0.6 |
| Lost to F.U | 2.8 ± 0.5 | 3.4 ± 0.5 | 3.4 ± 0.5 |

***Return of Fertility:*** All women discontinuing the use of the monthly contraceptive injection Cyclofem at any period during the study (including women who completed 12 months of use) and not opting for any other contraceptive method (exposed to the risk of pregnancy) were followed up after discontinuation of the method for a period of 12 months for return of fertility and outcome of pregnancy. 0ut of 1275 women 304 women were not willing to be enrolled and followed up for return of fertility. The remaining 971 women were enrolled for follow up. Of these 874 women adopted some method of contraception. Out of the 97 women who were exposed to the risk of pregnancy 86 women became pregnant within one year of discontinuation of the method..

***Analysis of Menstrual Bleeding Pattern*:** The menstrual pattern was analysed using the approach recommended by Rodriguez et al. Analysis has been done on different menstrual bleeding indicators as given below in a Reference period (Ref.) of 90 days:

**1. No of bleeding runs**: 2- 4 bleeding runs are taken as normal.
**2. No of bleeding days:** 6-20 days of bleeding are considered normal.
**3. Average episode length**: A period of 22-35 days is considered normal.

***Results 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. 54.6% of women had normal number of bleeding days (6-20) in the first 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 first reference period which increased to 46.8% at the end of 4th reference period. To summarise, the data reveals that 7.1% women have frequent / prolonged bleeding during the first reference period which decreased to 2.4 % women at 12 months of use of Cyclofem. The majority of the acceptors have either normal bleeding pattern (41.5%) or reduced / infrequent bleeding pattern (56.2%) at 12 months of use (Table 5).

**Table 5: Menstrual bleeding pattern in a reference period of 90 days**

| **PARAMETERS** | **1st ref. period (3 mths)** | **2nd ref. period (6 mths)** | **3rd ref. period (9 mths)** | **4th ref. period (12 mths)** |
|---|---|---|---|---|
| **No. of menstrual Diaries** | 1136 | 954 | 831 | 507 |
| **No. of bleeding runs** | | | | |
| | **% women** | **% women** | **% women** | **% women** |
| 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** | | | | |
| | **% women** | **% women** | **% women** | **% women** |

| | | | | |
|---|---|---|---|---|
| 1-5 | 13.6 | 13.3 | 10.3 | 11.6 |
| ***6-20*** | 29.8 | 21.9 | 25.8 | 25.9 |
| 21+ | ***54.6*** | ***63.3*** | ***62.8*** | ***61.7*** |
| Mean ± SD | 2.0 | 1.5 | 1.1 | 0.8 |
| | 6.9 ± 5.4 | 7.8 ± 5.3 | 7.5 ± 4.9 | 7.2 ± 4.9 |
| **Average Episode Length** | | | | |
| | **% women** | **% women** | **% women** | **% women** |
| 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 in a ref. period of 90 days** | | | | |
| | **% women** | **% women** | **% women** | **% women** |
| Frequent/prolonged | 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 |

***Women's perspective: This information was obtained from only Cyclofem acceptors and it was obtained in this study so as to ensure contraceptive choice. Therefore, the i***information is on women's perception about contraceptives in general and specifically for Cyclofem. This was obtained by administering a questionnaire after providing a balanced presentation of all contraceptive methods at the initiation of the study. The women were asked question about choices of family planning methods reasons for choosing a particular contraceptive, the intended duration of use, advantage of the methods and disadvantages. 43.9% of the women choose Cyclofem as they felt it to be a safe and convenient method, 18% because it is a new method, 15% because it is a once a month and a reversible method of contraception, 10% of the women were not sure as to why they choose the method. 88.3% of the women intended to use it for a duration of 1 year probably because they were aware that they would be provided the injections for only 12 months. 61.1% thought it to be better than other contraceptives and 56.6% felt it to be only once a month contraceptive and therefore more advantageous than other contraceptive methods. Around 71.3% of the women perceived menstrual irregularities as the main disadvantage of the method.

***Conclusions*****:** The results of the study indicate that the method is highly efficacious as no pregnancy has been reported in the study and the method is relatively acceptable to women indicated by the continuation rate of 63.2% at the end of 12 months. A total of 791 women took all the 12 injectionsThe menstrual bleeding pattern is not significantly disrupted and half of the women experience near normal menstrual cycles.

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 such methods. Due emphasis is needed in techniques and content of counseling and information provision, provision of quality care, training of staff, supervision, record keeping, logistics and supplies besides support from the program managers and policy makers. The present study was conducted at teaching hospitals in which trained staff and researchers conducted the study with rigorous follow-up of women which included personal reminders, home visits etc .

In order to validate the results of the present study and to study other logistics and supplies issues, training requirements, follow up needs and mechanisms it is imperative that a pre-program introductory study be carried out at the post partum (B&C) centres, through the existing health care delivery system and other effective health service delivery outlets.

**INDIAN COUNCIL OF MEDICAL RESEARCH**

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

## Information for participants

**PURPOSE**

The purpose of the study is to evaluate the clinical effectiveness and side effects and return of fertility associated with the use of Lunelle/Cyclofem - a monthly injectable contraceptive.

**PROCEDURE**

If you elect to use Lunelle/ Cyclofem you would be given a general physical and a gynaecological examination and you would give a medical history to determine your eligibility.

The monthly injectable Lunelle/ Cyclofem contraceptive (25mg MPA and 5 mg Estradiol cypionate) would be given every month ± 3 days for 12 months . You would need to return to the clinic at 1 month ± 3 days for 12 months. You would receive a total of 12 injections if you wish to continue with the method for 12 months. At each scheduled visit you will have your weight and blood pressure taken. At initiation of the study and at each follow up visit you will have a general, physical and a gynaecological examination if required. You will have to record menstrual events daily on a menstrual diary card provided to you.

You may discontinue use of the method at any point of time without any prejudice to your further medical treatment.

If you do not adopt any other method of contraception after discontinuing Lunelle/Cyclofem, you would be monitored for return of fertility for one year and outcome of pregnancy ..

**BENEFITS AND RISKS**

Lunelle/ Cyclofem is a very effective contraceptive method for avoiding pregnancy.

Following the injection there may be slight pain at the site of injection.

You may experience some irregularities in menstrual pattern like spotting, delayed menses, prolonged bleeding and sometimes heavy bleeding . In some women menstrual pattern may become regular during the course of its use.

Some women may also experience headache, dizziness nervousness, weight gain, change in appetite and nausea/ vomiting during use.

It is unlikely that you will become pregnant while using Lunelle/Cyclofem, In the rare event of your becoming pregnant during its use you should return to the clinic as soon as possible and seek medical advice regarding medical termination of pregnancy (M.T.P).

Instead of participating in this study you may choose to use any other contraceptive of your choice.

In addition to the above information on Lunelle/Cyclofem, you have also been provided with alternative methods of contraception available to enable you to make an informed choice.

If you wish to participate in this study, you may please sign the consent form.

Your participation in the study is completely voluntary. You have the right to withdraw from the study any time you desire without prejudice to your future medical care. Other contraceptives will be available to you should you decide to withdraw from the study.

I, the undersigned, have discussed and explained to the volunteer in her native language the risk of the study which may include uterine and ectopic pregnancy, menstrual irregularities including amenorrhea. I have explained the benefits and risks of the study as well as the intervals for repeat injections and check-up visits as stated above.

Signature of Principal Investigator/Research Officer

Date:_____

Subject No. _____

Name of the Volunteer_____

Name of HRRC____

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

**_____**

**CONSENT OF THE VOLUNTEER**

I_____ (full name) wife of

_____ Living at (full address)

_____

_____

have read/understood the information about this study that was given/read to me. I have been explained all the known side effects including menstrual irregularities that can occur during the use of the method. If I decide to continue use of the method for the period of study, I should come back for regular follow up for getting the injections and for return of fertility if I do not opt for any other method after discontinuation and am planning to become pregnant. .

I understand that confidentiality will be maintained of my participation in the trial and the records concerning my participation are to be used for the purpose of this research project only.

I consent to participate as a volunteer in this study and understand that I have the right to discontinue use of Lunelle without prejudice to my further medical care at the clinic.

Witness: Signature of Volunteer

1._____

Date _____

2._____

## PHASE III - CLINICAL TRIAL WITH ONCE A MONTH COMBINED INJECTABLE CONTRACEPTIVE - LUNELLE

**List of Participating Human Reproductive Reasearch Centres of ICMR**

1. Medical College, Jammu
2. PGI, Chandigarh
3. Kasturba Hospital, Delhi
4. LLRM Medical College, Meerut
5. MLN Medical College, Allahabad
6. Eden Hospital, Kolkata
7. JJ Group of Hospitals, Mumbai
8. BJ medical College, Pune
9. JIPMER, Pondicherry
10. SAT Hospital, Thiruvananthapuram

**New centres included in the study from May, 2002.**

1. Goa Medical College, Goa.
2. JLN Medical College, Belgaum.
3. Instt. of Obst. & Gynae., Chennai.
4. King George Medical College, Lucknow.
5. Guwahati Medical College, Guwahati.
6. S.P.Medical College , Bikaner