Study on 2 Monthly Injectable Contraceptive Norethisterone Enanthate (200mg)

Summary Report

The Family Planning Programme of India offers limited contraceptive choices like IUCD, oral pills, male condom, tubal ligation and vasectomy. There is substantial unmet need of 13% for contraception of which about 50% is for spacing methods (NFHS 3, 2005-06). It is essential to increase the range of contraceptive choices to fulfil this unmet need.

The idea of offering injectable contraceptive as a method of contraception is to widen the choices of contraceptives available for women. None of the available contraceptives is 100% effective, or completely free from side effects. However the side effects are more of an inconvenience than life threatening. The risk of morbidity and mortality associated with unwanted pregnancies must always be weighed against the side effects of contraceptive methods, which are much less.

Injectable contraceptives can be used as a long-term or short-term (1–3 months) method. They can be of use to women whose spouses visit them for short duration. They can be ideal contraceptive after vasectomy when contraception is required for 2 to 3 months till husband's sperm count becomes zero. Women who are breast-feeding, and cannot take oral pills or use intrauterine contraceptive devices can use injectable contraceptives.

Globally, about 32 millions of women are using injectable contraceptive. The 2 monthly Norethisterone Enanthate Net-En)- 200mg is registered in 91 countries including Germany, the country of origin. NET-EN 200 mg is available in the Indian market since 1994.

The Indian Council of Medical Research (ICMR) has generated considerable data on one monthly and 2 monthly injectable contraceptives in the 1970s and 1980s. In 2002 Government of India initiated a multi centre study on 2 monthly injectable contraceptive (Net-En) to obtain women's perception and acceptability of the methods in clinics where quality of care was ensured..

Objectives :

i. To assess user acceptability/continuation rates of injectable contraceptive NET-EN

ii. To evaluate the incidence of menstrual irregularities and other side effects

iii. To assess user's attitudes/perceptions towards injectable contraceptive

iv. To study return of fertility in eligible women

Study Methodology

Material:

Norethisterone Enanthate (Net-En) is a two monthly injectable contraceptive containing a synthetic hormonal progestrogen, which resembles the natural female progesterone. Each dose contains 200 mg of hormone in an oily base. The injection is marketed as Noristerat. The drug is released at a relatively constant rate into the blood stream from the site of injection after an initial peak level (serum levels between 10–20 mg/ml) and provides the users with a safe and effective form of birth spacing method. The method failure rate quoted in literature for NET-EN is 0.01–1.3 per 100 women years.

Design:

This is a multicentre study was initiated at 8 Human Reproduction Research Centres (HRRCs) of ICMR and NIRRH, Mumbai in June 2002 after approval of the Institutional Ethics Committee (IEC). Each centre was expected to enroll a minimum of 120 women participants over a period of 12-18 months. Women attending the family welfare clinics/gynaecological OPDs in public hospitals and requesting for spacing methods were given balanced presentation on all available contraceptive methods in the NFWP including 2- monthly injection Net-En. Healthy women between 20-40 years of age, having at least one living child, who met the eligibility criteria and were willing to participate and sign an informed consent form and be accessible for follow-ups were included in the study. These women were explained and provided with a detailed written information on injection Net-En including its advantages and disadvantages. The duration of injection Net-En use in this study was two years. The study was completed in March 2008.

The major emphasis in this study was on good counseling by qualified staff and provision of quality care services. All the health providers from the participating centers were trained to strengthen counseling and service provision skills through pre study and midterm workshops conducted at the Institute. The doctors/nurses were re-trained for the injection technique and safe injection practices. Counseling guidelines were prepared for implementation at various stages of use i.e. at initiation, during treatment and after discontinuation of the method and also for management of common side effects. The information for the participants included all the advantages and disadvantages of injectable contraceptive. The women were interviewed at discontinuation of injection/termination of the study by the qualified staff to know their views and attitudes towards this method. This is essential to determine the needs of the potential users before the method is introduced into the National Programme.

Enrolment Procedure: A thorough physical and pelvic examinations were done at enrollment including weight, height, blood pressure, haemoglobin, routine urine sugar and albumin. Pap smear was done at enrollment and thereafter at 1 and 2 years. They received injection Net-En 200mg deep intramuscular every 2 months, with a grace period of 7 days (either early or late). They were given menstrual diary card to record symbols for menstrual bleeding as instructed. The dates of subsequent injections were mentioned at the back of the menstrual card. One menstrual card was also kept with the case record form and information from the menstrual card given to the woman was transcribed into the card kept in the clinic.

Follow-up Procedures:

i. Each woman was to be followed up for scheduled injections at 60±7 days for a duration of 2 years.
ii. At each follow-up visit the menstrual diary card was completed and symptoms related to method recorded and appropriate counseling was given.
iii. Blood pressure, weight record, breast and pelvic examinations were to be done every 6 months and earlier if indicated.

In case of amenorrhoea, (> 6 weeks) pregnancy was excluded by symptoms, pelvic examination and urine pregnancy test if necessary before administering subsequent injection.

At discontinuation of the injection, women were interviewed to know their perceptions towards this method. Women who desired pregnancy following discontinuation of injection or who did not accept other contraceptives in the clinic after discontinuation

for any other reason including trial completion and therefore exposed to the risk of pregnancy were followed up every 3 months for return of fertility for a period of 2 years.

Results

A total of 2352 eligible women were given the choice of Net En under the cafetaria approach. Of these 1209 (51.4%) women accepted injection after signing an informed consent form . The remaining 1143 (48.6%) women desired other available spacing methods in the programme. The commonest reasons for refusal of this method were, frequent visits to the clinic for repeat injections (27.8%), anticipated side effects like irregular menstrual periods and weight gain (17.4%), etc. as indicated in Table 1.

Table 1: Eligible women - reasons for not accepting injection (n = 1143)

Reasons	Numbers	%
Frequent visits for repeat injection	**318**	**27.8**
Prefers IUCD	**201**	**17.6**
Fear of side effects(menstrual irregularity & weight gain)	**198**	**17.4**
Family members' objection	**132**	**11.5**
Scared of Injection prick	**120**	**10.5**
Prefers permanent method	**59**	**5.2**
Prefers Oral Pills / Condom	**49**	**4.3**
Likely to migrate	**31**	**2.7**
Regular contraception not required	**20**	**1.7**
New method	**9**	**0.8**
Fear of developing male characteristics	**6**	**0.5**

Thus, a total of 1209 healthy women aged between 20-40 years with proven fertility and at least having one living child were enrolled across India. The observations based on 17,268 women months of injection use indicated a continuation rate of 65%, 53.6% and 48.3% at the end of 12 18 and 24 months respectively.

Method failure and Discontinuation rate : Very few method failures (3 pregnancies) were reported during the study (0.24%). The major discontinuations were due to personal reasons and, loss-to-follow-up due to migration of floating population (18.7% and 16.7% respectively). The discontinuations for menstrual disruptions were observed in 15.3%, of women at the end of study period of two years as indicated in Table 2).

Table 2: Reasons for discontinuations of Net-En (women enrolled - 1209)

Reasons for discontinuation	6 mths %	12 mths %	18 mths %	24 mths %	Total %
Menstrual disruption & weight gain	8.4	4.2	2.2	0.4	15.3
Pregnancy (method failure)	0.16	0.0	0.08	0.0	0.24
Awaiting tubal ligation	1.6	1.9	1.5	0.9	5.9
*Other medical reasons	1.9	1.1	0.33	0.66	3.9
Personal reasons	6.2	5.1	4.8	1.9	18.0
Lost to follow up/ Migration	10.9	2.9	2.2	0.7	16.7

* TB, Hepatits A, Skin allergy, Headache, Accidental deaths, Malaria

Changes in Body Weight observed during Injection Use: A total of 709 participants had repeat weight record at the end of 1 year while 417 women had at the end of 2 years of injection use respectively. Although majority of the women (62.9%) had weight gain at 1 year of injection use, there was no significant increase in mean body weight compared to their body weight recorded before initiation of injection. The weight loss was also observed in about 16% of women although it was not significant compared to their body weight before injection use. Similarly, the increase in mean weight was observed in 76.5% cases at two year of injection use, although it was not significant

***Overall Effect on General Well-Being*:** At the discontinuation of injection, a total of 968 women were asked direct questions pertaining to certain side effects of the injection, although none of them directly complained about these side effects. About 55.7% of women had some of the following side effects like weight gain (21.6%), lethargy (20.6%), bloatedness (18.9%), irritability (15.2%), mood changes (13.7%), backache/leg pain (6.5%) and breast tenderness (3.5%) ,although there were no discontinuations due to these effects.

Menstrual Bleeding Pattern: For the analysis of the menstrual pattern, a 90 days reference period was considered and the statistical programme was developed based on the WHO guidelines by Belsey et al (1986) and modified as per Datey et al (1995). The following definitions were considered in a reference period of 90 days. Prolonged and frequent bleeding patterns were clubbed together for the analysis purpose:

a) Prolonged bleeding: At least one bleeding/spotting episode lasting more than 14 days

b) Frequent bleeding : More than four bleeding/spotting episodes during the reference period.

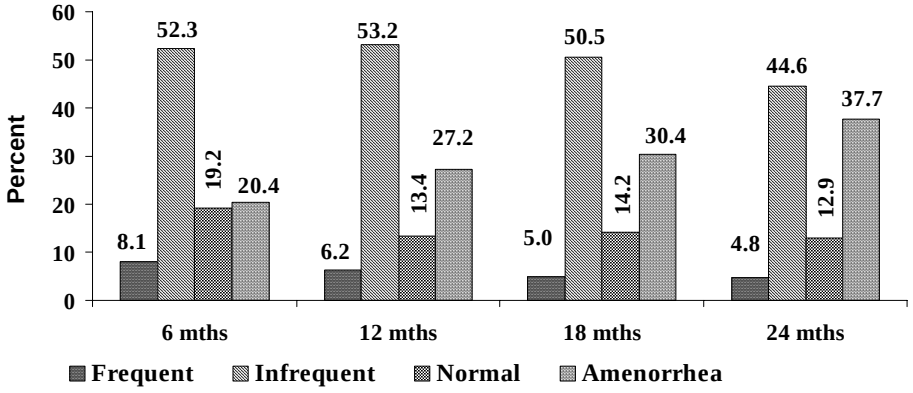
c) Infrequent bleeding : One or two bleeding or spotting episodes.

d) Amenorrhoea : No bleeding /spotting days during the reference period.

f) Regular pattern (Normal): . Three to four episodes of bleeding or spotting each lasting about five to seven days.

Thus a total of 5666 reference periods were studied during 2 year injection use. It was observed that through out the study period the infrequent bleeding (oligomenorrhoea) pattern was most commonly seen whereas regular or acceptable bleeding pattern was observed among 13.4% and 12.9% of women during the 4th and 8th reference period i.e. 1 and 2 years respectively. The frequent and prolonged bleeding pattern was observed only in 6.2% and 4.8% of women during these reference periods respectively. There was increase in amenorrheic pattern at the end of 2 years of injection use (37.7%) compared to 27.2% during the reference period at 1 year. It was observed in this study that infrequent bleeding pattern was well accepted by the women (Fig 1).

Fig.1: Percentage of different Menstrual Pattern in a two year study period (Total Reference Period – 5666)



WHO guidelines (Belsey et al., 1986),

Frequent Bleeding – More than 4 bleeding/spotting episodes during the ref. period
Infrequent Bleeding- 1- 2 bleeding or spotting episodes
Regular Pattern – 3- 4 episodes of bleeding or spotting each lasting about 5-7 days
Amenorrhea - No bleeding/ spotting days during the reference period

Return of fertility:

A total of 150 women were eligible for return of fertility following discontinuation of injection. The pregnancy was confirmed either by urine pregnancy test or ultrasonography. Of these, 75.3% conceived within 9 months whereas 24.7% conceived between 10 to 23 months. Of the 150 women, 135 continued pregnancy till term and had normal babies at birth, 3 women had first trimester spontaneous abortions while 12 women underwent medical termination of pregnancy. These 12 women wanted to continue injections beyond study period and did not accept other available

contraceptives in the programme. They underwent concurrent tubal ligation. There was no difference in timing of conception between women who discontinued injection for planning pregnancy compared to the women who discontinued method for other reasons like menstrual disruptions, personal reasons.

Women's perception: Of the 1209 women enrolled, 723 women (59.8%) had not heard or knew about injectable contraceptive prior to participation in this study, whereas 486 (40.2%) heard about this method (from their friends or relatives who had used injectables (54.8%), health personnel (41.2%), private doctor (14.8%) and media (5.6%)) About 89% women desired that the injections should be made available through National programme, since the method is more convenient compared with daily intake of oral pills, does not have effect on breast milk, offers a wider choice of Family Planning (FP) methods etc. Over 79% women were satisfied with the use of this method and also recommended this method to their friends and relatives**.** About 39% requested to provide them further injections after completion of the study.

Net EN and Bone Mass Density (BMD):

Following the issue of 'Black box' on the use of DMPA by Pfizer Company , to address to the concern of women's group, the Ethics Committee of NIRRH decided to add the additional parameter of DEXA studies for assessing bone density in the women who are still using injection Net-En. This additional study parameter was initiated in July 2005.

As this was not part of the initial study, the baseline levels of the BMD in these women (prior to initiation of injection Net-En) are not available. Three participating centres viz. Nagpur and Cuttack were excluded for DEXA study because of unavailability of the DEXA machine in these cities. The centre at Kolkatta could not participate because they had very few women Net En users at this time.

The DEXA investigations were planned to be conducted after every six months during injection Net-En use and one year after stopping. However, since some women desired to continue the injection beyond the 24 months study period, the Ethics committee of the Institute gave their approval for their continuation, hence some women have received injections until 30 months of use.

Salient Observations of DEXA Study :

- A total of 142 users of injection Net-En, at varying stages of the study, underwent initial BMD evaluation by DEXA scan at hip and lumbar spine (range of injection use 14 - 22 months).

- Of these, 73 eligible women, using injection Net-En for a period of 20-30 months, underwent 2nd DEXA scan at 6 months interval and one final DEXA scan one year after stopping the injection (n=109).
- Healthy women (n=59), who did not use hormonal contraceptives and were matched with respect to age and parity comprised the control group for DEXA study.
- There was no correlation between increasing duration of injection use and mean BMD.
- There was positive correlation between body mass index (BMI) and BMD. Women with BMI of 25 and above had significantly ($p<0.001$) higher BMD at both the sites compared to women having low BMI of less than 20.
- There was negative correlation between the parity and BMD. Mean BMD was significantly higher ($0.886 gm/cm^2$ $P<0.05$) among women having 1 or 2 children compared with women having 3 or more children ($0.769 gm/cm^2$).
- There was no significant difference in mean BMD among injection users compared with control group.

Conclusions:

The study was carried out through trained health personal and skilled counselors, ensuring quality of services at these tertiary hospitals and clinics. There were inter-centre variations with regard to continuation rates of injection. The educational status of the women did not have impact on 1 year continuation rate of the injection. The method was well accepted by majority of the women, thus can fulfil the unmet need for contraception. The findings of this study are useful in programme implementation of the injectable contraceptive. The limited DEXA study during injection use indicated that there was no significant difference in mean BMD among injection users compared with control group.

Acceptability and Continuation rates of 2 monthly Injectable contraceptive Norethisterone Enanthate

Information for the participants

(If the woman is illiterate, the investigator should read this information to the woman)

Injectable contraceptives are safe, effective family planning methods that protect women from unwanted pregnancies. All over the world about 14 million women use progestin only injectable contraceptive. In India two types of injectable contraceptives are available, one of which is administered every 2 months. This is marketed as Injection Noristerat.

The idea of offering this injection is to increase the choice of family planning methods. If you select this method for family planning, we would collect some information from you like your acceptance and views regarding this method. Please read the following information about this injection.

How does this injection prevents pregnancy?

- It stops release of eggs from the ovaries.
- It also causes thickening of cervical secretions/fluids at the entrance of womb making it difficult for the sperm to pass through.

Who can use this method?

- It can be used by women of any age or parity who want to space births.
- It provides effective and safe contraception after delivery and abortion.
- It is suitable for nursing mothers since it does not have effect on quality and quantity of milk.
- Suitable for women who may have side effects related to use of oestrogen containing contraceptive eg. Combined Oral pills.
- Women with certain medical diseases, who can not use other contraceptives eg. Combination oral pills, can use injectable contraceptive.

When is the first injection given?

- The first injection can be given anytime provided you are not pregnant, preferably during first 7 days of your normal menses.
- Immediately after an abortion.
- 6 weeks after delivery if you are breast feeding.

What are the benefits of using this injection?

- It is very effective (99.6%) and reversible.
- It is a convenient method and will ensure/maintain privacy.
- Once you take this injection, you will be carefree about contraception for 2 months. You will not need to take every day like for the pills.
- In some women it may reduce painful periods.

- The regular visits for injection offer an additional advantage of regular medical check up.

What are the likely disadvantages with this method?

- You may experience irregular periods like spotting, delayed menses, prolonged bleeding and rarely heavy bleeding.
- You may gain weight .
- You may experience headache.
- Once you take this injection, the effect will last for 2 months.
- If you wish to plan pregnancy you may conceive within 12 months after stopping injection (i.e. 4 to 9 months after the effect of the last injection).

What you need to do if you take this method?

- You will be given choice of all the contraceptive methods available and will have choice for yourself.
- If you choose this method you will have to undergo general and gynecological examination.
- You can choose to take this injection either in the buttock or arm.
- You have to visit the centre for repeat injection after 2 months.
- You will be given a diary card and explained to enter information on bleeding/menses. You have to bring this card at repeat visits to show us.
- We will offer this method for the duration of 2 years. You may decide to stop this method any time you wish.

What happens if I have any problem?

- If you have concerns or questions about this injection, please come to the centre. You may contact clinic doctor (_____) or any other staff at this address. _____
  _____

  Telephone No.

Please Note:

- Injectable contraceptive does not provide protection against HIV/AIDS.
- Treatment for any side effects due to this injection will be given at the centre free of cost.
- Only health providers at the centre will have access to your records. Your name or identity will not be revealed in any data reports.

Acceptability and Continuation Rates of 2 Monthly Injectable Contraceptive - Norethisterone Enanthate

INFORMED CONSENT

I _____(full name) have been made to understand that Institute for Research in Reproduction conducts clinical trials of various contraceptive methods. I have been fully informed about the aim of this study. I have been explained all the advantages and disadvantages including menstrual irregularities that can occur with the use of injectable contraceptive method. I have been also informed about the benefits and risks of other spacing methods like Cu-T 200, oral pills and condoms available in the National family planning programme. I have selected 2 monthly injectable method **Noristerat** willingly for spacing children. I have had all my questions and doubts about this method answered and clarified.

I am willing to undergo physical examination, come for follow-up. I am also aware of my right to withdraw from this study at any time without having to give any reason for doing so, without loss of benefits or utilizing the services of the clinic. I will not have to pay for the injections.

Signature / thumb impression of acceptor

Date:

Doctor's Name & Signature