Long Acting injectables - Acceptability and efficiacy in our family welfare programme

Usha Krishna, Ajita Mandlekar, Veena Raote
Clinic for Women, Ajit Villa, Laburnum Road, Mumbai 400 007.

Summary: About 12 million couples throughout the world are using long acting injectable preparations, DMPA 150mg and Norethisterone enanthate 200mg given intramuscularly are widely used progestin injectables. Combined estrogen and progestin preparations such as Mesigyna and Cyclofem are given once a month. Over last 19 years, authors have studied 454 women on Net-En injections and 175 patients on monthly injections. The continuation rate, menstrual pattern, side effects and failure rate are studied.

Of 454 cases enrolled for two monthly Net-En, 53 per cent continued the method for one year, 21 percent for two years. There were only 9 per cent women, who wanted to continue after 2 years. The continuation rate was highest (60 per cent) in the postpartum group and lowest (24 per cent) in postabortal group. 29.6 per cent discontinued for irregular bleeding and spotting, 7 per cent for amenorrhoea and 7 per cent for weight gain. The continuation rate with monthly preparation was 66 per cent at one year and 32 per cent at 2 years. Eighty per cent patients on monthly injections experienced regular cycles. There were 2 cases of method failure - one in the third cycle and other in the postabortal group.

Introduction

Fertility control plays a pivotal role in the reproductive health care of women. A good programme will not only reduce the population growth but will have an impact on adolescent health, gynaecological problems and maternal mortality. With expanding services of family planning, it is necessary that we offer one more choice of contraceptive i.e. injectable progestogens. There is no family planning method, which is suitable for all women, and each method has to be judged for the individual patient looking at the constraints, effectiveness and suitability as well as the duration for which it will be used.

Depot injectable preparations have been developed to obviate the need for sustained motivation required for the administration of oral pills. Although the low dose combined oral pills are effective and safe, the compliance and continuation rate are not satisfactory especially in our country. Unless we have acceptable interval methods to delay pregnancies, the demographic impact of India's family planning programme will not be satisfactory. Although female sterilisation continues to be the method of choice for majority of the rural family planning acceptors in our country, the decline in population growth is rather slow as most of the women who accept sterilisation already have 3 children. Of about 30% who follow spacing methods, intra-uterine contraceptive device is accepted by about 6%, condoms by about 10% and oral pills by about 3% to 4%. The rest claim to follow natural methods. As the compliance and continuation rate for condoms and oral pills are not satisfactory, there is some place for long acting injectable preparations.

About 12 million couples throughout the world now use injectable contraceptives. Progestin only injectables are the most widely used: DMPA (depot medroxyprogesterone acetate 150 mg Depo-provera) is an aqueous solution which is used three monthly and NET EN (norethindrone enanthate 200mg - Noristerat) oily preparation is used 2 monthly. Combined estrogen and progestin preparations are Cyclofem and Mesigyna. Cyclofem contains 25 mg. DMPA + 5mg. estradiol cypionate and Mesigyna contains 50 mg NET EN + 5 mg. estradiol valerate. Monthly injections of the above 2 preparations are well tested and are alternatives, which may be more acceptable. DMPA is now registered in more than 106 countries and NET EN in over 6 developed and developing countries.

There is a Chinese monthly preparation used by almost

one million women but with limited data.

Although research should continue to develop an ideal contraceptive method. It is important that the available methods are utilised appropriately to achieve population stabilisation. The choice and the acceptance as well as the continuation of the method is left to the client after proper counselling. It is essential to remember that pregnancy, childbirth and the risk of termination are of greater concern than some of the side effects and problems associated with the contraceptive use. Besides, injectables may not be the absolutely ideal method but suitable for short term use in women waiting to undergo sterilisation operation till their last child is of appropriate age, or during the postpartum period while breastfeeding when amenorrhoea is common and acceptable. Women whose husbands have undergone vasectomy can use the injection for protection during the first three months after the operation. Moreover, couples who find oral contraceptives, IUCD or condoms unsuitable can try the injectable methods. And about 20% of the patients continue this method for 2 years. This gives them the opportunity to consider sterilisation operation or other methods without resorting to termination of an unwanted pregnancy.

Material and Methods

Over last 19 years the authors have studied 454 patients enrolled for NET EN injections in a Municipal General hospital, an industrial health centre as well as the "Clinic for Women", their private clinic. The first 350 cases were part of WHO and ICMR studies and the remaining 104 cases were given NET EN injection as a spacing method of family planning as part of family welfare service. The injections were supplied by German Remedies as post-marketing surveillance study. Healthy informed women, between 18 and 40 years, requiring spacing method were offered this method with a cafeteria approach. The injection was started within the first 7 days of the menstrual cycle or 6 weeks postpartum or within 3 days after spontaneous or induced abortions. The injections were repeated at two monthly intervals irrespective of the menstrual cycles, which could be more or less regular or with intermenstrual spotting or oligo-amenorrhoea or amenorrhoea. The first 4 injections were given at 60 days interval and then switched over to 60 days or 90 days schedule.

Proper records of history, general examination, gynaecological examination, investigations and breast check up and follow-up examination were maintained for all the cases. The reason for discontinuation was noted. The patients with complaints and side effects were counselled and those who wished to discontinue the method could do so at their own discretion. Twenty four women were lost to follow up.

The women were taught to maintain a menstrual diary and details of menstrual disturbances were specially recorded as disruption of regular menstrual bleeding and amenorrhoea were the most common side effects of the injectables and the main medical reason for women to stop their use. The side effects such as headache, dizziness, abdominal discomfort and acne were noted. The blood pressure was recorded before starting injections and at 2 monthly intervals and at the time of discontinuation. haemoglobin levels were noted before starting the method and at 6 monthly intervals. Papsmears were collected before starting this method and at one yearly interval or at the time of discontinuation. The endometrial histopathology was studied in 50 cases with irregular bleeding, continous bleeding or amenorrhoea and also in some cases with more or less regular menstrual periods.

Metabolic changes were studied in 50 cases for carbohydrate metabolism, liver function, coagulation factors and lipid profile.

The effectiveness of treatment was studied as failure of method and pregnancy were noted. However, we could not study reversibility of the method as we could follow up only 40 cases after discontinuation. The bone density studies as well as fetal and child development after NET EN exposure during gestation were not studied. Long term studies for breast cancer, cervical cancer, endometrial cancer or epithelial ovarian and liver cancers were not possible.

One hundred & seventy five patients had received monthly injections in KEM Hospital Family Planning department and the factors mentioned above were studied in the same pattern. Monthly injections of esters of estradiol and NET EN were given post menstrually to 75 patients for 6 months. The patients were divided into 5 groups of 15 patients. First 4 groups were given either estradiol valerate 2.5mg or 5 mg and estradiol cypionate 2.5 mg or 5 mg along with 50 mg NET enanthate. The fifth group was given only 50 mg NET EN every month. This was part of ICMR multicentric study. We did not notice any difference between the 4 groups as the numbers were too small. The ICMR multicentric study demonstrated better cycle control with estradiol valerate 5 mg and 50 mg NET Enanthate group. Hence, we extended this study at KEM Hospital Family Planning centre on our own 100 patients for one year.

The continuation rate, menstrual pattern, side effects and failures were compared with 2 monthly injections. In this paper we are presenting our experience of 2 or 3 monthly injections as well as monthly injections.

Results

Of the 454 cases enrolled for 2 monthly NET EN injections, 53% continued the method for one year and 21% for two years. There were only 9% women who wanted to continue this method even after 2 years. As this method is generally used for spacing, many women desired to plan pregnancy after 2 years.

Amongst the medical reasons for discontinuation, irregular bleeding, spotting and prolonged bleeding were the commonest. 29.6% discontinued for irregular bleeding, 7% for amenorrhoea and 7% for weight gain. Less than 1% discontinued for headaches, mood changes or dizziness. Only 10% of women had more or less regular bleeding. The continuation rate at 12 months was highest, 60% in the postpartum group and lowest, 24% in the postabortal group.

The patients who were from lower socio-economic class and underweight did not mind the weight gain of 2 to 4 kilogram but those from higher income group discontinued the method even with moderate weight gain. The continuation rate of the method in women on monthly injection was higher; 66% continued the injections for one year and 32% for two years. The menstrual pattern was regular in 80% of these patients. There were no significant metabolic changes in the 50 patients studied on two monthly injectables. Author's experience - Table.1.

Table - 1

Author's Experience - 19 years

2 monthly NET EN Inj	454 cases
Monthly injection NET EN + E	175 cases

Centres - KEM Hospital, Industrial health centre, Private Clinic

Selection of cases

Group	%
Interval	40
Post abortal	40
Postpartum	20

Continuation Rate	Percent	
Duration of use	2/3 monthly	Monthly
At 12 months	53	66
At 24 months	21	32
At 24 months	9	-
Postpartum continuation highest		60%
Postabortal continuation lowest		24%

Discontinuation (Medical Reasons)	
Irregular Prolonged bleeding Spotting	29.6%
Amenorrhoea	7%
Weight gain	7%
Other medical	<1

Only 10% experience more or less regular menstrual pattern.

Failures

N=2

1 ICMR study (3rd cycle)

post marketing surveillance (post abortal)

The endometrial biopsy performed in patients with irregular bleeding or amenorrhoea did not show any specific changes. The majority showed extreme atrophy of the endometrium, which was more pronounced in patients with prolonged amenorrhoea. In 13 patients with amenorrhoea no endometrium could be obtained. No cases showed evidence of endometrial hyperplasia.

There were two cases of method failure - one who missed the injection at two months conceived in the second month. She was a post MTP patient. Both the women underwent termination of pregnancy.

Discussion

Research on injectable contraceptive began shortly after the development of oral contraceptives. Schering Ag snythesised the first injectable progestins in 1953 and in 1957 developed norethindrone enanthate (NET EN). The Upjohn Company synthesised medroxyprogesterone acetate (Provera) in late 1950's and conducted the first clinical trial in 1963. The monthly injectables have been tried later cyclofem in 1968 and the mesigyna in 1974. Tests of DMPA in beagle dogs and monkeys in the early 1970's raised questions about cancer that delayed US regulatory approval and held back its use in many countries.

Beagles developed breast tumours and some monkeys developed endometrial tumours. However, many experts questioned the relevance to human race and the WHO (1991) collaborative study of neoplasia and steroid contraceptives concluded that there was no increased overall risks of breast cancer but there was some increased risk fo several years after starting DMPA perhaps due to accelerated growth of existing tumours. There was no increased risk of cervical, ovarian or liver cancer and there was a protective effect on endometrial cancer.

Method failure:

The method failure could be due to improper technique of injection so that the full dose is not administered. At times the NET EN is not fully drawn into the syringe as it is a viscous solution. It is important that the injection is given with No: 21 needle deep in the muscle as the absorption and thus also should be avoided. It is safer to give injection NET EN at two monthly interval but a delay of two weeks is acceptable if the patient has missed the date of injections.

Non-contraceptive benefits.

Besides the contraceptive effects, these injections have some non-contraceptive benefits. These are reduced frequency of fibroids, ovarian cyst and pelvic inflammatory disease. Protection against ectopic pregnancy and prevention of anaemia due to oligmenorrhoea and amenorrhoea. The symptoms of endometriosis are reduced and the epileptic patients have reduced frequency of seizures. Besides the women come for regular medical check-ups and some of the medical and gyanecological problems are detected early.

Menstrual irregularity

The important disadvantages are menstrual cycle disturbances and weight gain. Irregular and prolonged bleeding episodes are common in the first 3 to 6 months and amenorrhoea is commonest with prolonged use of the method. The bleeding may be mild or moderate and generally does not require curettage or blood transfusion. The haemoglobin level does not drop. Yet this intramenstrual bleeding or spotting can certainly be bothersome. It could be controlled in some cases by using combined oral contraceptive pills for a few cycles. Amenorrhoea is well accepted in well counselled and well motivated clients and women in postpartum periods. Pregnancy test to rule out pregnancy and reassurance certainly helps. The bleeding irregularities and side effects are similar in Indian as well as Western studies

A WHO (1983) multicentric study by 13 investigators covering 1587 women over 20,550 months compared discontinuation rates of injection NET EN and DMPA. There was no significant difference in the two Progestin preparations. (Table II.)

Table II

Discontinuations of NET /DMPA

WHO Multicentric Study (1991)

13 investigators, 1587 patients, 20550 months.

NET 60 days - 789 pts. 10361 months

NET 84 days - 796 pts. - 10331 months

Discontinuations for Medical Reasons

Duration of use (mths)	Discontinuation for medical reasons		
	DMPA	NET EN	NET EN
8	12.4	14.2	11.7
12	20.7	24.5	22.8
18	30.4	33.6	34.1
24	30.8	47	40

Sapire (1991) studied the percentage of women with prolonged bleeding with DMPA and NET injection. 16.8% of 349 women in DMPA group and 15.6% of 304 women in NET EN group had prolonged bleeding. There was no significant difference in the amount and duration of bleeding between the two groups.

WHO study (1983) showed that 10% women on DMPA and 4% on NET EN experienced prolonged or heavy bleeding over 6 months.

An ICMR study (1990 & 1995) compared NET cumulative discontinuation rate after one monthly and two monthly injection NET EN. There was no difference in the discontinuation rate at 12 months. (Table III). However, our study using monthly combined Estrogen and Progestin preparations showed better continuation rate. ICMR (1995) carried out a randomised trial of injection, NET enthanate 50mgm and its combination with 2.5 or 5mgm of Estradiol Valerate or estradiol Cyprionate as monthly injectable. Addition of Estrogen provided significantly better control as seen in Table IV.

Table III

NET Cumulative Discontinuation At 12 months - ICMR

Reason for discontinuation	One monthly	Two monthly
Involuntary Pregnancy	0.2	1.1
Bleeding	12	14.8
Amenorrhoea	4.2	6.9
Other medical	9.4	4.3
Non medical	17.2	8.6
Discontinuation rate	55.9	54.3

Table IV

ICMR Study - monthly injections. Inj. NET EN alone and in combination with Estradiol Valerate and Cyprionate 2.4 & 5 mgm.

Reasons for Discontinuation	G.I	Gr.II	Gr III	Gr IV	Gr V
					Net Only
	NET+ 2.5mgE.V	NET+ 2.5mgE.V	NET + 2.5mgE.C	NET + 5E.C	
	N=76	N=78	N=81	N=77	N=52
Pregnancy	-	1	-		
Menstrual Irreg.	4	1	-	1	1
Discontinuation%	21	15	16	15	23

Some patients suffer from headache and dizziness. There is delayed return of fertility compared to the IUCD and oral contraceptive in the fist 6 to 9 months. After this the return of fertility is similar to other spacing methods. The largest study of return to fertility among users of DMPA was conducted in Thailand (Pardthousong T. 1980). It was noted that most women conceive 9 months on average after the last injection. An Indian study (ICMR, 1986) of 69 users of injection NET EN on two and then three month schedule, conceived on an average at 11 months after the last injection. Although there is no evidence that injectables cause infertility, it is prudent to avoid injectable preparations in nulliparous women.

There are some studies which show increased loss in bone density of premenopausal women who are given DMPA. A Thai study (Virutamsen et al 1994) reported no difference in bone density, between 75 women who used DMPA for three years and 147 who had not used it. However, a New Zealand study (Cundy T et al 1991) found a difference of about 7% in density of lumbar spine and femoral neck in women between 25 to 51 years old who had been using DMPA for at least five years when compared with other pre-menopausal women.

Pharmacokinetic studies

Pharmacokinetic studies were carried out with 300, 15[illegible] 100, 50 mg. doses of NET EN. Increasing the dose above 200mg cannot increase the antifertility effect. But the dose can be reduced to 150mg, if the interval betw[illegible]

injections is maintained at 60 days. The initial peak of the drug is between 8 and 14 days after which there is a gradual decline. After 45 days, the concentration is 1ng/ml. Ovulation is suppressed during this period but can occur during the 12th week of treatment and therefore it is necessary to give the second injection after 60 days.

The largest multicentric clinical trials conducted by WHO (1991) ICMR (1990 & 1995) and other investigators also report the similar discontinuation rate as ours.

Metabolic Studies

Chaudhari et al (1987) carried out blood tests in 150 women unto 24 months. The authors reported significant reduction in serum cholesterol and triglycerides at 10-16 months of use, which returned to normal at 24 months. There was no change in serum proteins and phospholipids. Blood sugar increased significantly at 12 months and remained elevated. Kandeel (1984) reported results of lipid profile studies in 26 women and showed significant reduction in serum cholesterol, total lipids, triglycerides, phospholipids and free fatty acids. Fotherby et al (1987) reported the long term effect of DMPA and NET EN on lipid metabolism. Total cholesterol triglycerides, HDL, LDL and VLDL were estimated. There was significant reduction of HDL by 20%. The levels were not corelated with the duration of use and norethisterone dose, nor was it affected by obesity or smoking. The HDL level decreased with first injection and further decrease was minimal. The findings with DMPA were similar. Howard et al (1982) estimated total cholesterol, triglycerides, lipoproteins, glucose tolerance, plasma factor X, antithrobin III in 75 women receiving NET. There were 21 controls not using any steroidal contraceptives. HDL cholesterol levels were significantly lower in treated group. There was no change in any other parameters. Effect of long acting injectables on carbohyrate metaolism was evaluated by Amatayakul and Jaron (1985) from Thailand in 19 women - 10 on DMPA and 9 on NET. The carbohydrate metabolism not impaired by either of the progestogen injectables. Pyruvate cortisol concentrations did not change. Griffin et al (1988) studied the long term effect of NET-EN on carbohydrate metabolism. Plasma glucose and serum insulin levels were evaluated. The authors concluded that long term use of NET-EN was associated with decrease in insulin sensitivity, but there was no change in oral glucose tolerance.

Conclusion

Injectable NET-En is a safe and good alternative to oral pills & has no major adverse effects on the human body. However it is certainly not free from problems and the women should have the choice of accepting or discontinuing the method. The problem of irregular menstrual bleeding could be tackled by proper counselling before starting the method and at every follow-up visit. In case of prolonged and disturbing bleeding, either combined pills or a short course of estrogen can help to stop the bleeding and improve the continuation rates. The patients with amenorrhoea may continue the injections if they are reassured about not being pregnant by a simple pregnancy test. Monthly injectables though not available at present, seem to have higher possibility of acceptance.

In a workshop on improving contraceptive choices in the National Family Welfare Programme on 17th and 18th December, 1998, it was concluded that there is no single contraceptive that suits all at all times and the contraceptive choice needs to be expanded to fill the un-met contraceptive need. Injectable contraceptive could be one more available method for approrpiate patients who have been properly counselled given the choice to continuous or discontinue the method specially when she developes any problem or side effects. The method will need continues evaluation and can be introuced selectively at suitable centres where there is good clinical practice, surveillance and patient care.

Acknowledgement

We thank the Dean of K.E.M. Hospital & G. S. Medical College, Director General of Indian Council of Medical

Research, Management of Larsen & Toubro Limited and all our colleagues and social counsellors who helped us to carry out the studies.

References

1. Amatayakul K. & Suriyanon V. Int. J. Gyn. Obst. 23, 361, 1985
2. Chaudhuri Chandra, Bhowmik Tapasi Mukherjea Manju; International Journal of Fertility 32:240, 1987.
3. Cundy T, Evans M, Roberts H, Wattie D, Ames R, Reid IR: BMG 303:6798:13-6, 1991
4. Fotherby K, Howard C, Shrimanker K, Elder M, and Bye P.G. Contraception Vol: 16(No:6) 591, 1977.
5. Fotherby K., Trayner I. Howard C., Hamawi A., Elder M.G., Contraception 25:435:1982.
6. Griffin M., Heaton D.A., McEwan JA. Contraception 37:53:1988.
7. Howard G, Blair M, Trayner I, Hamawi A, Elder M.G. Lancet 1:423, 1982
8. ICMR Task Force on Hormonal Contraception. Contraception: 34:11:573, 1986.
9. ICMR Task Force on Hormaonal Contraception. Contraceptive 42:179, 1990.
10. ICMR Task Force on Hormonal Contraception. Contraception 32:383:1995.
11. Kandeel K.M., Sayed A Navel & Mohamed Salem I Abaza. Biomed, Biochim Acta 43:111; 1984.
12. Pardthousong T: Lancet, 1, 509; 1980.
13. Sapire K. E. Advances in Contraception : 7:379, 1991
14. Virutamsen P, Wangsuphachart S, Reinprayoon D, Kriengsinyot R, Leepipatpalboon S, Gua C: Asia Oceania J. Obst. & Gyn: 20: 3: 269; 1994.
15. WHO special programme of research, development and research training in human reproduction : Contraception 1983.