A COMPARATIVE CLINICAL TRIAL WITH NORETHISTERONE ENANTHATE AND DEPO-MEDROXY PROGESTERONE ACETATE

By

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SUMMARY

A comparative clinical trial of norethisterone enanthate (NET-EN, 200 mg every 2 months) and depo-medroxyprogesterone acetate (DMPA, 150 mg every 3 months) was carried out in a few Calcutta hospitals, to determine the patient acceptance of these therapy. 310 women were enrolled in the study for 4723 women-months of experience. Continuation rates at the end of 2 years were 35.5% for NET-EN and 27.5% for DMPA. Four pregnancies occurred. Both drugs disrupted normal menstrual cycle; amenorrhea being higher in case of DMPA than NET-EN, while irregular bleeding was higher for NET-EN than DMPA clients. However, higher percentage of NET-EN clients showed regular cyclic bleeding after 2 years than DMPA. Significant increase in body weight and atrophic changes in endometrium were observed in DMPA users. Both gestagens appear to be an acceptable and effective means of fertility control for women and NET-EN is better than DMPA.

Introduction

Long-acting injectable formulations of gestagens are now being increasingly used both in developed and developing countries. Depo-medroxyprogesterone acetate (DMPA, Depo-Provera, Upjohn, U.S.A.) and norethisterone enanthate (NET-EN, Norigest, Schering AG, Germany) are licensed for use in about 100 countries, (Fraser and Weisberg, 1981).

There has been increasing interest in the use of NET-EN because of the lower rate of amenorrhea associated with it, which makes it more acceptable than DMPA. However, occurrence of pregnancy is higher in case of NET-EN users, the majority occurring during third month of therapy (WHO studies, 1978). Our present investigation deals with a collaborative contraceptive study for a period of more than four years utilizing DMPA 150 mg 3 monthly and NET-EN 200 mg 2 monthly dosage schedule with a view to ascertain the acceptability of such injectable formulations amongst women of this part of India. DMPA being used from 1976-1978 and NET-EN from 1981-1983.

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Accepted for publication on 7-8-87.

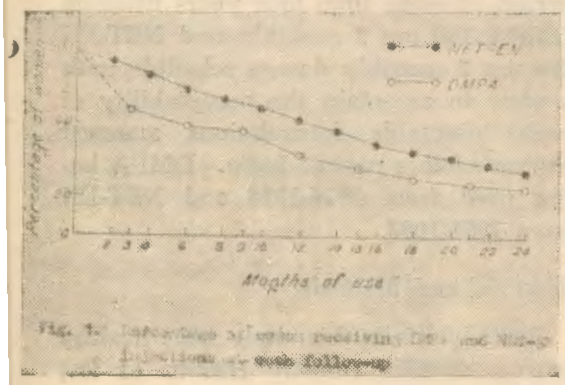
Material and Methods

Participants in this study were healthy parous women (mostly Hindus of low

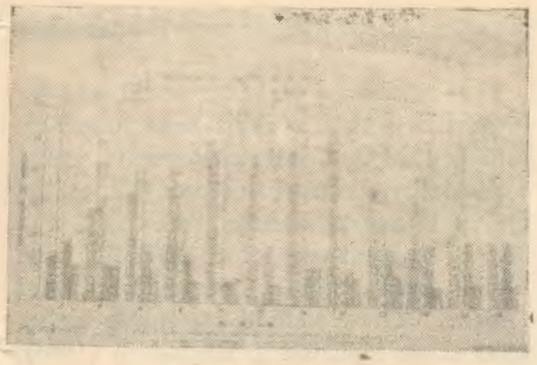
socio-economic class, age 18-35 years and parity 1-5) who visited the Family Planning Centres of two local hospitals in Calcutta for contraception and gave preference for a long-acting injectable one. A total of 310 women were enrolled and consisted of two subgroups. 138 women received DMPA 150 mg/ml at 90-day intervals for 1869 women-months while 172 women were injected with NET-EN (200 mg/ml in oil) at 60-day intervals for 2854 women-months. Women having past history of diabetes mellitus, jaundice, hypertension etc. were excluded from the study. At each follow-up visit, a thorough clinical and gynecological examination were performed. Patients were asked to record any episode of bleeding and/or spotting during each injection interval on a menstrual diary card and also to report to the clinic any side-effects. NET-EN (SH 8.0393) and DMPA (a gift from Upjohn, U.S.A.) were injected i.m. deep into the gluteal region after 5 days of the last menstrual cycle or within one week of abortion or 6 weeks after childbirth.

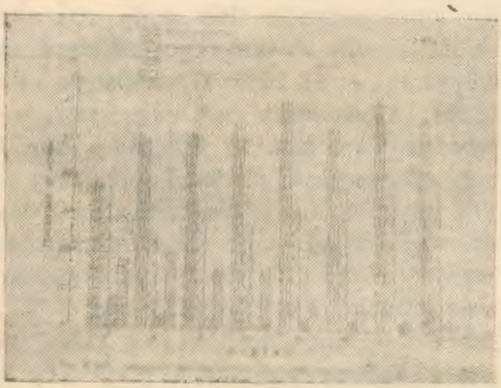
Results

The percentage of women receiving the drugs at each follow-up for 2 years is shown in Fig. 1. The percentage of patients at each follow-up visit was much higher in the case of NET-EN than DMPA.



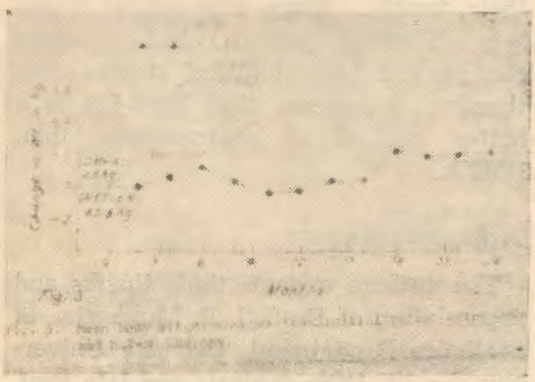
The median age of the volunteers was 25 years for both drugs. Most of the women were aged 21-30 years (77.3% for NET-EN and 74.5% for DMPA). The majority of women had 2 children (42% for DMPA, 44% for NET-EN) and the percentage of women using other methods of contraception prior to these injectables was 59% for NET-EN and 40% for DMPA. Approximately 32% of NET-EN clients and 11% of DMPA users were lactating at the time they were enrolled. Three of the NET-EN clients and one DMPA user became pregnant during the earlier part of study and were advised to discontinue. Table I lists the primary reasons for discontinuation and the incidence of side-effects resulting from both therapies. Termination of therapy due to amenorrhea, irregular bleeding and/or spotting and excessive bleeding was higher amongst DMPA users than that of NET-EN users. Headache, abdominal pain and giddiness occurred more often in NET-EN users than in DMPA users but no patient discontinued for these causes. Life-table analysis of dropouts in case of NET-EN therapy is given in Table II. The menstrual flow was irregular and unpredictable for the majority of women using these drugs. Figures 2 (a) and 2 (b) illustrate graphically the menstrual bleeding patterns after NET-EN and DMPA therapy, respectively. For both drugs, disruption of the menstrual cycle was observed in most cases which turned to amenorrhea with long-term use. However, the percentage of amenorrhea was higher amongst DMPA clients than in NET-EN subjects, while the percentage of women experiencing bleeding for 1-7 days, was





much higher (53%) after 2 years amongst NET-EN users than in DMPA subjects (40%).

Figure 3 shows a plot of mean body weight changes from initial values for both drugs. DMPA patients gained weight significantly, 6.5 kg. after 2 years



($p < 0.001$), while no significant changes in body weight were observed with NET-EN clients. The mean systolic blood pressure was initially 105.5 ± 1.14 mm of Hg for DMPA and 107.9 ± 0.9 mm for NET-EN, while the diastolic blood pressure was 70.0 ± 1.2 mm and 72.2 ± 0.7 mm Hg for DMPA and NET-EN, respectively. Both therapies did not alter the blood pressure after long-term use. The blood picture, e.g. total and differential count and hemoglobin (Hb) was evaluated in NET-EN clients for one year. The Hb level was 9.4 ± 0.09 gm% initially and 13.1 ± 0.2 gm% at the end of one year. The RBC count also increased significantly ($P < 0.001$) from initial value of $(423 \pm 0.9) \times 10^4$ to $(440 \pm 0.1) \times 10^4$ after 12 months (Chaudhuri *et al* 1985).

Discussion

Past studies with injectable contraceptives have indicated that the most common side-effect and the most frequent reason for discontinuation of such formulations are the disruption in normal menstrual cyclicity (WHO studies, 1982). NET-EN has been reported to cause less distruption than DMPA (WHO studies, 1978). Earlier reports from this laboratory (Mukherjea, 1981) confirmed that DMPA therapy has been associated with a high proportion of women experiencing amenorrhea. The findings in this study partly concur with the results of these previous studies (Swenson *et al* 1980; Kesseru *et al* 1973) that NET-EN users did experience less amenorrhea than DMPA users (Figs. 2a and 2b) and a higher percentage of NET-EN clients showed regular cyclic bleeding after long-term use of 2 years than DMPA users. Furthermore, the proportion of women

experiencing amenorrhea by the end of the first years among both the DMPA and NET-EN users was higher (62% and 46%, respectively) than that reported in other studies (Howard *et al* 1985; WHO studies, 1978). The occurrence of heavy vaginal bleeding requiring estrogen replacement therapy was rarely necessary in NET-EN uers.

The endometrial biopsy studies at various injection intervals reflected that the endometrial tissues were proliferative in the first few months of both NET-EN and DMPA use and during the course of therapy at 6-12 months the biopsies showed the overall tendencies to turn from proliferative to quiescent type. This view was in accord with earlier studies with DMPA (Jeppsson *et al* 1977) and NET-EN (Achari, 1969). With long-term use extreme atrophy in the endometrium were observed only in DMPA users.

Increase in body weight after DMPA therapy has been observed by previous workers (Schwallie and Assenzo, 1973; Fajumi, 1983) and our present study also showed a significant increase in body weight after DMPA therapy, even though little changes occurred in body weight amongst NET-EN clients. This is in conformity with the findings of Dhall *et al* (1977) although there has been reports of increase in body weight after NET-EN therapy (WHO studies, 1982; Howard *et al* 1982). No correlation between bleeding pattern and body weights could be obtained in our study with both drugs. Moreover, little or no change in blood pressure was observed for both injectables, while minor changes in these parameters have been record previously (Howard *et al* 1982). Actually none of the clients had hypertension before the therapy and sporadic elevations of blood pressure above 130/80 mm Hg was uncommon.

The return of fertility could not be judged due to the short-term follow-up in this study. Continuation rates, using a life-table technique of analysis, at the end of 12 and 24 months were 61.6% and 35.5%, respectively, for NET-EN and 43.4% and 27.5%, respectively, for DMPA. These values are much higher than those reported in Bagladesh (1980). The proportion of women discontinuing for amenorrhea in this study was more or less similar to that reported elsewhere (Swenson *et al* 1980; Giwa-Osagie et al 1978). However, a certain percentage of women were lost to follow-up due to non-adherence to protocol since they did not return to the clinic even after 8 days of a scheduled visit. The failure rates were 0.87 and 0.36 per 100 women-years, respectively, for NET-EN and DMPA. MacDaniel and Pardthaisong (1974) reported failure rate of 0.90 pregnancy for DMPA, while Howard *et al* (1985) observed pregnancy rates ranging from 010.7 per 100 women year for NET-EN.

This study reinforces our previous studies (Mukherjea, 1981; Chaudhuri and Mukherjea, 1984) that DMPA and NET-EN appear to be safe and acceptable methods of contraception for women, particularly to those who have completed their family. From endometrial histology, bleeding pattern, body weight changes and haematological studies after therapy, it appears that NET-EN is a better method of contraception than DMPA.

Acknowledgements

The authors express their thanks and appreciation of Prof. S. P. Mukherjee of Statistics Department, Calcutta University, for life-table analysis and late Prof.

Sreemanta Banerjee and Dr. S. P. Banerjee of R. G. Kar Medical College and Hospital, Calcutta, for clinical assistance. This work was supported by research grants from the Indian Council of Medical Research, New Delhi, and the W.B. State Planning Board, Calcutta.

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