Multinational comparative clinical trial of long-acting injectable contraceptives: norethisterone enanthate given in two dosage regimens and depot-medroxyprogesterone acetate. A preliminary report.*

WHO SPECIAL PROGRAMME OF RESEARCH, DEVELOPMENT AND RESEARCH TRAINING IN HUMAN REPRODUCTION

Task Force on Long-Acting Agents for the Regulation of Fertility

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*This investigation received financial support from the Special Programme of Research, Development and Research Training in Human Reproduction, World Health Organization

Submitted for publication October 22, 1981

Accepted for publication December 14, 1981

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ABSTRACT

A multicentre phase III clinical trial has been undertaken to compare norethisterone enantate (NET-EN) given by two different treatment regimens and depot-medroxyprogesterone acetate (DMPA). After 18 months of observation, preliminary findings are reported for 1,589 women who received DMPA 150mg every 90 days; 790 women who received NET-EN 200mg every 60 days; and 796 women who received NET-EN, 200mg every 60 days for 6 months, then 200mg every 84 days.

The overall discontinuation rates per 100 women were similar for all three treatment groups over the 18 months observation (61.8 - 63.5 per 100 women). The discontinuation rates for bleeding problems and for personal reasons were also similar for all three treatment groups. However, terminations due to amenorrhoea were significantly higher among DMPA users (12.1 and 17.4 per 100 women at 12 and 18 months) as compared with both NET-EN groups (6.8 - 8.2 per 100 women at 12 months and 10.4 - 10.9 per 100 women at 18 months).

The only significant difference in pregnancy rates observed between the three groups was a higher rate at 18 months among NET-EN (84 days) users (1.6 per 100 women), as compared with DMPA users (0.2 per 100 women). There was no overall significant difference between the two NET-EN groups, although between the 6 and 18 month's follow-up when the two NET-EN regimens diverged, the NET-EN (84 days) users' pregnancy rate rose significantly, wherease in the NET-EN (60 days) group the pregnancy rate did not change. There was a significantly higher weight gain in those subjects using NET-EN at 60-day intervals compared with those using it at 84-day intervals.

1. Introduction

Two long-acting progestogen injectable contraceptives, depot-medroxyprogesterone acetate (DMPA or Depo-Provera) and norethisterone enantate (NET-EN or Norigest), have been in widespread use in industrialized and non-industrialized countries(1). The WHO Special Programme of Research, Development and Research Training in Human Reproduction conducted a randomized comparative multicentred trial of 150 mg of DMPA and 200 mg of NET-EN administered at 3-monthly intervals(2). The three-month regimen of NET-EN was associated with a twelve-month life-table pregnancy rate of 3.6 per 100 women-years which exceeded a predetermined criteria for the termination of the study. The majority of pregnancies occurred during the third month after injection, and this observation in conjunction with pharmacological data suggested that the contraceptive effect of NET-EN lasts for less than three months after initiation of treatment (2,3). The WHO clinical trial also showed that DMPA caused substantially more amenorrhoea than NET-EN, and after one year the termination rates due to amenorrhoea were 11.5 per hundred women-years with DMPA compared to 1.8 per hundred women-years with NET-EN (2,4).

There has been increasing interest in the use of NET-EN because the lower prevalence of amenorrhoea associated with this drug may make it more acceptable than DMPA in many populations. NET-EN is marketed for contraceptive use in 40 countries and is undergoing field trials in several others(1,5). However, there are insufficient data available from large-scale studies with which to determine the optimal dosage schedule for NET-EN so that pregnancy rates can be reduced to a more satisfactory level(6,7).

To provide information on alternative NET-EN regimes, the WHO Special Programme of Research, Development and Research Training in Human Reproduction initiated in 1976 a multinational comparative trial of NET-EN administered at 60-day intervals, and NET-EN given at 60-day intervals for 6 months and then 84-day (twelve week) intervals thereafter. DMPA administered at 90-day intervals was used as a reference standard. The intervals between injections were based upon recommendations of the manufacturers. A final report of this ongoing trial will be published when all subjects have completed two years of observation. However, in the interim, it was considered important to report upon the preliminary results of this study up to 18 months of observation so as to assist physicians and Ministries of Health in deciding upon the most appropriate long-acting contraceptive and the most suitable treatment schedule for clinical use.

Patients and methods

The 13 centres shown in Table I collaborated in the comparative trial. Women who chose to use injectable contraception were informed of the nature of the drugs and of the study. Non-breastfeeding women who volunteered to enter the trial had a medical history and examination, including cervical cytology, to exclude contra-indications to long-acting injectable contraceptives. Subjects were then randomly allocated to either DMPA or NET-EN and the injection was given within the first 5 days of the menstrual cycle.

Women were followed-up for re-injection using the following schedule. All NET-EN users were seen at 60 ±5-day intervals for six months (three injections) and then randomly allocated to either a continuing 60 ± 5-day schedule or to an 84 ±5-day (12-week) injection interval. These two regimens of treatment will be referred to as NET-EN (60 days) and NET-EN (84 days), respectively. DMPA users were seen every 90 ± 5 days.

At each follow-up contact, a medical history was taken and a physical examination performed, and information on vaginal bleeding patterns was obtained from a menstrual diary card kept by the subject herself. The present interim report focuses on discontinuations due to pregnancy, amenorrhoea, bleeding problems and personal reasons. Women who failed to return for a scheduled injection visit were discontinued from the study. Follow-up was attempted to ascertain the reasons for their failure to return and to provide alternative methods of contraception.

The data processing was conducted by WHO in Geneva. Cumulative non-competing risk, multiple decrement life-table discontinuation rates were calculated using the Chiang method(8), and tests of statistical significance between life-table rates are based on a Chi-square with one degree of freedom(9). The cut-off date for the present analysis was 25 March 1981.

Results

Table I shows the number of women admitted and the duration of observation for each centre. More than 90% of the total women-months of observation were derived from the 9 developing country centres, and although Ljubljana admitted a substantial number of subjects, the other 3 European centres (Luxemburg, Milan and Utrecht) recruited very few women. On admission, there were no differences between women allocated to the three treatment groups with respect to age, parity, interval since last pregnancy, body weight and height.

TABLE I. Number of women recruited and duration of observation

Center	DMPA		NET-EN (60-days)		NET-EN (84-days)	
	No.	Woman-months	No.	Woman-months	No.	Woman-months
Alexandria (Egypt)	194	2836	99	1378	98	1472
Bangkok (Thailand)	113	1512	57	701	57	612
Ibadan (Nigeria)	168	2625	84	1226	86	1276
Karachi (Pakistan)	195	1968	97	1232	99	1078
Ljubljana (Yugoslavia)	130	1139	63	672	65	686
Lusaka (Zambia)	73	688	36	383	35	320
Luxemburg	48	385	22	119	24	193
Manila (Philippines)	198	2806	100	1397	100	1546
Mexico City (Mexico)	161	1914	81	940	80	929
Milan (Italy)	20	190	7	84	9	92
Salvador Bahia (Brazil)	200	2698	99	1450	100	1359
Santiago (Chile)	77	845	38	447	38	440
Utrecht (Holland)	12	124	7	50	5	32
Total	1,589	19,730	790	10,079	796	10,035

Table II shows the cumulative life-table discontinuation rates for pregnancy, amenorrhoea, bleeding problems and personal reasons, and the total discontinuation rate for all reasons combined. The pregnancy rate with the NET-EN (84-day) regimen is significantly higher than with DMPA after 18 months' observation ($X^2 = 4.26, P < 0.05$), but there were no other significant differences between pregnancy rates for the three treatment groups. All the accidental pregnancies with the NET-EN (60-day) regimen and with DMPA occurred during the first six months of use, whereas the pregnancy rate continued to rise with the NET-EN (84-day) treatment schedule. The increase in the pregnancy rate for the NET-EN (84-day) group over the one year period between six and eighteen months of use was 1.3 per hundred women-years, which is statistically significant ($X^2 = 4.23, P < 0.05$).

Terminations because of amenorrhoea were significantly higher among DMPA users compared to both NET-EN groups at 12 and 18 months of observation. The discontinuation rates for bleeding problems were comparable in all three treatment groups, and there were no significant differences in terminations for personal reasons. Also, there was no particular change in the termination rate for personal reasons after six months associated with the transition from a 60- to 84-day injection schedule with the NET-EN (84-day) regimen. The total termination rates for all reasons were similar in the three treatments at all durations of observation.

Losses to follow-up as a percentage of admissions were 11.5%, 10.2% and 10.5% after 18 months, for the DMPA, NET-EN (60-day) and NET-EN (84-day) regimens, respectively.

As shown in Table III, there was a slight decline in blood pressure over the 18-month period, but no clinically important differences were observed between treatment groups. There was a moderate rise in mean body weight with all three treatments over the 18 months, and women receiving the NET-EN (84-day) regimen had a significantly smaller increase in weight compared to the NET-EN (60-day) regimen ($t = 5.4$, $P < 0.001$) or the DMPA group ($t = 2.04$, $P < 0.05$).

Discussion

The interim results of the present study show that NET-EN given at 60-day intervals for the first six months of use avoids the excessive pregnancies previously observed with a three-monthly injection interval(2). Even the upper 95% confidence limit for the 18-month cumulative pregnancy rate for NET-EN (84-days) regimen in the present study (2.8 per 100 women years) is

TABLE II. Cumulative life-table discontinuation rates and standard errors

Months of use	Pregnancy			Amenorrhea			Bleeding problems			Other medical reasons		
	DMPA	NET-EN (60-day)	NET-EN (84-day)	DMPA	NET-EN (60-day)	NET-EN (84-day)	DMPA	NET-EN (60-day)	NET-EN (84-day)	DMPA	NET-EN (60-day)	NET-EN (84-day)
6	0.2 ±0.1	0.6 ±0.3	0.3 ±0.2	4.5 ±0.6	2.0** ±0.5	3.7 ±0.7	9.2 ±0.8	8.0 ±1.1	7.1 ±1.0	4.4 (±0.6)	4.3 (±0.8)	5.5 (±0.9)
12	0.2 ±0.1	0.6 ±0.3	0.7 ±0.4	12.0 ±1.0	6.8** ±1.1	8.2* ±1.2	15.1 ±1.0	13.6 ±1.4	13.4 ±1.4	8.9 (±0.9)	9.3 (±1.2)	9.7 (±1.2)
18	0.2 ±0.1	0.6 ±0.3	1.6* ±0.6	17.4 ±1.3	10.9** ±1.5	10.4** ±1.4	16.8 ±1.1	16.7 ±1.6	16.8 ±1.6	11.8 (±1.1)	13.6 (±1.6)	12.4 (±1.4)

Months of use	Discontinuation for personal reasons			Total discontinuations			Lost to follow-up			Number commencing the interval		
	DMPA	NET-EN (60-day)	NET-EN (84-day)	DMPA	NET-EN (60-day)	NET-EN (84-day)	DMPA	NET-EN (60-day)	NET-EN (84-day)	DMPA	NET-EN (60-day)	NET-EN (84-day)
6	10.9 ±0.9	12.2 ±1.2	10.8 ±1.2	32.2 ±1.2	31.1 ±1.7	29.9 ±1.6	8.0 (±0.7)	8.6 (±1.1)	6.9 (±6.9)	1589	790	796
12	18.9 ±1.1	21.9 ±1.7	21.5 ±1.7	51.7 ±1.3	49.8 ±1.8	50.1 ±1.8	12.3 (±0.9)	11.4 (±1.3)	10.4 (±1.2)	1070	541	555
18	28.2 ±1.4	31.0 ±2.0	31.4 ±2.0	63.5 ±1.2	61.9 +1.7	62.5 ±1.7	15.9 (±1.1)	13.6 (±1.5)	14.9 (±1.6)	743	385	388

significant difference relative to DMPA *P<0.05 **P<0.01

TABLE III. Change in blood pressure and body weight over 18 months (mean + SE)

	DMPA	NET-EN (60 day)	NET-EN (84 day)
Mean change in systolic blood pressure (mm Hg)	-1.84 (±0.51)	-2.1 (±0.73)	-1.6 (±1.06)
Mean change in diastolic blood pressure (mm Hg)	-0.42 (±0.29)	-1.85 (±0.47)	-1.04 (±0.57)
Mean change in body weight (kg)	3.1* (±0.09)	3.6** (±0.10)	2.0 (±0.19)
Number of women completing 18 months observation	520	273	296

significant difference relative to NET-EN (84 days)
* $P < 0.05$ ** $P < 0.001$

substantially lower than the one year pregnancy rate of 3.6 per 100 women-years reported with the previous 3-month regimen[2]. Giwa-Osagie et al.(6) reported no pregnancies with a NET-EN treatment schedule similar to the NET-EN (84-day) treatment employed here. However, this failure to observe any conceptions was probably a chance finding, since these investigators only studied 295 women for 1606 women-months of observation, compared to the present 796 women studied for 10,035 months.

The 18-month cumulative pregnancy rate (1.6 per 100 women-years) observed with the NET-EN (84-day) treatment was significantly higher than that observed with DMPA, but not significantly different from the rate of 0.6 per 100 women-years observed with the NET-EN (60-day) regimen. However, all the conceptions with the latter treatment schedule occurred during the first six months, whereas with the NET-EN (84-day) regimen, accidental pregnancies continued to occur throughout the period of observation, and the pregnancy rate rose significantly between 6 to 18 months of treatment. This would suggest that an 84-day injection interval is associated with a somewhat higher risk of pregnancy than the 60-day interval, and the difference in pregnancy rates between the two treatment regimens is likely to be around 1 per 100 women-years after 18 months of use.

As was observed in the previous WHO trial, NET-EN is associated with a lower termination rate for amenorrhoea than DMPA(2). However, it is noteworthy that the discontinuation rates for amenorrhoea with both NET-EN regimens employed here, are substantially higher than the amenorrhoea discontinuation rates with the 3-monthly NET-EN regimen employed in the previous study. The one year termination rates for amenorrhoea in the present study were 6.8 and 8.2 per 100 women-years for NET-EN 60 and 84 days, respectively, compared to the previously reported 1.8 per 100 women-years for NET-EN given at 3 monthly intervals. In contrast, the termination rate for amenorrhoea with DMPA was 12.1 per 100 women-years in the present study as compared to 11.8 per 100 women-years in the previous investigation(2). This suggests that the shorter 60-day NET-EN injection interval given either for 6 months or continuously, is associated with more amenorrhoea than the 3-monthly injection interval, and this might reduce the differential advantage of NET-EN relative to DMPA.

The discontinuations for personal reasons were comparable with both NET-EN regimens and DMPA throughout the study. This suggests that a 60-day as compared to an 84- or 90-day injection interval is acceptable to the women, and that the change from a 60-day to 84-day schedule with NET-EN (84 days) after six months did not cause excess terminations.

The overall discontinuation rates in the present study (Table II) are much higher than the previous trial in which the twelve-month termination rates were 24.4 and 28.8 per 100 women for NET-EN and DMPA, respectively. This probably reflects differences in the centres and populations, and in the attitudes of the patients or their physicians towards the acceptability of injectable contraceptives.

Women gained weight with all three treatments, although women receiving DMPA and NET-EN (60 days) gained significantly more weight than those subjects receiving the NET-EN (84 days) regimen. In the previous study, women receiving DMPA gained more weight than women receiving NET-EN at three monthly intervals, but the differences were not statistically significant(4).

In conclusion, if NET-EN is given at 60-day intervals for the first six months, there is a substantial decrease in the risk of pregnancy compared to the previous 3-month regimen, but the differences between the continuing 60-day regimen or switching to an 84-day injection interval are relatively small (0.6 to 1.6). Thus, health authorities must decide whether the slightly higher risk of pregnancy associated with the NET-EN (84-day) schedule outweigh the logistical disadvantages, additional cost and higher drug load associated with a continuing NET-EN (60-day) regimen. However, both modalities provide contraception with slightly greater effectiveness and similar acceptability in comparison with combined oral preparations tested by the World Health Organization(10).

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