MULTINATIONAL COMPARATIVE CLINICAL TRIAL OF LONG-ACTING INJECTABLE CONTRACEPTIVES: NORETHISTERONE ENANTHATE GIVEN IN TWO DOSAGE REGIMENS AND DEPOT-MEDROXYPROGESTERONE ACETATE. FINAL REPORT.*

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

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

H.K. Toppozada: Department of Obstetrics and Gynaecology, Shatby Maternity Hospital, Alexandria University, Alexandria, Egypt

S. Koetsawang: Family Planning Research Unit, Siriraj Hospital, Mahidol University, Bangkok, Thailand

V.E. Aimakhu: Department of Obstetrics and Gynaecology, University of Ibadan, Ibadan, Nigeria

T. Khan: National Research Institute of Fertility Control, Karachi, Pakistan

A. Pretnar-Darovec: Family Planning Institute, University Clinical Hospital, Ljubljana, Yugoslavia

T.K. Chatterjee: Department of Obstetrics and Gynaecology, School of Medicine, University of Zambia, Lusaka, Zambia

M.-P. Molitor-Peffer: Mouvement luxembourgeois pour le planning familial, Luxembourg

R. Apelo: Reproductive Biology Centre, Department of Obstetrics and Gynaecology, College of Medicine, University of the Philippines, Manila, The Philippines

R. Lichtenberg: Department of Reproduction Biology, National Institute of Nutrition, Mexico City, Mexico

P.G. Crosignani: Department of Obstetrics and Gynaecology, Università degli Studi di Milano, Milan, Italy

J.C. de Souza: Maternidade Climerio Oliveira, Faculdade de Medicina, Universidade Federal de Bahia, Salvador de Bahia, Brazil

M. Garcia Huidubro: Department of Obstetrics and Gynaecology, University of Chile, Hospital J.J. Aguirre, Santiago, Chile

A.A. Haspels: Department of Obstetrics and Gynaecology, University of Utrecht, Utrecht, The Netherlands

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CONTRACEPTION

J. Annus*, G. Benagiano**, P. Diethelm, R. Gray***, P.E. Hall, S.E. Holck,
Special Programme of Research in
Human Reproduction,
World Health Organization,
Geneva, Switzerland

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* Department of Obstetrics and Gynaecology, University Medical School of Szeged, Szeged, Hungary

** Cattedra di Endocrinologia Ginecologia dell'Università di Roma, Policlinico Umberto 1°, Rome, Italy

*** Department of Population Dynamics, Johns Hopkins University, School of Hygiene and Public Health, 615 North Wolfe Street, Baltimore, Maryland 21205, U.S.A.

Requests for reprints: P. E. Hall,
Special Programme of Research, Development and
Research Training in Human Reproduction
World Health Organization
1211 Geneva 27, Switzerland

ABSTRACT

Final results are presented from a two-year WHO multinational comparative trial of three regimens: depot-medroxyprogesterone acetate (DMPA) given at 90-day intervals, norethisterone enantate (NET-EN) given at 60-day intervals for the entire study period (NET-EN (60-day)), and NET-EN given at 60-day intervals for six months and thereafter at 84-day intervals (NET-EN (84-day)). 1587 DMPA subjects were observed for 20,550 woman-months, 789 NET-EN (60-day) subjects were observed for 10,361 woman-months, and 796 NET-EN (84-day) subjects were observed for 10,331 woman-months. This clinical trial represents the largest clinical trial undertaken on injectable contraceptives.

After two years, the pregnancy rate with NET-EN (84-day) was 1.4 (±0.6 S.E.) per 100 women, as compared with the two-year rates of 0.4 (±0.3 S.E.) per 100 women observed with DMPA and 0.4 (± 0.2 S.E.) with NET-EN (60-day). Both discontinuation rates for amenorrhea and the prevalence of amenorrhea lasting more than 90 days were significantly higher with DMPA than with either NET-EN regimen. Terminations for bleeding problems were similar with the three treatments, despite a better cyclic pattern for the first six months with the NET-EN regimens. The three treatments were comparable with respect to discontinuation rates for other medical or personal reasons, and for all reasons combined.

For family planning programs, NET-EN (60-day) has the advantage of low pregnancy rates compared to NET-EN (84-day), and a schedule of administration that does not change. Both NET-EN regimens produce less amenorrhea than DMPA. However, the NET-EN (60-day) regimen has the logistic and economic disadvantage of requiring more frequent injections. All three injectable regimens compare favourably with oral contraceptives in terms of pregnancy and total continuation rates observed in clinical trial settings.

INTRODUCTION

The WHO Special Programme of Research, Development and Research Training in Human Reproduction conducted a multicentred Phase III trial of three injectable contraceptive regimens: depot-medroxyprogesterone acetate (DMPA) 150 mg given at 90-day intervals, norethisterone enantate (NET-EN) 200 mg

given at 60-day intervals, and norethisterone enanthate given at 60-day intervals for six months, then 84-day intervals thereafter. In a previous publication (1), preliminary results of use-effectiveness, blood pressure and body weight changes up to 18 months of observation were reported. The present paper describes the completed two-year study, the largest single clinical trial of injectable contraceptives to date, and provides more detailed information on inter-centre differences in continuation rates.

PATIENTS AND METHODS

Recruitment to the trial began in 1977 and the final two-year follow-up was completed in March 1982. Thirteen centres listed in Table I participated in the trial, nine from developing countries and four from developed countries. The objective was to recruit 200 subjects on each drug in each centre. However, because of slow recruitment in centres 2, 3, 5, 7 and 10, late entry into the trial in centres 11 and 12, and premature closure of the trial due to the absence of the local investigator (centre 9), these targets could not be attained. With the exception of centres 9, 11 and 12, the data reflect two full years of observation following enrolment, for more than 99% of women.

Non-breastfeeding women who chose to use injectable contraception were informed of the nature of the drugs and of the study. On entry into the trial, the volunteers had a medical history taken and were examined, 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 five days of the menstrual cycle.

Women returned for re-injection according to the following schedule. All NET-EN users came for injection at 60 $\pm$ 5-day intervals for six months (three injection intervals) and were then randomly allocated to either a continuing 60 $\pm$ 5-day schedule or to an 84 $\pm$ 5-day (12-week) injection interval schedule. These two regimens of treatment will be referred to as NET-EN (60-day) and NET-EN (84-day), respectively. DMPA users returned for injection every 90 $\pm$ 5 days. At each injection, the DMPA treatment group received 150mg of Depo-Provera, manufactured by Upjohn, and the NET-EN groups received 200mg of Norigest, manufactured by Schering AG.

TABLE I. NUMBER OF SUBJECTS ADMITTED AND WOMAN-MONTHS OF OBSERVATION FOR EACH CENTRE

CENTRE AND COUNTRY	TREATMENT GROUP					
	DMPA		NET-EN (60 days)		NET-EN (84 days)	
	No.	Woman-Months	No.	Woman-Months	No.	Woman-Months
1. ALEXANDRIA (EGYPT)	194	2850	98	1385	98	1474
2. BANGKOK (THAILAND)	113	1638	57	748	57	674
3. IBADAN (NIGERIA)	168	2698	84	1249	86	1311
4. KARACHI (PAKISTAN)	195	1976	97	1238	99	1081
5. LUSAKA (ZAMBIA)	72	689	36	385	35	320
6. MANILA (PHILIPPINES)	197	2811	100	1402	100	1549
7. MEXICO CITY (MEXICO)	161	1947	81	957	80	942
8. SALVADOR (BRAZIL)	200	2711	99	1452	100	1361
9. SANTIAGO (CHILE)	77	847	38	448	38	441
10. LJUBLJANA (YUGOSLAVIA)	130	1198	63	710	65	743
11. LUXEMBOURG	48	775	22	246	24	296
12. MILAN (ITALY)	20	286	7	91	9	107
13. UTRECHT (NETHERLANDS)	12	124	7	50	5	32
DEVELOPING COUNTRIES[a]	1377	18,167	690	9,264	693	9,153
DEVELOPED COUNTRIES[b]	210	2,383	99	1,097	103	1,178
TOTAL	1587	20,550	789	10,361	796	10,331

a) Centres 1-9

b) Centres 10-13

At each follow-up visit, complaints elicited spontaneously were recorded, 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. These procedures have been described previously (2). Women who failed to return for a scheduled injection visit were considered to have discontinued from the study, and follow-up was attempted to ascertain the reasons for the failure to return and/or to provide alternative methods of contraception. Detailed reasons for discontinuation were recorded, but for simplicity of presentation in the life-table analysis, these have been aggregated into five major categories of pregnancy, amenorrhea, bleeding problems, other medical reasons and personal reasons. All reasons given for discontinuation were examined, however, to assess whether there was any evidence of serious illness which might be attributable to an adverse effect of the drugs.

Data processing was carried out by WHO in Geneva. Cumulative non-competing risk, multiple decrement life-table discontinuation rates were calculated using the Chiang method (3), and tests of statistical significance between life-table rates are based on a chi-square with one degree of freedom (4).

The analysis of vaginal bleeding patterns used a series of program packages developed for the Special Programme of Research in Human Reproduction by the WHO Information Systems Support Division. These programmes provide both counts of events and life-table procedures to estimate the duration of events. Technical details of the methodology will be published. The summary statistics used in the present report consist of a plot of the daily frequency of bleeding and spotting relative to the timing of each injection, the duration of episodes of bleeding and spotting, and the frequency of amenorrhea. Amenorrhea was defined as an interval of more than 90 days duration between episodes of bleeding or spotting. Results are expressed, where appropriate, as $\pm$ the standard error.

RESULTS

STUDY POPULATIONS

The number of subjects admitted and woman-months of observation for each centre are shown in Table I. Eighty-seven per cent of subjects came from the 9 developing country centres. There were no significant differences between the treatment groups with respect to age, parity, interval since last birth or body weight on admission. For the whole study population, the mean age was 27.4 ± 5.2 years, mean parity 3.3, mean interval since last birth 4.4 ± 1.7 months and mean body weight 55.5 ± 12.1 kg.

USE-EFFECTIVENESS

A total of 12 pregnancies were reported during the study period, one half of which occurred during the first six months of treatment. Three of the pregnancies occurred in the DMPA group, 3 in the NET-EN (60-day) group, and 6 in the NET-EN (84-day) group. Table II shows the cumulative life-table accidental pregnancy rates for each of the three treatment groups. At 12, 18 and 24 months, the highest cumulative pregnancy rate was in the NET-EN (84-day) group, although the higher rate was statistically significant only at 18 months and only as compared with DMPA. At 24 months, the pregnancy rate was 0.4 per 100 women for both the DMPA and NET-EN (60-day) groups, and 1.4 for the NET-EN (84-day) group.

REASONS FOR DISCONTINUATION

The discontinuation rates for amenorrhea with DMPA were significantly greater than with the two NET-EN regimens from 12 to 24 months of study. There were no significant differences between treatment groups with respect to discontinuation for bleeding problems, other medical reasons, personal reasons or termination rates for all reasons combined. Losses to follow-up as a percentage of admissions were similar in the three treatment groups.

Table III summarizes the total cumulative discontinuation rates for each centre after one and two years of observation. There is considerable variation between centres, and within some centres there are significant differences in discontinuation rates between drugs. The centres with lowest

TABLE II. CUMULATIVE LIFE-TABLE NET DISCONTINUATION RATES AND STANDARD ERRORS, NUMBER OF SUBJECTS AND LOSS TO FOLLOW-UP

DURATION OF USE (MONTHS)	ACCIDENTAL PREGNANCY			AMENORRHOEA			BLEEDING PROBLEMS			DISCONTINUATION FOR 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	0.1 (±0.1)	0.4 (±0.2)	0.2 (±0.2)	4.5 (±0.6)	2.0** (±0.6)	3.7 (±0.7)	9.2 (±0.8)	8.0 (±1.1)	7.1 (±1.0)	4.3 (±0.6)	4.3 (±0.8)	5.6 (±0.9)
12	0.1 (±0.1)	0.4 (±0.2)	0.6 (±0.3)	11.9 (±1.0)	6.8** (±1.1)	8.4* (±1.2)	15.0 (±1.0)	13.6 (±1.4)	13.7 (±1.4)	8.7 (±0.9)	9.3 (±1.2)	9.9 (±1.2)
18	0.1 (±0.1)	0.4 (±0.2)	1.4* (±0.6)	17.5 (±1.2)	10.7** (±1.5)	10.5** (±1.4)	16.8 (±1.1)	16.8 (±1.6)	16.7 (±1.6)	11.8 (±1.0)	13.7 (±1.6)	12.7 (±1.5)
24	0.4 (±0.3)	0.4 (±0.2)	1.4 (±0.6)	24.2 (±1.5)	14.7** (±1.9)	14.6** (±2.0)	18.8 (±1.2)	18.4 (±1.7)	21.8 (±2.2)	15.8 (±1.3)	16.0 (±1.8)	16.7 (±2.0)

DURATION OF USE (MONTHS)	DISCONTINUATION FOR PERSONAL REASONS			TOTAL DISCONTINUATIONS			NUMBER COMMENCING INTERVAL			LOSS TO FOLLOW-UP (PER CENT OF ADMISSIONS)		
	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	12.4 (±0.9)	14.2 (±1.3)	11.7 (±1.2)	32.1 (±1.2)	31.0 (±1.7)	29.9 (±1.6)	1587	789	796	5.7	5.8	5.3
12	20.7 (±1.2)	24.5 (±1.7)	22.8 (±1.7)	51.4 (±1.3)	49.7 (±1.8)	50.3 (±1.8)	1075	543	556	8.1	7.1	7.4
18	30.4 (±1.4)	33.6 (±2.0)	34.1 (±2.0)	63.4 (±1.2)	62.2 (±1.7)	63.0 (±1.7)	762	392	390	9.5	8.2	8.9
24	38.8 (±1.6)	42.6 (±2.2)	40.2 (±2.3)	73.5 (±1.1)	70.7 (±1.7)	72.4 (±1.7)	574	290	285	10.7	8.9	9.8

Significant difference relative to DMPA, *$P < 0.05$, **$P < 0.01$

TABLE III. CENTRE-SPECIFIC CUMULATIVE TOTAL DISCONTINUATION RATES PER 100 WOMEN AND STANDARD ERRORS AFTER ONE AND TWO YEARS OBSERVATION

CENTRE	DMPA		NET-EN (60-DAY)		NET-EN (84-DAY)	
	12 months	24 months	12 months	24 months	12 months	24 months
Alexandria	45.4 (±3.6)	60.7 (±3.5)	48.0 (±5.0)	62.3 (±4.9)	39.8 (±4.9)	58.8 (±5.3)
Bangkok	41.6 (±4.6)	68.3 (±4.4)	49.1 (±6.6)	75.7 (±5.7)	56.1 (±6.6)	81.5 (±5.7)
Ibadan	35.1 (±3.7)	61.6 (±3.8)	41.7 (±5.4)	70.6 (±5.0)	33.7 (±5.1)	66.0 (±5.5)
Karachi	64.6 (±3.4)	91.3 (±2.0)	53.6 (±5.1)	76.3** (±4.3)	64.7 (±4.8)	91.8++ (±3.0)
Lusaka	75.0 (±5.1)	91.7 (±3.3)	61.1 (±8.1)	83.3 (±6.2)	71.4 (±7.6)	95.7 (±3.7)
Manila	42.1 (±3.5)	69.4 (±3.4)	47.0 (±5.0)	66.8 (±4.8)	37.0 (±4.8)	56.0* (±5.1)
Mexico City	53.4 (±3.9)	79.3 (±3.2)	53.1 (±5.5)	75.4 (±4.8)	56.3 (±5.6)	85.1 (±4.4)
Salvador Bahia	52.5 (±3.5)	69.1 (±3.3)	43.4 (±5.0)	59.6 (±4.9)	48.0 (±5.0)	60.0 (±5.1)
Santiago	49.6 (±5.9)	85.0 (±5.5)	36.1 (±8.1)	56.2* (±10.5)	43.3 (±8.6)	58.6* (±10.0)
Ljubljana	73.1 (±3.9)	87.9 (±2.9)	60.3 (±6.2)	81.1+ (±5.0)	63.1 (±6.0)	75.4* (±5.3)
Luxemburg	33.3 (±6.8)	49.5 (±7.5)	63.6* (±10.3)	82.3** (±9.5)	62.5* (±9.9)	74.1* (±9.8)
Milan	50.0 (±11.2)	60.0 (±11.0)	42.9 (±18.7)	85.7 (±13.2)	44.4 (±16.6)	88.9 (±10.5)
Utrecht	75.0 (±12.5)	83.3 (±10.8)	85.7 (±13.2)	85.7 (±13.2)	100	100

* significant differences relative to DMPA, $p < .05$

** significant differences relative to DMPA, $p < .01$

++ significant difference relative to NET-EN (60-day), $p < 0.01$

termination rates, between 50-70 per 100 women over two years, were Alexandria, Ibadan, Manila and Salvador, whereas the centres with high rates of discontinuations, around 90 per 100 women over two years, were Karachi, Lusaka and Utrecht. Significant differences were observed between treatment groups in Karachi, Santiago, Ljubljana, and Luxembourg, but no one drug regimen was consistently better than another.

The most common medical reasons for discontinuation, other than menstrual disturbances or pregnancy, are shown in Table IV. Abdominal distention or discomfort and weight gain were reported more frequently by women discontinuing DMPA than among women discontinuing the NET-EN (84-day) regimen. There were no other significant differences between the three treatment groups.

Table V summarizes the changes in blood pressure and body weight. There were declines in mean systolic and diastolic blood pressure with all regimens, but the decline in systolic blood pressure was least in the NET-EN (84-day) group. Increases in mean body weight of comparable magnitude were observed in all three treatment groups.

Two women discontinued because of cervical neoplasia. Both women had suspicious cervical cytology on admission. Repeat cervical cytology indicated cervical neoplasia, and the women were referred for treatment. One woman received one, and the other two, doses of DMPA.

Four deaths were reported among subjects in Alexandria, Lusaka and Manila during the course of the study. One woman, aged 28, had completed chemotherapy for a hydatidiform mole four months prior to admission to the study. She received two injections of DMPA and two months later was hospitalized for metastatic choriocarcinoma. She died approximately two weeks later. One woman, aged 22, died of tuberculosis following a two-week period of hospitalization, and a second woman, aged 23, died the day after being hospitalized, also with a diagnosis of tuberculosis. Both women received NET-EN - two and eight injections, respectively. The fourth death occurred after a two-week period of generalized illness including fever, cough, and malaise. The woman, aged 22, was hospitalized for a day, though no abnormalities were noted on physical examination. According to her family, she became unconscious on the way home from the hospital and died the

TABLE IV. SELECTED MEDICAL REASONS FOR DISCONTINUATION OVER TWO YEARS OBSERVATION

MEDICAL REASONS	DMPA		NET-EN (60-DAY)		NET-EN (84-DAY)	
	No.	Rate per 100 woman-years	No.	Rate per 100 woman-years	No.	Rate per 100 woman-years
Abdominal distention or discomfort	19	1.1	5	0.6	3	0.3**
Weight gain	36	2.1	14	1.6	7	0.8**
Anxiety/depression	13	0.7	8	0.9	3	0.3
Fatigue	15	0.9	8	0.9	8	0.9
Dizziness	20	1.2	14	1.6	13	1.5
Headaches	40	2.3	17	2.0	18	2.1
Decreased libido	15	0.9	5	0.6	5	0.6
Hypertension	9	0.5	6	0.7	7	0.8
TOTAL	167		77		64	

** significant difference relative to DMPA $p < .01$

TABLE V. CHANGE IN BLOOD PRESSURE AND BODY WEIGHT, AND STANDARD ERRORS AFTER ONE AND TWO YEARS OF USE

	DMPA	NET-EN (60-DAY)	NET-EN (84-DAY)
Mean change in systolic blood pressure (mm Hg) ± SE			
0-12 months observation	-2.8 (±0.6)	-2.0 (±0.8)	-0.9* (±0.7)
0-24 months observation	-3.0 (±1.0)	-2.5 (±1.1)	+0.1* (±0.9)
Mean change in diastolic blood pressure (mm Hg) ± SE			
0-12 months observation	-1.3 (±0.4)	-1.5 (±0.6)	-1.1 (±0.5)
0-24 months observation	-1.6 (±0.7)	-1.8 (±0.8)	-0.4 (±0.8)
Mean change in body weight (kg) ± SE			
0-12 months observation	1.9 (±0.3)	1.7 (±0.3)	1.7 (±0.2)
0-24 months observation	3.3 (±0.5)	3.3 (±0.5)	3.4 (±0.4)
Number of subjects completing:			
0-12 months observation	764	398	424
0-24 months observation	390	214	239

* significant difference relative to DMPA $p < 0.5$

following day, of undetermined cause. She had received three injections of DMPA. No autopsies were performed on the women who died.

BLEEDING PATTERNS

The overall menstrual bleeding patterns are summarized in Figure 1 which shows the frequency of bleeding or spotting over the first year of use. For one to two weeks after each injection, there was a decline in bleeding and spotting with all three drugs. This was followed by a substantial rise in the frequency of spotting with DMPA, and a bimodal peak of both bleeding and spotting with the two NET-EN regimens. This bimodal pattern diminished with time and was no longer present after the first six months of use. With all three treatments, there was a decline over time in the frequency of bleeding or spotting. This was more marked with DMPA.

Table VI shows the mean duration of bleeding and spotting episodes, and the percent of episodes which persisted for more than 21 days. During the first six months, there were significantly longer episodes of bleeding and spotting with DMPA than with the NET-EN regimens. The duration of episodes and the frequency of prolonged episodes in excess of 21 days diminished with time, and this trend was more marked for DMPA and NET-EN (60-day) than for the NET-EN (84-day) regimen.

Table VII shows the percent of women with amenorrhea lasting more than 90 days. In all treatment groups there was a progressive increase over time in the prevalence of amenorrhea; however, this was significantly more frequent with DMPA as compared to the two NET-EN regimens. After 24 months of use, the percentage of women with amenorrhea was significantly greater among NET-EN (60-day) than NET-EN (84-day) subjects.

DISCUSSION

This study is the largest comparative trial of long-acting injectable contraceptives that has been conducted and provides 3,429 woman-years of experience to assess the relative merits of the three contraceptive regimens under investigation.

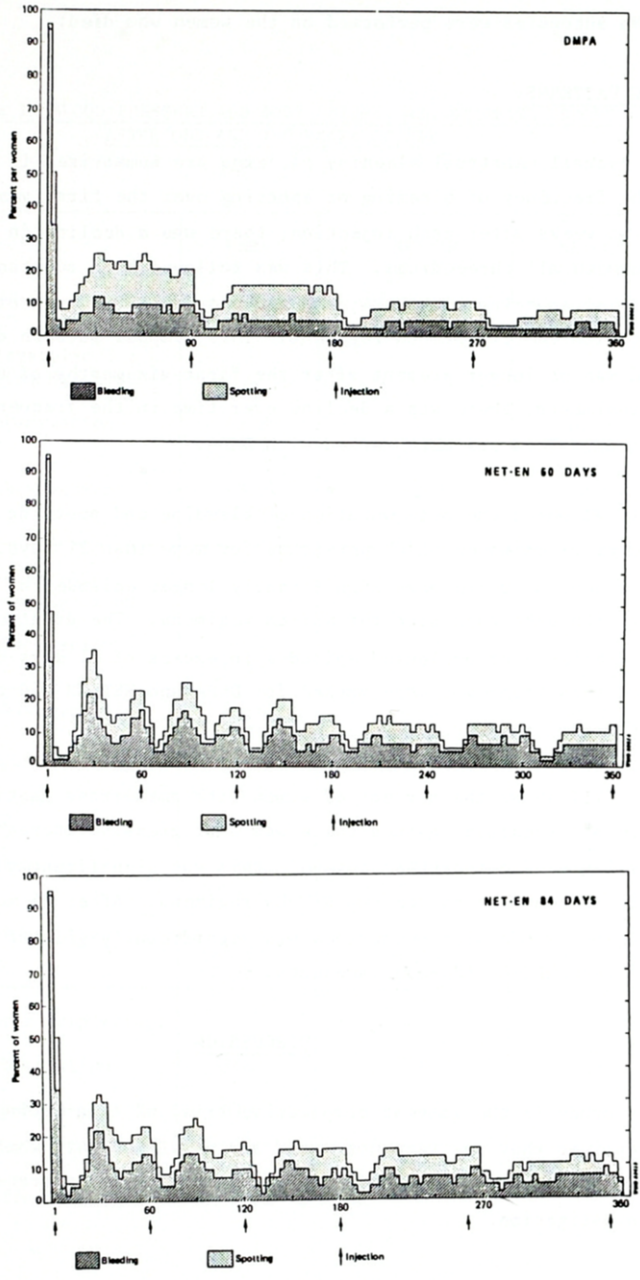

Figure 1. The frequency of bleeding and spotting relative to timing of each injection.

TABLE VI. DURATION OF BLEEDING AND SPOTTING EPISODES AND STANDARD ERRORS

PERIOD OF OBSERVATION	DURATION OF EPISODES OF BLEEDING AND/OR SPOTTING					
	DMPA		NET-EN 60 DAYS		NET-EN 84 DAYS	
	Mean No. Days±SE	Percent of women with episodes 21 Days	Mean No. Days±SE	Percent of women with episodes 21 Days	Mean No. Days±SE	Percent of women with episodes 21 Days
0-6 months	10.2++ (±0.3)	10.5%++	6.9*** (±0.2)	4.1%	7.2*** (±0.2)	4.4%
7-12 months	6.5 (±0.3)	4.6%	6.1 (±0.2)	2.4%	6.2 (±0.2)	3.3%
13-18 months	5.0 (±0.2)	2.6%	5.4 (±0.3)	1.8%	6.1*** (±0.2)	4.1%
19-24 months	4.9 (±0.3)	1.9%	4.7 (±0.2)	0.9%	+++ 6.6** (±0.5)	3.5%

** Significant difference relative to DMPA $p < .01$
*** Significant difference relative to DMPA $p < 0.001$
+++ Significant difference relative to NET-EN (60-days) $p < 0.001$

TABLE VII. PERCENT OF WOMEN WITH AMENORRHOEA FOR MORE THAN 90 DAYS

PERIOD OF OBSERVATION	PERCENT OF WOMEN WITH AMENORRHOEA OF MORE THAN 90 DAYS DURATION					
	DMPA		NET-EN (60-day)		NET-EN (84-day)	
	No. of subjects[a]	Percent	No. of subjects[a]	Percent	No. of subjects[a]	Percent
0-6 months	1262	33.9+	645	14.0	652	12.7
6-12 months	844	54.1+	453	27.4	453	30.9
12-18 months	612	61.2+	328	33.5	317	28.7
18-24 months	457	61.9+	241	40.7++	245	24.5

+ Significant difference relative to both NET-EN regimens $p < .001$

++ Significant difference relative to NET-EN (84-day) $p < .001$

a. The number of women commencing each interval, with complete menstrual diary data for 90 days or more during each 6-month period.

With regard to contraceptive efficacy, there was a significantly higher pregnancy rate with the NET-EN (84-day) regimen compared to DMPA only at 18 months (Table II). Although the pregnancy rate for the NET-EN (84-day) regimen was usually higher than for the NET-EN (60-day) regimen, the difference is not statistically significant. Both the NET-EN (84-day and 60-day) regimens used in this study resulted in a much lower pregnancy rate than that reported from an earlier trial when NET-EN was given at three-month intervals (3.6 per 100 woman-years) (2). The pregnancy rates presented in this report are lower in all treatment groups than the pregnancy rates reported in the preliminary analysis. Two factors account for this difference. First, more woman-months of experience were accumulated after the preliminary report, while no additional pregnancies were reported. Secondly, two of the pregnancies included in the preliminary analysis were reported subsequently by the principal investigators not to have been confirmed pregnancies, and were not included as pregnancies in this final report.

As reported previously (2,5), terminations for amenorrhea were significantly higher with DMPA than with either NET-EN regimens (Table II) and DMPA was associated with a higher prevalence of amenorrhea (Table VII). There were no significant differences between drugs in the discontinuation rates for bleeding problems, despite the fact that the NET-EN regimens had a more defined cyclic pattern and less protracted episodes of bleeding and spotting during the first six months of use (Figure 1 and Table VI). Also, discontinuations for other medical reasons were similar with the three regimens (Table II), although DMPA was associated with significantly more terminations due to "abdominal distention or discomfort" and "weight gain", than the NET-EN (84-day) regimen (Table IV). The total discontinuation rates were comparable with the three methods.

The centre-specific total discontinuation rates shown in Table III illustrate the local variability observed in the study. In some centres such as Alexandria, Ibadan and Manila, the discontinuation rates were relatively low after one and two years of use, whereas in other centres such as Karachi, Lusaka and Utrecht, a very high proportion of women discontinued use by the end of the second year. This may reflect variation in the acceptability of injections as a mode of drug administration, or culturally determined tolerance of menstrual disturbances associated with long-acting progestogen contraceptives. The attitudes of clinic staff towards injectable methods may also have influenced continuation rates.

Serious illnesses reported included two cases of cervical neoplasia and four deaths, none of which could be related to drug use. Both cases of cervical neoplasia had abnormal cervical cytology on admission. Neoplasia was diagnosed on repeat cytology, and the two women received only one and two injections of DMPA, respectively. These two cases of cervical neoplasia are thus unlikely to be drug-related.

Four reported deaths over a period of two years is not surprising among more than 3,000 women living primarily in developing countries. One woman, who had received three injections of DMPA, died at home of unknown causes, after a 2-week illness. One woman died of confirmed miliary tuberculosis and another with a diagnosis of suspected tuberculosis. Even if two deaths were due to tuberculosis, the corresponding death rate from tuberculosis among the study population would be 0.58 per 1000 woman-years. Reliable tuberculosis mortality rates are not available for either of the two countries where the women died, nor for women of the ages included in the study. However, the estimated death rate from tuberculosis world-wide is approximately 100 times greater than that reported in the study population (6).

The fourth reported death occurred in a 28-year-old woman with a history of methotrexate-treated hydatidiform mole. After two injections of DMPA, she was diagnosed as having metastatic choriocarcinoma. The two published studies on the effect of oral contraceptives on the development of post-molar trophoblastic tumours report conflicting results. In one study, from London, the use of oral contraceptives in the post-evacuation period was associated with a 3-fold increased risk of the need for chemotherapy (7). In the other study, from Boston, oral contraceptives given after molar evacuation were not associated with an increased risk of post-molar trophoblastic tumours (8). While effective contraception is important following molar evacuation, the role of steroid contraceptives during the post-evacuation is unclear. It is not possible to say what effect, if any, DMPA had on the outcome in the one case of trophoblastic disease in this study. None of the four deaths or either of the two cases of cervical neoplasia appear to be related to drug use.

One of the main objectives of multinational clinical trials is to provide information of relevance to health programme administrators and providers of family planning services. The total discontinuation rates of about 50 per 100 women after one year observed with the three injectable contraceptives in the

present study, are comparable to those reported for oral contraceptives in similar clinical trial settings (9). However, the 12-month pregnancy rates with the injectable methods (0.1-0.7 per 100 women) are generally lower than with oral contraceptives (1.0-6.0 per 100 women) (6). Thus, injectable preparations appear to provide an effective alternative to oral methods of interval contraception.

The choice of the most appropriate injectable regimen for a given context will depend upon a variety of medical and family planning programme considerations. Although the pregnancy rates with the NET-EN (84-day) regimen are slightly higher than with the other two regimens, the NET-EN (84-day) schedule has the logistic and economic advantage of fewer injections and less frequent re-visits compared to the NET-EN (60-day) treatment. However, the NET-EN (60-day) schedule has the advantage of a consistent interval between injections. Both NET-EN regimens have the advantage of less amenorrhea as compared to DMPA, and may be more appropriate in those societies with a low cultural tolerance of amenorrhea.

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