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5. Author(s)

1. TC de Cetina	AJ Rowan
LP Reyes	CS Waszak
2. LV Gamboa	MB Weaver
3. TR Dunson	

6. Contributing Organization(s)

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A comparative clinical trial of Norinyl 1+35 versus Norinyl 1+50 in Merida, Yucatan, Mexico

T.C. DE CETINA (1), L.P. REYES (1), L.V. GAMBOA (1), T.R. DUNSON (2),
A.J. ROWAN (2), C.S. WASZAK (2) and M.B. WEAVER

(1) Centro de Investigaciones Regionales Hideyo Noguchi, Merida, Yucatan, Mexico

(2) Family Health International, PO Box 13950, Research Triangle Park, NC 27709, USA

Abstract

A comparative clinical trial of two combined oral contraceptives differing only in estrogen type and dosage was conducted at the Centro de Investigaciones Hideyo Noguchi in Merida, Yucatan, Mexico. The trial was designed to determine the differences between Norinyl 1+50 (Syntex) and Norinyl 1+35 (Syntex) in rates of discontinuation and frequency of selected side-effects which might contribute to method discontinuation.

Three hundred women were randomly assigned to either the Norinyl 1+35 group or to the Norinyl 1+50 group and follow-up visits were scheduled at 1, 4, 8 and 12 months after admission. In the Norinyl 1+35 group, more women experienced an increase in intermenstrual bleeding (primarily staining and spotting) ($p < 0.05$), breast discomfort ($p < 0.05$) and nausea than in the Norinyl 1+50 group. There was a significantly higher discontinuation rate for personal reasons, such as desired change of method and method not needed, among the women taking Norinyl 1+35 ($p < 0.05$). The largest number of discontinuations comprised women discontinuing for menstrual problems in both groups.

The life-table total discontinuation rate at 12 months was 52.0 for the Norinyl 1+35 group and 50.7 for the Norinyl 1+50 group. The lost-to-follow-up rates at 12 months were 17.8 for the Norinyl 1+35 group and 22.8 for the Norinyl 1+50 group.

Introduction

While both the estrogen and progestogen components of combined oral contraceptives (OCs) give rise to certain side-effects, higher doses of the estrogen component ($> 50 \mu\text{g}$) of OCs have been associated with both short-term minor side-effects such as nausea, vomiting and headache, and long-term adverse effects

including thromboembolic disease and hepatic disorders [1]. In recent years, there has been a gradual shift toward an increased use of low-dose pills (30–35 μg of estrogen). With a lower estrogen dose, while some undesirable side-effects may be minimized, the incidence of breakthrough bleeding may increase, although how this affects discontinuation rates is uncertain. Overall, the health benefits may be more advantageous if such minor side-effect rates are not unacceptably high or do not affect the rate of discontinuation [2].

An international multicenter clinical trial was designed to determine the differences in discontinuation rates, reason for discontinuation, and the frequency of selected symptoms contributing to method discontinuation between Norinyl 1+35 (Syntex), a low-dose combined oral contraceptive, and Norinyl 1+50 (Syntex), a standard-dose OC. Described here are the results from one center in Mexico which participated in this trial coordinated by Family Health International (FHI).

Methods and materials

At the time of study admission, each woman was randomly assigned by means of preprinted sealed envelopes to one of the two types of OCs being evaluated in this study; Norinyl 1+35 ($n=150$) and Norinyl 1+50 ($n=150$). Assignment to OCs was not blinded, as the products were presented as they are normally marketed.

The purpose of this study, as well as the benefits and risks, were explained to each woman before she entered the study. Women who chose to participate were fully informed of the risks and benefits of participation and signed informed consent forms. A medical history was taken, including contraceptive practices prior to admission, and an examination was performed to ensure that the woman did not have contraindications to OC use.

Follow-up visits were scheduled at 1, 4, 8 and 12 months after admission to the study. At the 12-month follow-up, the patient was terminated from the study. At follow-up, women were questioned about menstrual problems and side-effects they might have experienced, and about reasons for discontinuation, if applicable. The term 'side-effects' includes nausea, vomiting, headaches, dizziness, vaginal discharge and breast discomfort. Other less serious problems were considered 'other complaints'. The term 'complication' was used for serious problems that occurred during the follow-up period.

Pharmacology

Each of the oral contraceptives administered in this study was provided in 28-day packages of 21 active steroid tablets and seven inert tablets. Each cycle of Norinyl 1+35 contained 21 tablets of 1.0 mg norethindrone and 35 μg ethinyl estradiol. In each cycle of Norinyl 1+50 the 21 steroid tablets contained 1.0 mg norethindrone and 50 μg mestranol. Both OCs are manufactured by Syntex Laboratories, Inc. of Palo Alto, California.

Admission criteria

Women were admitted from January 1983 through January 1984. Women in good physical health desiring to use OCs for contraceptive purposes who could be followed-up for at least 12 months were asked to participate in this study. In addition, patient selection criteria designated by the study protocol required that each woman be between the ages of 18 and 40 years and have no known or suspected contraindication to oral contraceptive use. In addition, each woman had to be sexually active, have terminated her last pregnancy at least 42 days prior to admission to the study and have had at least one normal menstrual period since the termination of her pregnancy (or since last use of a steroidal contraceptive), and not be breastfeeding at admission. All women admitted to the study met protocol requirements.

Methods of analysis

The results reported here were part of a multicenter clinical trial in which a total of 4500 women were to be recruited, 2250 being assigned to Norinyl 1+35, and three groups of 750 being assigned, each to one of three control pills; Norinyl 1+50 would be the focus of study at the Mexican center. The studies were conducted at five clinics. Each clinic was to enroll 300 women with 150 women being randomly assigned to each product being evaluated. The studies were not blinded because an evaluation of the study products as they appear on the market was desired.

For sample size derivations, it is assumed that the continuation rate at 12 months of the 'standard' pill is 60%. To detect a difference of 8% in the rates (i.e., a rate as small as 52% or as large as 68%) with power = 0.9 and $\alpha = 0.1$, a sample size of 750 per treatment is required if 20% of the patients are expected to be lost-to-follow-up. The data for each comparison were to be collected at five different centers with approximately 150 subjects for each of two treatments. At each clinical site (here, the Mexican center), a difference in the continuation rates as large as 8% from the standard continuation can be detected with power = 0.5 and a difference as large as 18% can be detected with power = 0.9.

Data were recorded on standard forms by clinic staff and were sent to FHI for processing and analysis. Frequency data were compared using standard Chi-square tests. Rates of discontinuation for specific reasons were calculated, as were overall discontinuation rates using the life-table method [3]. The rates were compared using the log-rank statistic which permits the overall comparison of cumulative life-table event rates [4]. Data were analyzed using Chi-square and life-table statistics by means of SPSS (Statistical Package for the Social Sciences) and FHI's life-table computer program.

Results

Sociodemographic characteristics

Table 1 Selected sociodemographic characteristics

	Norinyl 1+35 (n = 150)		Norinyl 1+50 (n = 150)	
	No.	%	No.	%
Age (years)				
Less than 20	13	8.7	11	7.3
20-24	52	34.7	41	27.3
25-29	52	34.7	39	26.0
30-34	23	15.2	39	26.0
35-39	10	6.7	19	12.7
40+	0	0.0	1	0.7
Mean**		26.6		28.4
Education (years)				
None	17	11.3	23	15.3
1-6	103	68.7	106	70.7
7-12	28	18.7	19	12.7
13+	2	1.3	2	1.3
Mean**		4.4		3.7
Total live births				
1	22	14.7	17	11.3
2	41	27.3	24	16.0
3	29	19.3	26	17.3
4+	58	38.7	83	55.3
Mean**		3.4		4.0
Contraceptive method used in the month prior to admission				
None	39	26.0	38	25.3
Oral contraceptives	74	49.3	70	46.7
IUD	13	8.7	15	10.0
Injectables	6	4.0	16	10.7
Condoms	8	5.3	3	2.0
Withdrawal/rhythm	9	6.0	8	5.3
Other barrier	1	0.7	0	0.0

* $p < 0.05$, using the Welch approximation test

** $p < 0.01$, using the Welch approximation test

The population served by the Centro de Investigaciones Hideyo Noguchi is largely urban working class. Select patient characteristics for both groups (Table 1) show that despite random allocation, there were differences in sociodemographic characteristics between the two groups of women. The mean age for the Norinyl 1+35 group was 26.6 years and the mean age for the Norinyl 1+50 group was 28.4 years ($t = -2.91$, d.f. = 297, $p < 0.01$). The mean educational level was 4.4 for the Norinyl 1+35 group

and 3.7 for the Norinyl 1+50 group ($t = 1.96$, d.f. = 300, $p < 0.05$); the mean number of live births was 3.4 and 4.0, respectively ($t = -2.47$, d.f. = 300, $p < 0.01$). While the Norinyl 1+50 group were on average older (1.8 years) and had had more live births (0.6 births), the Norinyl 1+35 group although younger had had more education (0.7 years). The two groups were similar in the distribution of contraceptive use in the month prior to admission. The predominant method used in both treatment groups was oral contraceptives (49.3% vs 46.7%).

Side-effects, complications and complaints

Table 2 Complications since admission

	Norinyl 1+35 <i>n</i> = 143)		Norinyl 1+50 <i>n</i> = 140)	
	No.	%	No.	%
Serious complications				
Severe headaches	1	0.7	1	0.7
Eye problems	1	0.7	0	0.0
Severe leg pain	0	0.0	1	0.7
Total women with serious complications	2	1.4	2	1.4
Other complications				
Cervicitis	0	0.0	2	1.4
Hypertension	3	2.1	2	1.4
Dyspareunia	1	0.7	1	0.7
Numbness in upper arms	1	0.7	1	0.7
Influenza	1	0.7	0	0.0
Parasites	1	0.7	0	0.0
Chloasma	3	2.1	1	0.7
Abdominal pain	0	0.0	1	0.7
Diaphoresis	0	0.0	1	0.7
Pruritus, generalized and intense	0	0.0	2	1.4
Total women with 1+ other complications	10	7.0	10	7.1

n represents the number of women ever followed-up

* Multiple symptoms may be reported per woman

Problems experienced during the study period were grouped in the following categories: serious complications and other complaints, menstrual complaints, and selected side-effects. The severity of complications and complaints reported in this study is based on the self-report of the study participant and does not necessarily reflect the medical opinion of the physician in charge. Two women in each group reported serious complications during the study period (Table 2). One woman in the Norinyl 1+35 group complained of severe headaches and discontinued OC use for that reason. Another woman in the Norinyl 1+35 group reported severe eye problems at her one-month follow-up but continued with the method and completed the study

without further reports of this complaint. In the Norinyl 1+50 group, one woman reported severe headaches and discontinued for hypertension (BP > 140/90), and another woman reported severe leg pain and discontinued for that reason. Ten women in each group reported one or more 'other complications'. Hypertension was the most commonly reported 'other complication' noted by three women (2.1%) in the Norinyl 1+35 group and two women (1.4%) in the Norinyl 1+50 group. All of the women with hypertension discontinued OC use.

Table 3 Menstrual complaints since admission

Complaint	Norinyl 1+35 (n = 143)		Norinyl 1+50 (n = 140)	
	No.	%	No.	%
Intermenstrual bleeding				
None	77	53.8	125	89.3
Staining/spotting**	60	42.0	12	8.6
Moderate	5	3.5	3	2.1
Severe	1	0.7	0	0.0
Change in intermenstrual bleeding				
Never reported	75	52.4	123	87.9
No change	3	2.1	1	0.7
Decrease	2	1.4	2	1.4
Increase	0	0.0	0	0.0
New reports**	63	44.1	14	10.0
Other menstrual complaints				
None	89	62.2	48	34.3
Scanty menses**	34	23.8	61	43.6
Amenorrhea	15	10.5	29	20.7
Dysmenorrhea	1	0.7	0	0.0
Menorrhagia	3	2.1	1	0.7
Intermenstrual pelvic discomfort or cramps	1	0.7	0	0.0
Late menses	0	0.0	1	0.7
Total women with 1+ menstrual complaints[†]	100	69.9	100	71.4

n represents the number of women ever followed-up

* $p < 0.05$, χ^2 2x2 test

** $p < 0.01$, χ^2 2x2 test

[†] Multiple symptoms may be reported per woman

New reports = complaints reported by women at some time during follow-up which were not previously reported at admission

Menstrual complaints ever reported at follow-up and changes in menstrual events since admission were evaluated (Table 3). One-hundred women in each group (69.9% of the Norinyl 1+35 group and 71.4% of the Norinyl 1+50 group) reported at least one menstrual problem during the follow-up period. Significantly more women in the Norinyl 1+35 group (44.1%) than in the Norinyl 1+50 group (10.0%) reported an increase in intermenstrual bleeding, primarily staining and spotting, from admission to follow-up ($\chi^2 = 29.3$, d.f. = 1; $p < 0.05$). Significantly more women in the Norinyl 1+50 group (20.7%) reported amenorrhea at follow-up than in the Norinyl 1+35 group (10.5%) ($\chi^2 = 13.2$, d.f. = 1; $p < 0.05$). In addition, significantly more Norinyl 1+50 users (43.6%) reported scanty menses at follow-up than did Norinyl 1+35 users (23.8%) ($\chi^2 = 5.6$, d.f. = 1; $p < 0.05$).

Table 4 Changes in primary other menstrual complaints from admission to follow-up

Changes in complaints	Norinyl 1+35 (n = 150)		Norinyl 1+50 (n = 150)	
	No.	%	No.	%
No complaints				
Reports at admission:	93	62.0	92	61.3
Reports at follow-up:				
Never reported	23	15.3	49	32.7
No change	55	36.7	39	26.0
Decrease				
No complaint	0	0.0	0	0.0
Different complaint	35	23.3	46	30.7
Lapse	3	2.0	7	4.7
New reports**	34	22.7	9	6.0
Amenorrhea				
Reports at admission:	0	0.0	0	0.0
Reports at follow-up:				
Never reported	135	90.0	121	80.7
No change	0	0.0	0	0.0
Decrease				
No complaint	0	0.0	0	0.0
Different complaint	0	0.0	0	0.0
Lapse	0	0.0	0	0.0
New reports**	15	10.0	29	19.3
Dysmenorrhea				
Reports at admission:	24	16.0	31	20.7
Reports at follow-up:				
Never reported	125	83.3	119	79.3
No change	0	0.0	0	0.0
Decrease				
No complaint	13	8.7	5	3.3
Different complaint**	10	6.7	25	16.7
Lapse	1	0.7	1	0.7
New reports	1	0.7	0	0.0

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Table 4 continued

Changes in complaints	Norinyl 1+35 (n = 150)		Norinyl 1+50 (n = 150)	
	No.	%	No.	%
Menorrhagia				
Reports at admission:	7	4.7	3	2.0
Reports at follow-up:				
Never reported	141	94.0	146	97.3
No change	1	0.7	0	0.0
Decrease				
No complaint	4	2.7	2	1.3
Different complaint	2	1.3	1	0.7
Lapse	0	0.0	0	0.0
New reports	2	1.3	1	0.7
Scanty menses				
Reports at admission:	0	0.0	0	0.0
Reports at follow-up:				
Never reported	100	66.7	81	54.0
No change	3	2.0	11	7.3
Decrease				
No complaint*	11	7.3	2	1.3
Different complaint	2	1.3	5	3.3
Lapse	3	2.0	0	0.0
New reports**	31	20.7	51	34.0
Intermenstrual pelvic discomfort or cramps				
Reports at admission:	7	4.7	6	4.0
Reports at follow-up:				
Never reported	142	94.7	144	96.0
No change	0	0.0	0	0.0
Decrease				
No complaint*	6	4.0	0	0.0
Different complaint	1	0.7	4	2.7
Lapse	0	0.0	2	1.3
New reports	1	0.7	0	0.0

* $p < 0.05$, χ^2 2x2 test** $p < 0.01$, χ^2 2x2 test

Lapse = complaints reported by women at admission but who did not return to the clinic for a follow-up visit

New reports = complaints reported by women at some time during follow-up which were not previously reported at admission

Table 4 examines the changes in other menstrual complaints (see Table 3) reported at admission to those reported at follow-up. Significantly more Norinyl 1+35 users reported no complaints ($p < 0.01$) at follow-up compared to the Norinyl 1+50 group; half of these women had reported either scanty menses or intermenstrual pelvic discomfort at admission. Significantly more Norinyl 1+50 users reported a complaint of amenorrhea ($\chi^2 = 5.2, p < 0.05$) or scanty menses ($\chi^2 = 6.7, p < 0.01$) at

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follow-up which had not been reported at admission. In addition, significantly more Norinyl 1+50 users who had reported dysmenorrhea at admission did not report the complaint at follow-up ($\chi^2 = 7.3$; $p < 0.01$) compared to the women who had reported dysmenorrhea in the Norinyl 1+35 group.

Selected side-effects associated with OC use include nausea, vomiting, headaches, dizziness, vaginal discharge and breast discomfort. One hundred and six women (74.1%) in the Norinyl 1+35 group and 95 women (67.9%) in the Norinyl 1+50 group reported at least one type of side-effect during the study period (Table 5). Nausea was reported by significantly more women in the Norinyl 1+35 group (35.7%) than in the Norinyl 1+50 group (22.9%) ($\chi^2 = 4.1$, d.f.=1; $p < 0.05$). Headaches were the side-effects reported most often by women in this study; 40% of the women in each group experienced headaches during the study period. Drowsiness and frigidity were the most frequently reported 'other complaint' for both groups; there were no significant differences between the groups for any other complaint (Table 5).

Table 5 Side-effects since admission

Side-effects	Norinyl 1+35 (n = 143)		Norinyl 1+50 (n = 140)	
	No.	%	No.	%
Nausea	51	35.7	32	22.9
Vomiting	13	9.1	10	7.1
Headache	60	42.0	56	40.0
Dizziness	21	14.7	20	14.3
Vaginal discharge	54	37.8	47	33.6
Breast discomfort	19	13.3	9	6.4
Other complaints				
Drowsiness	4	2.8	6	4.3
Frigidity	4	2.8	3	2.1
Nervousness	2	1.4	2	1.4
Galactorrhea	0	0.0	2	1.4
Irritability	0	0.0	1	0.7
Total women with 1+ side-effects or complaints	106	74.1	95	67.9

n represents the number of women ever followed up

A summary of the changes in side-effects that occurred since admission is presented in Table 6. Changes in occurrence for each side-effect (including intermenstrual bleeding) were ranked by severity of report (e.g. none, sometimes, often) with increase > decrease > no change over the course of the study period. The changes in side-effects that occurred from admission to follow-up show that the Norinyl 1+35 group had about three times as many women reporting an increase in

Table 6 Changes in side-effects since admission

Changes in side-effects†	Norinyl 1+35 (<i>n</i> = 143)		Norinyl 1+50 (<i>n</i> = 140)	
	No.	%	No.	%
Nausea				
Never reported	84	58.7	102	72.9
No change	6	4.2	2	1.4
Decrease	8	5.6	6	4.3
Increase	0	0.0	0	0.0
New reports	45	31.5	30	21.4
Vomiting				
Never reported	126	88.8	128	91.5
No change	0	0.0	1	0.7
Decrease	4	2.8	2	1.4
Increase	0	0.0	0	0.0
New reports	13	8.4	9	6.4
Headaches				
Never reported	73	51.0	71	50.7
No change	14	9.8	8	5.7
Decrease	10	7.0	14	10.0
Increase	4	2.8	4	2.9
New reports	42	29.4	43	30.7
Dizziness				
Never reported	117	81.8	119	85.1
No change	5	3.5	3	2.1
Decrease	5	3.5	1	0.7
Increase	0	0.0	1	0.7
New reports	16	11.2	16	11.4
Vaginal discharge				
Never reported	78	54.5	65	46.4
No change	13	9.1	12	8.6
Decrease*	13	9.1	28	20.0
Increase	1	0.7	4	2.9
New reports	38	26.6	31	22.1
Breast discomfort				
Never reported	113	79.0	121	86.4
No change	2	1.4	4	2.9
Decrease	11	7.7	10	7.1
Increase	0	0.0	1	0.7
New reports*	17	11.9	4	2.9

n represents the number of women ever followed up

* $p < 0.01$, χ^2 2x2 test

† Multiple symptoms may be reported per woman

New reports = complaints reported by women at some time during follow-up which were not previously reported at admission

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breast discomfort as did the Norinyl 1+50 group (11.9% vs 3.6%) ($\chi^2 = 6.8$, d.f. = 1; $p < 0.05$). For example, in the Norinyl 1+35 group, 84 women (58.7%) never reported nausea (neither at admission nor during follow-up), while 6 women (4.2%) reported no change in incidence since admission; 8 women (5.6%) reported a decrease in occurrence since admission; no women reported an increase in the complaint since admission and 45 women (31.5%) reported nausea at some time during the follow-up period who had not previously reported the complaint at admission (e.g. new report). While preadmission vaginal discharge was reported more often in the Norinyl 1+50 group, significantly more women ($\chi^2 = 6.8$, $p < 0.01$) in this group reported a decrease in this complaint at follow-up.

Discontinuation

Twelve-month gross cumulative life-table rates for discontinuation assessed 53 women (37.1%) in the Norinyl 1+35 group and 42 women (30.0%) in the Norinyl 1+50 group who discontinued during the 12-month study period (Table 7). The highest rate of discontinuation, excluding lost-to-follow-up, for both groups was due to menstrual problems, particularly for amenorrhea (reported by 12 women in the Norinyl 1+35 group and 17 women in the Norinyl 1+50 group). The only reason for discontinuation for which there was a significant difference ($p < 0.05$) between groups was for 'other personal' reasons. At 12 months this rate was 9.7 for the Norinyl 1+35 group (11 women discontinued) and 2.1 for the Norinyl 1+50 group (2 women discontinued). Specific personal reasons given by women in the Norinyl 1+35 group included forgetfulness (2 cases), desires method change (5 cases) and method not needed (4 cases). Both cases in the Norinyl 1+50 group were due to a desire to change method.

The lost-to-follow-up rate was similar for each group: 17.8 for the Norinyl 1+35 group and 22.8 for the Norinyl 1+50 group (Table 7). The difference in the rate of other personal discontinuations was not reflected as a significant difference between the two groups in the rate of total discontinuation; the 12-month total discontinuation rate was similar for each group at 52.0 for the Norinyl 1+35 group and 50.7 for the Norinyl 1+50 group ($p > 0.05$) (Table 7). There were no accidental pregnancies reported during the study period.

Continuation and regularity of use

One hundred and forty-three women in the Norinyl 1+35 group and 140 women in the Norinyl 1+50 group returned for follow-up. Compliance was assessed by self-report and from the date the last pill was taken prior to the date of follow-up visit contact. Follow-up visit data indicate that 21 women in the Norinyl 1+35 group (14.7%) and 9 women in the Norinyl 1+50 group (6.4%) missed at least one pill during the follow-up period ($p < 0.05$).

Table 7 Gross cumulative life-table discontinuation rates

<i>Discontinuation reason</i>	<i>Norinyl 1+35 (n = 150) Rate ± S.E.</i>	<i>Norinyl 1+50 (n = 150) Rate ± S.E.</i>
Menstrual problems		
1 month	3.6 ± 1.6	2.9 ± 1.4
4 months	7.5 ± 2.3	8.5 ± 2.5
8 months	13.1 ± 3.1	14.3 ± 3.2
12 months	15.3 ± 3.4	17.4 ± 3.6
Side-effects		
1 month	1.4 ± 1.0	2.9 ± 1.4
4 months	3.2 ± 1.6	6.3 ± 2.2
8 months	5.2 ± 2.1	6.3 ± 2.2
12 months	6.4 ± 2.4	6.3 ± 2.2
Other medical reasons		
1 month	0.0 ± 0.0	0.7 ± 0.7
4 months	1.7 ± 1.2	1.7 ± 1.2
8 months	3.7 ± 1.8	4.8 ± 2.1
12 months	4.9 ± 2.2	6.7 ± 2.8
Planned pregnancy		
1 month	0.0 ± 0.0	0.0 ± 0.0
4 months	0.9 ± 0.9	0.0 ± 0.0
8 months	3.9 ± 1.9	2.1 ± 1.5
12 months	5.1 ± 2.2	2.1 ± 1.5
Other personal reasons		
1 month	2.2 ± 1.2	0.0 ± 0.0
4 months	5.5 ± 2.0	0.9 ± 0.9
8 months*	8.5 ± 2.6	2.1 ± 1.5
12 months*	9.7 ± 2.8	2.1 ± 1.5
Method unrelated reasons		
1 month	2.2 ± 1.2	1.5 ± 1.0
4 months	3.0 ± 1.5	2.4 ± 1.4
8 months	5.1 ± 2.1	3.4 ± 1.7
12 months	6.3 ± 2.3	3.4 ± 1.7
Lost-to-follow-up rate		
1 month	4.8	7.4
4 months	8.9	11.4
8 months	12.3	17.5
12 months	17.8	22.8
Total discontinuations†		
1 month	5.3	9.3
4 months	26.0	26.7
8 months	42.7	41.3
12 months	52.0	50.7

* $p < 0.05$

† Total discontinuation rate includes all women discontinuing from the study including those women lost to follow-up

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Discussion

Evaluated in terms of discontinuation rates, both dosages of the Norinyl OCs demonstrated similar levels of acceptability in this study. Though more women in the Norinyl 1+35 group experienced the side-effects of intermenstrual bleeding, nausea, and breast discomfort, this difference was not reflected in a significant difference between the two groups in discontinuation rates for side-effects or menstrual problems, nor in the lost-to-follow-up rates.

There was a significant difference in the rate of discontinuation for other personal reasons. One might argue that 'desires method change' is related to dissatisfaction with the particular type of OC used, though this particular reason only accounted for part of the difference between the groups. The other discontinuations in the Norinyl 1+35 group were due to 'forgetfulness' and 'method not needed'; neither of these reasons would necessarily be related to dissatisfaction with the OC used. It cannot, therefore, be easily argued that this difference in discontinuation rate was due to differences in estrogenic content of the study products.

The finding of more nausea and breast discomfort in the Norinyl 1+35 group is unexpected as they are side-effects usually associated with higher dosage levels of estrogen [2,5]. However, while the term 'low dose' implies lower potency, there is some controversy over whether the potencies of different estrogenic compounds found in low and standard dose OCs can be compared on a milligram by milligram basis. By some estimates, the potency of ethinyl estradiol is considered to be 1.2 to 1.4 times greater than mestranol [6]. Other researchers have found no differences between the potency of the two compounds when testing was done in humans [2]. Still others consider the ratio of progestogen to estrogen of the specific compound the critical factor in determining the efficacy and cycle control for low-dose OCs rather than the absolute estrogenic potencies or dosages found in the preparation [7]. Since the effect of the ratio of estrogen to progestogen is not entirely known, it is difficult to interpret the relationship of the progestogen/estrogen ratios when the estrogenic component is different. Exactly how the difference in dosage is related to these results is unclear, however, since a lower dosage of two distinct, synthetic estrogenic steroids does not necessarily imply lower potency. In any case, none of these side-effects led to a difference between the groups in discontinuation rates for any reason.

We might infer that Norinyl 1+35 had the lower potency as more intermenstrual bleeding was reported by women in the Norinyl 1+35 group, and since low-dose OCs are associated with early and midcycle spotting [2,5,8]. However, more women in the Norinyl 1+35 group (21 women compared to 9 women in the Norinyl 1+50 group) missed taking at least one pill during the study which may have contributed to the higher percentage of women experiencing intermenstrual bleeding. Furthermore, Norinyl 1+50 users experienced a higher incidence of amenorrhoea while Norinyl 1+35 users also experienced amenorrhoea to a lesser extent. The incidence of amenorrhoea or the failure of withdrawal bleeding, and of intermenstrual bleeding, is increased for women using low-dose OCs. Other studies have noted that an inadequate progestin effect on the endometrium is linked to less cycle control in women taking low-dose OCs [8]. There was no clear division between the two groups

in this study. In both groups, the reason provided most often for discontinuation was menstrual problems, primarily amenorrhea (reported by 12 women in the Norinyl 1+35 group and 17 women in the Norinyl 1+50 group). The 12-month life-table rates for discontinuation for menstrual problems were 15.3 ± 3.4 for the Norinyl 1+35 group and 17.4 ± 3.6 for the Norinyl 1+50 group.

Both treatment groups had relatively high lost-to-follow-up rates, with a 12-month rate of 17.8 in the Norinyl 1+35 group and 22.8 in the Norinyl 1+50 group. The lost-to-follow-up rate was the highest rate of discontinuation and was similar for both groups. These rates may reflect a level of patient dissatisfaction with the study product which is not reflected in the frequency of side-effects or particular reasons for discontinuation. As neither study product was singled out, it is possible that this result was due to a particular preference or characteristics within the study population itself.

Considering the high discontinuation rate for menstrual problems, it is more likely a reflection of dissatisfaction with product side-effects in both groups. Factors which might improve patient satisfaction are more thorough counseling of patients of expected side-effects and screening of women less likely to tolerate these side-effects.

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Resumé

Dans un essai clinique conduit au Centro de Investigaciones Hideyo Noguchi à Merida dans la province du Yucatan au Mexique, on a comparé deux contraceptifs oraux combinés qui ne différaient que par le type d'oestrogène et ses doses. Cet essai avait pour but de déterminer les différences existant entre le Norinyl 1+50 (Syntex) et le Norinyl 1+35 (Syntex) en termes de pourcentages d'abandon et de la fréquence d'effets secondaires précis pouvant contribuer à l'abandon de la méthode. Trois cents femmes ont été choisies au hasard pour faire partie de deux groupes. A l'un des groupes, on a prescrit le Norinyl 1+35 et à l'autre le Norinyl 1+50. Les visites de contrôle ont été fixées à 1, 4, 8 et 12 mois après l'admission. Les femmes ayant eu des saignements intermenstruels (essentiellement des traces et microrragies) ($p < 0,05$), une gêne mammaire ($p < 0,05$) et des nausées ont été plus nombreuses dans le groupe du Norinyl 1+35 que dans le groupe du Norinyl 1+50. Le pourcentage d'abandon pour des raisons personnelles, telles que le désir de changer de méthode ou de ne plus avoir recours à la contraception, était aussi significativement plus élevé chez les femmes utilisant le Norinyl 1+35 ($p < 0,05$). Dans les deux groupes, l'abandon a été le plus fréquent chez des femmes ayant eu des problèmes menstruels.

La table de survie du taux d'abandon total établie à 12 mois indique 52,0 pour le groupe du Norinyl 1+35 et 50,7 pour le groupe du Norinyl 1+50. Les taux d'interruption du suivi établis à 12 mois se montent à 17,8 pour le groupe du Norinyl 1+35 et à 22,8 pour le groupe du Norinyl 1+50.

Resumen

En un ensayo clínico realizado en el Centro de Investigaciones Hideyo Noguchi, de Mérida, provincia de Yucatán, México, se compararon dos anticonceptivos orales combinados que sólo diferían en cuanto al tipo de estrógeno y a sus dosis. El objetivo de este ensayo era determinar las diferencias existentes entre Norinyl (1+50) (Syntex) y Norinyl 1+35 (Syntex) en cuanto a porcentajes de abandono y a la frecuencia de efectos secundarios precisos que pudieran contribuir al abandono del método.

Trescientas mujeres fueron elegidas al azar para formar parte de dos grupos. A uno de los grupos se le prescribió Norinyl 1+35 y al otro Norinyl 1+50. Las visitas de control se fijaron en 1, 4, 8 y 12 meses después de la admisión. Las mujeres que experimentaron pérdidas intermenstruales (esencialmente manchas y microrragias) ($p < 0,05$), molestias en las mamas ($p < 0,05$) y náuseas fueron más numerosas en el grupo de Norinyl 1+35 que en el de Norinyl 1+50. El porcentaje de abandono por motivos personales, tales como el deseo de cambiar de método o de no recurrir a la anticoncepción, fue asimismo significativamente más elevado en las mujeres que empleaban Norinyl 1+35 ($p < 0,05$). En los dos grupos, el abandono fue más frecuente entre las mujeres con problemas menstruales.

La tabla de supervivencia de la proporción de abandono establecida a los 12 meses indica 52,0 para el grupo de Norinyl 1+35 y 50,7 para el grupo de Norinyl 1+50. Las proporciones de interrupción de supervivencia a los 12 meses ascendieron a 17,8 para el grupo de Norinyl 1+35 y a 22,8 para el de Norinyl 1+50.

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Department of Obstetrics and Gynecology
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