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AN ASSESSMENT OF THE SIDE EFFECTS OF SWITCHING
FROM ONE ORAL CONTRACEPTIVE TO ANOTHER

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Abstract

AN ASSESSMENT OF THE SIDE EFFECTS OF SWITCHING
FROM ONE ORAL CONTRACEPTIVE TO ANOTHER

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Side effects associated with three oral contraceptives were evaluated in a study in which women were switched to Norlestrin 1 from either Ovrал (64 subjects) or Norinyl 1/50 (26 subjects). In the cycle prior to crossover, breast discomfort was more frequent among Norinyl users than among Ovrал users. The prevalence of all other reported side effects was not significantly different for Norinyl and Ovrал. The crossover to Norlestrin did not significantly change the numbers of patients reporting side effects. By the end of the third Norlestrin cycle, rates of all side effects were similar for women who were switched from either Ovrал or Norinyl.

I. INTRODUCTION

Although oral contraceptives are relatively safe and highly effective for most women, minor side effects occur with varying frequency especially during the initial months of use^{5 11}. Breakthrough bleeding or spotting, nausea, and headaches are the reasons frequently given for discontinuing use of these agents.

Some investigators have reported that rates of side effects increase when women are switched from one brand of oral contraceptives to another^{10 12}. However, in two double-blind, crossover studies^{5 11} in which subjects were switched from one type of oral contraceptive to another, there was no significant increase in the proportions of women with side effects when the two oral contraceptives contained comparable doses of estrogen and progestagen. Whether changes in rates of side effects are true responses to a change in the dose or type of estrogen or progestagen, or whether they are a psychological response to the change in medication has not been adequately evaluated.

The present study was undertaken to assess the effects of switching from either Ovral* or Norinyl 1/50** to Norlestrin 1***. It was initiated because of reports from the Philippines¹ of an increase in side effects following a change from either Ovral or Norinyl to Norlestrin.

*Wyeth brand of dl-norgestrel, 0.50 mg, and ethinylestradiol 0.05 mg per tablet.

**Syntex brand of norethindrone, 1.0 mg, and Mestranol, 0.05 mg, per tablet.

***Parke-Davis brand of norethindrone acetate, 1.0 mg, and ethinylestradiol, 0.05 mg per tablet.

II. MATERIALS AND METHODS

Ninety women who attended the Planned Parenthood Clinic of Seattle volunteered to participate in the study to evaluate the effects of switching from either Norinyl (26 subjects) or Ovral (64 subjects) to Norlestrin. After admission to the study, current users of Norinyl or Ovral were continued on three further cycles of their oral contraceptive; subjects who were not currently using an OC were assigned to either Norinyl or Ovral. All subjects were requested to return to the clinic after three cycles. At the second clinic visit, all subjects were given a three-cycle supply of Norlestrin.

Throughout the study period a nurse (MJL) contacted all subjects every 10 to 15 days and, using a checklist of 15 side effects commonly associated with oral contraceptives, questioned each one about specific side effects and their duration.

SUBJECTS

Of the 64 Ovral and 26 Norinyl users, 70.3% and 76.9% respectively were using these contraceptives before they were admitted to the study. Distributions by age, parity, marital status, and race were similar for the two groups of women. When women from both groups were combined, most were less than 25 years of age (83.3%), single (73.3%), white (83.3%), and nulliparous (85.5%).

Definitions and Criteria

Breakthrough bleeding was defined as bleeding requiring the use of sanitary pads or tampons during the period of drug ingestion. Comparisons

of the frequency and durations of side effects reported by subjects while taking either Norinyl or Ovrал and while taking Norlestrin were analyzed using standard statistical tests (t-tests, chi-square test of homogeneity) and by the methods of Grizzle, et al⁸. Only the significance levels (p-values) of the tests are presented.

III. RESULTS

Side Effects of Ovrал and Norinyl

The proportions of Ovrал and Norinyl users with specific side effects during the cycle preceding the crossover to Norlestrin are presented in Table I. Breast discomfort occurred more frequently ($p < .05$) among Norinyl users. The mean duration of breast discomfort was not significantly different ($p > .10$) for the two groups of subjects. There were no significant differences ($p > .10$) between the two groups of subjects in the rates for all other side effects listed.

Side Effects After Crossover to Norlestrin

The proportions of subjects with specific side effects were generally lower for the first Norlestrin cycle than for the last Ovrал cycle before crossover (Tables I and II). There were no significant differences ($p > .10$) between the reported rates of any side effects as a consequence of changing from Ovrал or Norinyl to Norlestrin.

The crossover from Norinyl to Norlestrin was associated with no significant changes ($p > .10$) in the proportions of patients with specific side effects (Tables I and II).

When the women had completed the third Norlestrin cycle, the proportions of women with side effects (Table II) were similar ($p > .10$) for women who switched from Ovral and women who switched from Norinyl.

During the three Norlestrin cycles, only one woman (a previous Ovral user) discontinued use of Norlestrin. The reason for discontinuing was persistent episodes of breakthrough bleeding. Although the reported rates of breakthrough bleeding during the cycle prior to crossover to Norlestrin were not significantly different among Ovral and Norinyl users, there did appear to be some differences in the patterns of breakthrough bleeding both before and after the crossover (Figure 1). However, the number of subjects in this study was too small to assess the statistical significance of these differences. During the first Norlestrin cycle, breakthrough bleeding was more frequently reported by women who were switched from Ovral. However, by the completion of the third Norlestrin cycle, patterns of breakthrough bleeding were similar for women switched from either Ovral or Norinyl.

IV. DISCUSSION

Based on the results of this small study of 90 subjects, there is no clinically significant increase in the occurrence of side effects after subjects were switched from either Ovral or Norinyl to Norlestrin. Although the proportions of both Ovral and Norinyl users who reported side effects after switching to Norlestrin increased, these increases were not statistically significant ($p > .10$). By completion of the third Norlestrin cycle, the rates of side effects were similar for both groups of women who were switched to Norlestrin.

Ovral and Norlestrin 1 contain the same estrogen (ethinylestradiol, 0.05 mg per tablet) and Norinyl 1/50 contains 0.05 mg mestranol per tablet. Goldzieher^{4 6 7} has shown that these two estrogens are approximately equipotent. The three oral contraceptives contain different progestins: Ovral, dl-norgestrel; Norinyl 1/50, norethindrone; Norlestrin 1, norethindrone acetate. Based on the occurrence of systemic side effects and on other criteria for assessing the relative potency of progestins, dl-norgestrel is the most potent and norethindrone and norethindrone acetate are about equipotent². However, the alleged progestin-associated side effects such as fatigue, decreased libido, and increased appetite and the advantage of diminished breakthrough bleeding associated with higher progestational potency were not apparent in this study. The observed differences in the levels of side effects may be due to factors other than the relative potency of the steroids contained in each of the three oral contraceptives evaluated.

Generally, the reported levels of side effects were higher than in other studies^{3 5 9 11}. This certainly reflects the method used for obtaining information on side effects; all subjects were contacted every 10 to 15 days and "probed" about whether specific side effects had occurred. "Probed" investigations usually yield much higher levels of side effects.

Since this study is based on side effects reported by only 90 women attending the Seattle Planned Parenthood Clinic, the results may not be applicable to other populations, especially those in developing nations. Differences in the nutritional status, health, and psychological makeup

of different populations are likely to have a direct bearing on subjective phenomena such as side effects. Additional studies in various populations will be required to evaluate the incidence of side effects associated with different steroidal contraceptives and the effects of switching from one agent to another.

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12. Unpublished data from Siriraj Hospital, Bangkok, Thailand.

TITLES AND LEGENDS

Tables I and II: Titles on tables.

**Figure 1: Title: Percent of Women With Breakthrough Bleeding by Day
of Contraceptive Cycle.**

Legend: None

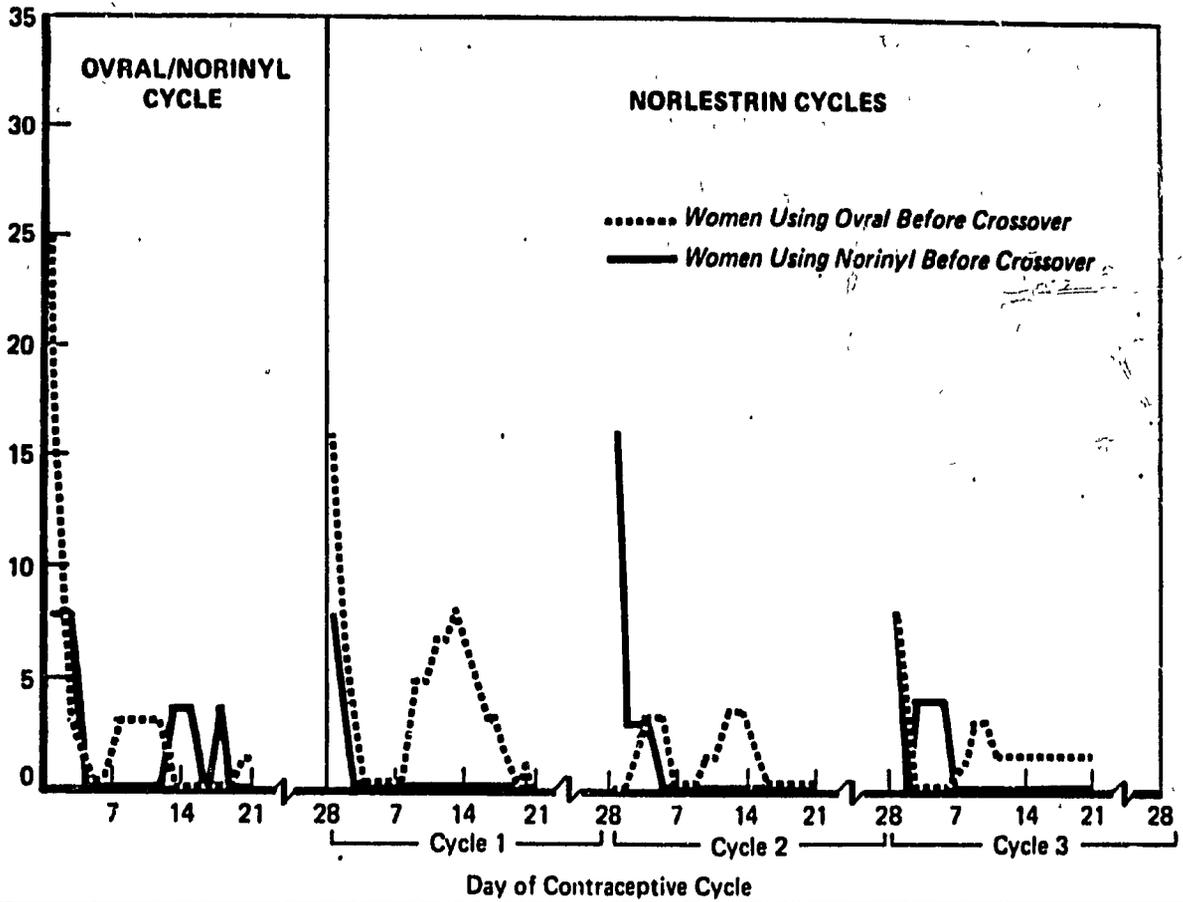
TABLE I
PROPORTION OF SUBJECTS WITH SIDE EFFECTS FOR
OVRAL AND NORINYL 1/50 USERS IN
CONTRACEPTIVE CYCLE BEFORE CROSSOVER TO NORLESTRIN

Side Effects	Ovral (N = 64) %	Norinyl 1/50 (N = 26) %
Breakthrough bleeding	28.1	15.4
Nausea	6.3	7.7
Vomiting	6.3	3.8
Headaches	23.4	36.9
Breast discomfort	12.5	38.5
Abdominal bloating	28.1	23.1
Fatigue	14.1	23.1
Depression	23.4	11.5
Appetite		
Increased	10.9	7.7
Decreased	4.7	7.7
Acne		
Increased	25.0	23.1
Decreased	10.9	7.7
Libido		
Increased	10.9	11.5
Decreased	1.6	0.0
Vaginal discharge	25.0	26.9

TABLE II
PROPORTION OF SUBJECTS WITH SIDE EFFECTS AND
AVERAGE DURATION OF SIDE EFFECTS FOR OVRAL AND NORINYL 1/50 USERS
AFTER CROSSOVER TO NORLESTRIN 1

Side Effects	Norlestrin Cycle After Crossover From Ovrал		Norlestrin Cycle After Crossover From Norinyl 1/50	
	1	3	1	3
Breakthrough bleeding	23.4	15.9	11.5	15.4
Nausea	17.2	14.3	19.2	15.4
Vomiting	7.8	6.3	0.0	3.9
Headaches	20.3	20.3	19.2	26.9
Breast discomfort	9.4	17.2	23.1	7.7
Abdominal bloating	25.0	20.3	30.8	26.9
Fatigue	14.1	20.3	11.5	19.2
Depression	15.6	12.7	7.7	11.5
Appetite				
Increased	14.1	7.8	7.7	3.8
Decreased	9.4	12.5	3.8	3.8
Acne				
Increased	25.0	10.9	30.8	15.4
Decreased	15.6	4.7	3.8	0.0
Libido				
Increased	7.8	6.3	3.8	0.0
Decreased	7.8	7.8	3.8	3.8
Vaginal discharge	31.3	18.8	26.9	15.4

Percent of Women



Percent of Women

