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THE PROBABILITY OF SIDE EFFECTS WITH OVRAL, NORINYL 1/50 AND NORLESTRIN 1

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ABSTRACT

This report provides specific information on the prevalence rates of the most common side effects during the first 3 cycles of use of 3 combination oral contraceptives (OCs) containing 50 mcg estrogen. The probabilities of a symptom occurring for the first time, or persisting once present, during the initial cycles of OC use are given for each of the 3 combined OCs.

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CONTRACEPTION

INTRODUCTION

Although not as harmful as the less frequent but more serious complications associated with oral contraceptive (OC) use, the occurrence of unpleasant side effects and uncertainty regarding their persistence are the reasons most frequently cited by patients for discontinuing oral contraception. Despite strong clinical opinions on the subject, little quantitative information exists, based on comparative studies, of the probabilities of experiencing specific side effects for different OC preparations and of the persistence of such side effects into subsequent cycles. The present analysis was undertaken to provide this information.

MATERIALS AND METHODS

In this study, Norinyl 1/50, Norlestrin 1 and Ovral* were each randomly assigned to groups of 160 healthy women who had consented to participate in the study. Women included in the study were regularly menstruating, of reproductive age, had not used hormonal contraception for at least 3 months prior to enrollment, and had no contraindications to OC use. For each woman, a standardized history, physical examination, and set of laboratory tests were obtained at the beginning and end of the study. Each woman also was telephoned every other week by a public health nurse who inquired specifically about the presence or absence of a variety of side effects. Neither the patient nor the nurse was aware of the specific OC brand which a given patient was assigned, thus avoiding a potential source of bias in the reporting or recording of the desired information. Further details have been reported previously by Ravenholt *et al.* (1) regarding the methodology and demographic characteristics of the patients in the study which provided the data base for the present analyses.

Since the purpose of this paper is to provide quantitative information to the physician about probabilities of experiencing specific side effects and of their continuing into the subsequent cycles, the results are presented in two sets of tables. The first set (Table I) indicates the probabilities of *ever* having a side effect in the first 3 cycles of OC use and thus relates to all women initiating OC use. The second set of tables (Tables II-IV) gives for each of the 3 OCs the probabilities of (a) specific symptoms occurring in the second and the third cycles of OC use for those subjects who had the symptom in the first cycle and (b) specific symptoms occurring in the second or third cycles among woman who did not have the symptom in the first or second cycle.

*Norinyl 1/50 (norethindrone 1.0 mg and mestranol 0.05 mg), Norlestrin 1 (norethindrone acetate 1.0 mg and ethinyl estradiol 0.05 mg), and Ovral (dl-norgestrel 0.5 mg and ethinyl estradiol 0.05 mg).

RESULTS

Shown in Table I are the percentages of women who reported experiencing each of 10 specific symptoms during any of the first 3 cycles of use of the 3 OCs studied. The relatively high rates of side effects reported are related in part to the study design used in which the women were contacted every 2 weeks and specifically questioned about the presence or absence of each of these symptoms.

The most commonly reported symptoms were acne and breast discomfort. The rate of breakthrough bleeding associated with Ovral use in the first 3 cycles (16.6%) was significantly ($p < 0.05$) lower than that associated with the use of either Norinyl (46.0%) or Norlestrin (51.7%). The differences in other individual side effects were not significantly different ($p > 0.05$) among the 3 OC types. Except for breakthrough bleeding, Norlestrin users generally reported a lower incidence of side effects in the first 3 cycles compared with Ovral and Norinyl users.

Once a woman experiences a given side effect, a frequently asked question is how likely is this side effect to persist if OC use is continued. The answer to this question is given for the 3 OCs under study in Tables II-IV. These tables give the probability of a woman experiencing a side effect in the second and in the third cycle of OC use, given that the woman had already experienced the side effect in the first cycle, for each of 10 side effects. In addition, the probability that a woman will have a particular side effect in the second or third cycle, given that she did not experience it in the previous one or two cycles, is also given.

The probabilities of a side effect's being experienced in the second or third cycles, given that it was experienced in the first cycle, are given in Tables II-IV, for Ovral, Norinyl and Norlestrin users, respectively. Overall, for all 3 OCs, the probabilities significantly ($p < 0.05$) decreased from the second to the third cycles.

The probabilities that a side effect from Ovral will occur in the second or third pill cycle among women who did <u>not</u> experience that symptom in prior cycles are also shown in Table II (third and fourth columns). In each instance, the probabilities are significantly lower ($p < 0.05$) than the corresponding probabilities where the symptom had been experienced in a previous cycle. For example, the chance of continuing to experience one of the side effects studied ranged from 0.20 to 0.60 in the second cycle and 0.13 to 0.39 by the third cycle, while the chance of first starting to experience symptoms in the second cycle ranged from 0.09 to 0.31 and in the third cycle from 0.04 to 0.15. Similar results were obtained for Norinyl users (Table III) and Norlestrin users (Table IV).

Table I. Percent of women reporting symptoms in any of the first three cycles of oral contraceptive (OC) use, by OC type.

Symptom	Ovral % (N=150)*	Norinyl % (N=145)*	Norlestrin % (N=147)*	p-Value**
Acne	70.7	70.3	63.9	NS
Breast discomfort	63.3	67.5	59.9	NS
Nausea	61.3	52.4	58.5	NS
Abdominal bloating	47.3	44.8	52.4	NS
Headache	53.3	44.1	44.2	NS
Fatigue	49.3	48.2	38.2	NS
Depression	44.7	45.5	38.1	NS
Irritability	47.3	37.9	37.4	NS
Vaginal discharge	40.0	45.5	34.7	NS
Breakthrough bleeding	16.6	46.0	51.7	<0.01

*Number of women followed-up by telephone contact.
**NS = not significant, $p > 0.05$.

Table II. Conditional probabilities of experiencing symptoms in subsequent cycles: Ovral.

Symptom	Probability of Symptom Given Presence of Symptom in the First Cycle		Probability of Symptom Given Absence of Symptom in the Previous Cycle	
	2nd Cycle	3rd Cycle	2nd Cycle	3rd Cycle
Acne	0.59	0.35	0.31	0.14
Breast discomfort	0.60	0.29	0.18	0.06
Nausea	0.47	0.23	0.20	0.09
Abdominal bloating	0.59	0.39	0.19	0.15
Headache	0.33	0.20	0.19	0.15
Fatigue	0.33	0.18	0.19	0.09
Depression	0.36	0.16	0.12	0.08
Irritability	0.52	0.29	0.23	0.04
Vaginal discharge	0.43	0.23	0.15	0.09
Breakthrough bleeding	0.20	0.13	0.09	0.07

Table III. Conditional probabilities of experiencing symptoms in subsequent cycles: Norinyl 1/50

Symptom	Probability of Symptom Given Presence of Symptom in the First Cycle		Probability of Symptom Given Absence of Symptom in the Previous Cycle	
	2nd Cycle	3rd Cycle	2nd Cycle	3rd Cycle
Acne	0.50	0.25	0.34	0.10
Breast discomfort	0.60	0.53	0.21	0.13
Nausea	0.31	0.10	0.14	0.12
Abdominal bloating	0.46	0.30	0.07	0.04
Headache	0.35	0.13	0.10	0.09
Fatigue	0.32	0.16	0.18	0.15
Depression	0.31	0.24	0.17	0.09
Irritability	0.38	0.10	0.08	0.03
Vaginal discharge	0.36	0.11	0.16	0.11
Breakthrough bleeding	0.50	0.16	0.08	0.08

Table IV. Conditional probabilities of experiencing symptoms in subsequent cycles: Norlestrin 1.

Symptom	Probability of Symptom Given Presence of Symptom in the First Cycle		Probability of Symptom Given Absence of Symptom in the Previous Cycle	
	2nd Cycle	3rd Cycle	2nd Cycle	3rd Cycle
Acne	0.48	0.30	0.22	0.07
Breast discomfort	0.65	0.29	0.25	0.10
Nausea	0.36	0.10	0.12	0.15
Abdominal bloating	0.48	0.20	0.19	0.07
Headache	0.33	0.10	0.12	0.11
Fatigue	0.33	0.09	0.12	0.11
Depression	0.34	0.11	0.11	0.08
Irritability	0.41	0.09	0.13	0.08
Vaginal discharge	0.46	0.32	0.16	0.07
Breakthrough bleeding	0.36	0.18	0.15	0.11

COMMENTS

The present analysis was undertaken to obtain data regarding the pattern of occurrence of side effects and their conditional probabilities of continuation associated with 3 of the most widely prescribed 50-mcg estrogen dose combination OCs. Despite the extensive literature on side effects of OCs, information on such conditional probabilities has not been available previously.

In this study, the high rates of occurrence of all side effects (Table I) were undoubtedly related to the fact that each patient was questioned about each specific side effect every other week. Despite these relatively high rates and because of the comparative nature of the study, the conditional probabilities shown in Tables II-IV are minimally affected and may be regarded as reliable estimates that can be used to predict the persistence or future occurrence of various side effects among OC users.

Few significant differences were found in the pattern of side effects occurring in the first 3 cycles of use of the different OC preparations. The exception to this was the significantly lower rate of breakthrough bleeding associated with Ovral use than with the other 2 preparations. For most symptoms, once a woman has become symptomatic, the likelihood of persistence of the symptom into the third cycle is one in three or less. Thus, if this woman continues to take the OC, the symptom will resolve within 2 months in more than two thirds of such cases.

In short, the data support the clinical opinion that side effects experienced on initiation of OC use should not prohibit its continuation because "most symptoms will disappear as the patient becomes accustomed to the hormonal preparation" (2).

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