The 20 Microgram Ethinyl Estradiol plus 150 Microgram Desogestrel[(1)] Pill Multicenter Study on 235 Women for 6 Months

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[(1)]Mercilon® (Organon Company)

The efficacy and clinical tolerance of a new oral contraceptive, Mercilon (20 mcg ethinyl estradiol + 150 mcg desogestrel) were studied in 235 women for 1305 cycles. This was an open, non-comparative, multicenter study, lasting 6 cycles, carried out by 37 French physicians.

- No pregnancies were observed.
- Cycle control was satisfactory (only 5.5% of the women in the study discontinued this contraceptive due to irregular bleeding).
- The incidence of subjective side effects, particularly breast tenderness, which is known to be estrogen-dependent, was very low.
- The Mercilon total continuation rate at 6 months was high for a low-dose oral contraceptive: 86%.
- Because of the clinical characteristics and excellent metabolic tolerance already shown, this 20 α EE pill can be prescribed as the first-line choice to all women seen for contraception and having no contraindications for combination oral contraceptives.

Key words: pill, 20 mcg ethinyl estradiol, desogestrel, French multicenter clinical study, 235 women, efficacy, cycle control and continuation rate are good.

INTRODUCTION

The composition of oral contraceptives (OCs) has evolved considerably since the 1960s when the contraceptive pill first appeared, by decreasing the side effects and increasing the acceptability of this contraceptive method.

Three main changes should be noted:

- Reduction in estrogen dose from 150 mcg ethinyl estradiol (EE) per pill to 40 or 30 mcg; the latter are known as low-dose combined oral contraceptives (COCs). There are several reasons for this reduction in estrogen:
  - the frequency of thromboembolic complications of OCs is estrogen dose-dependent;
  - the changes in hemostasis associated with COCs are estrogen-dependent;
  - many of the side effects sometimes reported by pill users such as breast tenderness and nausea are attributable to the estrogen compound.

Since this reduction in estrogen doses (from 100 to 30 mcg EE), the frequency of venous thromboembolic incidents has decreased.

- Reduction in progestin dose, because the frequency of cardiovascular and cerebrovascular

episodes from OCs depends on the progestin dose; and the metabolic changes, particularly lipid changes, sometimes observed in pill users also depend on the progestin dose. This reduction in progestin dose is illustrated in the three-phase pills.

• Development of a new generation of progestins with powerful progestin properties and low androgenic activity that are metabolically very well tolerated. Three progestins used in oral contraception appear among these new progestins: desogestrel (DSG), gestodene, and norgestimate.

It was logical to try to reduce the estrogen dose still further by comparison to the low-dose combined pills already in existence; and, for example, to use pills with 20 mcg of EE in the hope of further increasing the acceptability of oral contraceptives and further reducing the vascular risk of this contraception.

This was first tried by combining a first-generation progestin, norethisterone (EE 20 mcg + norethisterone acetate 1 mg: Preston S. N.,1972; Bounds W. et al., 1979), then with a second-generation progestin, norgestrel (NG) (EE 20 mcg + NG 300 mcg or EE 15 mcg + NG 400 mcg or EE 20 mcg + NG 500 mcg: Arnt I.C. et al, 1977).

However, the first 20 mcg or 15 mcg EE pills were rapidly abandoned due to inadequate contraceptive efficacy and/or poor cycle control resulting above all in unacceptably irregular bleeding.

The appearance of the third-generation progestins (1982, desogestrel) led to the possibility of once more developing COC pills containing less than 30 mcg EE.

A contraceptive preparation containing 150 mcg desogestrel and 20 mcg ethinyl estradiol (Mercilon® was the subject of a European multicenter study involving 1684 women and 25,970 cycles.

This study showed excellent contraceptive efficacy, satisfactory cycle control, and a minimal incidence of side effects.

My goal is to report the results of a French multicenter study of this ultra-low dosed COC pill already on the market in six countries.

MATERIALS AND METHODS

The goal of this study was to confirm the efficacy and acceptability of Mercilon, a single-phase low-dose combined oral contraceptive containing 20 mcg ethinyl estradiol and 150 mcg desogestrel (1). It was an open-label con-comparative multicenter study in which 37 French physicians collaborated:

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The study lasted 6 months, i.e., 6 Mercilon cycles.

The patients were seen at the screening visit, after 3 Mercilon cycles, and after 6 cycles. During the cycles, the patients filled out a bleeding diary indicating the days on which the pill was taken, the withdrawal bleeding days, and any irregular bleeding.

At each office visit, the investigator reported in the case report form:

- cycle control data (using the diary that the patient was to bring back at each visit);
- weight;
- blood pressure;

- any side effects reported by the patient (effects occurring in the first 3 months and in months 4 to 6);
- reasons for dropout if any.

Patients eligible for the study were supposed to be fertile, in good health, and aged over 30* (but 17 women under the age of 30 were nonetheless included in this study). They were to have none of the classical COC contraindications, no history of significant cycle disturbances on oral contraceptives, not have used contraception by injected progestogen within the past six months or oral progestogens (micropill or macrodosed progestogens for the last three months, due to a possible atrophic effect on the endometrium), nor have given birth or had a termination within the 3 months prior to entering the study. Also, women who smoked more than 10 cigarettes a day were excluded.

One tablet of this pill (20 mcg ethinyl estradiol + 150 mcg desogestrel) was to be taken each day, preferably at the same time of day, for 21 days. The first tablet was taken on the first day of the period. When the first strip was completed, a drug-free interval of 7 days had to elapse after which the women started a new strip. Women who were switching the oral contraceptive were to observe a drug-free interval of 7 days (or 6 as the case may be) before starting this new combined pill.

Evaluation of cycle control was based on highly precise definitions

• *Withdrawal bleeding*: bleeding occurring in the drug-free interval.

• *Irregular bleeding*: bleeding occurring during the 21 days in which the contraceptive was taken; but bleeding starting on or after the 18th day of taking Mercilon and continuing for the drug-free interval was counted as withdrawal bleeding, as the women themselves considered this type of bleeding as their normal "periods."

In the case of bleeding beginning before the 18th day and continuing during the rest days, the bleeding days were counted as irregular bleeding until day 21 and as withdrawal bleeding starting on day 22.

• *Spotting*: irregular bleeding requiring only one protection item per day.

• *Metrorrhagia*: irregular bleeding requiring the use of at least 2 protection items per day.

All the patients were counted in the cycle control analysis, including those who skipped pills or had a history of metrorrhagia.

CHARACTERISTICS OF PATIENTS AT SCREENING

The analysis was conducted on 235 patients.

The number of cycles studied was 1305.

The patient characteristics at the screening visit (235 patients) are listed in Table 1.

Table 1: Characteristics of patients at screening (235 patients)

Age	M + sd	35.3 ± 5.4
	< 30	7.3%
	30 to 35	46.1%
	36 to 40	30.8%
	> 40	15.8%
Parity	Nulliparous	24.3%
	Multiparous	75.7%
Smoking	0	76.4%
	< 5 cigarettes/day	10.3%
	> 5 cigarettes/day	13.3%
Contraception before screening		
	None	20.9%
	Oral	59.1%
	IUD	14.9
	Local	5.1%
Cycle characteristics before Mercilon		
	Cycle duration (d)	28.3 ± 1.9

* In the European multicenter study on 1684 women totaling 25,970 use cycles, cited by D. Serfaty (1), 387 women (23.0%) were less than 20 years of age. The Pearl index was 0.05 when this pill was taken correctly. The efficacy of Mercilon has hence been demonstrated for all ages.

	M ± sd	
	Regular cycle	93.2%
	Irregular cycle	6.8%
	Length of period (d)	4.4 ± 1.4
Menstruation volume		
	Low (1-2 protect/d)	28.5%
	Moderate (3-4 protect/d)	60.0%
	High (≥ 5 protect/d)	11.5%
Irregular bleeding during pre-screening cycle		
	Spotting	8.1%
	Metrorrhagia	2.1%
	Total	10.2%
Systolic blood pressure (mm Hg) m ± sd		120.3 ± 10.7
Diastolic blood pressure (mm Hg) m ± sd		71.1 ± 7.3
Weight (kg)		57.2 ± 8.3

RESULTS

Evaluation of an oral contraceptive is based on three criteria: efficacy, cycle control, and tolerance.

Efficacy

In terms of efficacy, no pregnancies were observed even though 1 to 3 pills had been skipped in 5.9% of the cycles studied.

Cycle control

The results obtained for cycle control are fully comparable to those of other low-dose oral contraceptives.

Withdrawal bleeding was present in 98.7% of the cycles studied, and only 2 patients interrupted the study before the 6th cycle for "amenorrhea." The rates of amenorrhea per cycle are listed in Table 2.

Table 2: % Amenorrhea per cycle

	n	%
Cycle 1	233	1.7%
Cycle 2	228	1.7%
Cycle 3	223	1.3%
Cycle 4	211	0.5%
Cycle 5	203	1.5%
Cycle 6	201	1.0%

Table 3: Duration of withdrawal bleeding

	n	m ± sd
Before Mercilon	235	4.4 ± 1.4
Cycle 1	229	4.1 ± 1.7
Cycle 3	220	3.9 ± 1.3
Cycle 6	198	3.9 ± 1.3

Overall, withdrawal bleeding was shorter ($p < 0.0000$ – Student's T test for matched series) and of the same or less volume than the cycle preceding Mercilon ingestion (Tables 3 and 4); these two effects are generally considered beneficial by the patients.

Table 4: Menstruation volume relative to pre-screening cycle

Menstruation volume	↘	Unchanged	↗
Cycle 1	32.7%	51.9%	15.3%
Cycle 3	34.9%	49.5%	15.6%
Cycle 6	36.9%	50.5%	12.6%

Table 5: Incidence of irregular bleeding.

	Cycle 1 n = 235	Cycle 3 n = 225	Cycle 6 n = 201
Metrorrhagia	3.4%	0.0%	1.0%
Spotting	17.6%	14.3%	6.5%
Metrorrhagia + spotting	2.9%	1.3%	1.0%
Total	23.9%	15.6%	8.5%

Table 6: Overall percentage of cycles with irregular bleeding

Metrorrhagia	1.4%
Spotting	10.7%
Metrorrhagia + spotting	1.4%
Total	13.5%

With respect to irregular bleeding, it should be noted that all the patients were counted in the evaluation of this criterion, including those who had irregular bleeding before their inclusion (10.2%) and those who reported having skipped Mercilon pills. The incidence of these irregular bleedings is listed in Tables 5 and 6.

As is normal with low-dose oral contraceptives, this incidence decreases as the cycles progress; moreover, it should be noted that the great majority of these irregular bleedings is represented by spotting. The main factor in evaluating irregular bleeding is its acceptability; with this new combination pill, acceptability is high, as only 13 patients out of 235, or 5.5%, stopped taking the pill during the study or after completing the 6 months due to metrorrhagia and/or spotting.

Tolerance

This multicenter study looked at clinical tolerance of this contraceptive preparation containing only 20 mcg of ethinyl estradiol. The side effects occurring in the first 3 months of the pill and between months 4 and 6 were gathered.

Table 7 lists the main side effects reported. To be noted is the high frequency, before the contraceptive studied was taken, of breast tenderness (acknowledged to be estrogen-dependent) (17.4%), headache (20.8%), and nervousness (14%).

The benefits of reducing by 33% the estrogen dose in EE 20 mcg + DSG 150 mcg are clearly evident when we look at the change in these symptoms, particularly breast tenderness, in patients who had them before starting this contraceptive (Figure 1).

Over half these symptoms disappeared in the first three months of switching to this new contraceptive.

Weight is a very important parameter in acceptability of an oral contraceptive. Weight gain is a very frequently invoked reason for stopping the pill. If we consider the patients who completed the study and whose weight was known prior to screening and after 6 months of taking this pill, there was no significant change in weight (Student's T test for matched series). Only one patient (0.4%) stopped this pill before the end of the study due to weight gain.

As in the case of weight, the blood pressure numbers did not change statistically significantly (Student's T test for matched series) during the study. Only one woman (0.4%) stopped this pill before the 6 months were up due to increased blood pressure.

Dropouts

Of the initial 235 patients, 33 withdrew from the study before the end of the 6th cycle, namely 14.0%. Of these 33, 25 patients stopped treatment due to intolerance, namely 10.6%.

The reasons for these dropouts are listed in Table 8.

The side effects causing this new pill to be dropped before 6 months, in 25 patients, are shown in Table 9. (One patient may have more than one side effect.)

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