Advances in Contraception, 1998; **14**: 15–26.

Contraceptive efficacy and acceptability of a monophasic oral contraceptive containing 30 μg ethinyl estradiol and 150 μg desogestrel in Latin-American women

M.R. COMPARATO (1), J.A. YABUR (2) and M. BAJARES (3)

(1) Hospital Juan A. Fernandez, Buenos Aires, Argentina
(2) Servicio de Ginecologia y Reproduccion Humana, Hospital Jose Ignacio Baldo, Caracas, Venezuela
(3) Servicio de Ginecologia, Hospital Clinico Universitario, Caracas, Venezuela

Abstract

Contraceptive efficacy, subject acceptability (cycle control, side-effects, acne score and weight gain) and blood pressure of a monophasic oral contraceptive containing 30 μg ethinyl estradiol plus 150 μg desogestrel (Marvelon) were assessed in an open-label 6-cycle multicenter study in Argentina (7 centers) and Venezuela (5 centers). Of the 407 participating women, 389 (95.6%) completed six cycles of treatment, providing data for a total of 2383 cycles. No pregnancies occurred during the course of the study, confirming the high contraceptive reliability of Marvelon. Cycle control was excellent; the duration of withdrawal bleeding decreased during consecutive treatment cycles and the incidence of spotting and breakthrough bleeding was low. The desogestrel/ethinyl estradiol combination was well tolerated and the incidence of minor side-effects, which was already low in the first treatment cycle, in most cases decreased during the subsequent cycles. The preparation was effective in reducing pre-existing acne, whereas it did not induce clinically relevant changes in blood pressure and body weight.

Marvelon was shown to provide effective oral contraception, with good tolerance and excellent cycle control in Latin-American women.

Introduction

Since the introduction of oral contraceptives (OCs) in the 1960s, many efforts have been made to minimize side-effects and risks while providing optimal contraceptive

efficacy and cycle control. To that end, the daily dosage of ethinyl estradiol has been reduced and more selective progestogens have been developed with fewer effects on hemostatic and metabolic parameters [1].

The first of these highly selective progestogens available was desogestrel, a 19-nortestosterone derivative which combines strong progestogenic properties with a low intrinsic androgenic activity. In 1981, Marvelon was introduced, a combined monophasic OC containing 150 μg desogestrel in addition to 30 μg ethinyl estradiol. The preparation has been proven to be a very reliable and well-tolerated OC with no adverse effects on lipid metabolism and a positive effect on hyperandrogenic skin disorders [1–7]. This was confirmed in several clinical trials, involving over 44 000 women and a total of more than 190 000 cycles [8].

Marvelon was introduced in Argentina in 1984 and in Venezuela in 1985. The majority of studies with the preparation have been carried out in Europe and North America in Caucasian women. The objective of the present study was to confirm the findings of those trials regarding the contraceptive efficacy, cycle control, and acceptability of Marvelon in a multicenter study in Latin-American women.

Subjects and methods

Study design

The study was designed as an open-label multicenter study with a duration of 6 treatment cycles in 400 women who requested contraception. The outcome of the use of a monophasic combined OC containing 30 μg ethinyl estradiol plus 150 μg desogestrel (Marvelon, N.V., Organon, Oss, The Netherlands) was evaluated. The study was performed in 7 Argentinian and 5 Venezuelan study centers (see acknowledgements for details). Some of the results from the Argentinian arm of the study have been published locally [9].

Selection of subjects

Subjects eligible for enrollment were healthy women of fertile age with regular ovulatory cycles who were exposed to the risk of pregnancy. Exclusion criteria were contra-indications to OC use, complete breast-feeding, the regular use of drugs that could impair the reliability of OCs, and poor physical condition (e.g. malnutrition). The study comprised both 'pill starters' (i.e. women who had not used any combined OC in the 2 months preceding study entry) and 'pill switchers' (i.e. women who were switching from another combined OC preparation). The study period encompassed a baseline assessment and six consecutive treatment cycles. The OC was administered orally in a 28-day cycle regimen, i.e. 21 days on medication followed by a tablet-free interval of 7 days, during which a withdrawal bleeding was expected.

Assessments

All subjects included in the trial gave their voluntary informed consent to participate in the study, which was performed in accordance with local rules and regulations. Before treatment was started, information was obtained about the medical history, contraceptive history, menstrual characteristics, acne and presence of complaints that could be regarded as side-effects of OC use during the trial. In addition, blood pressure and body weight were measured.

Each woman was instructed to record daily tablet intake, the characteristics of any vaginal blood loss, and any side-effects on a diary card. For vaginal bleeding, the following definitions were used:

- Withdrawal bleeding: vaginal bleeding starting in the tablet-free period;
- Irregular bleeding: any vaginal bleeding starting during the tablet-taking period, which is further divided into:
  - Spotting: vaginal bleeding requiring no or at most one sanitary towel per day
  - Breakthrough bleeding: vaginal bleeding requiring two or more sanitary towels per day

The women returned to the investigators after 1, 3 and 6 cycles of OC use. At these follow-up visits, blood pressure and body weight were measured and information was obtained on the occurrence of side-effects in the previous cycle and the presence and severity of acne. These data together with the data on the diary cards were filled out on follow-up record forms and evaluated. For rating of the severity of acne, the following definitions were used:

- Absent: no sign of acne;
- Mild: less than 6 comedones or papules (no inflamed lesions);
- Moderate: 6–15 comedones or papules and/or no more than 3 inflamed lesions;
- Severe: more than 15 comedones or papules and/or more than 3 inflamed lesions.

All data obtained during the study were recorded on case report forms. A descriptive analysis was made and means and standard deviations were calculated. To analyze changes in body weight throughout the study period, Student's *t*-test was used. Wilcoxon matched-pairs signed-ranks test was used for evaluation of blood pressure and acne score. All statistical analyses were performed using the SAS statistical package.

Results

Demographic data

The baseline demographic data are summarized in Table 1. Of the participating women, 76.4% were 'pill starters' and 23.6% were 'pill switchers'. As could be expected, the average age and the number of previous pregnancies of the 'pill switchers' group was slightly higher than that of the 'pill starters'. The contraceptive method used by one subject preceding the trial remained unknown and was only included in the 'total' group. Of the 407 women (2383 cycles) who entered the trial, 213 subjects (1287 cycles) had been recruited in Argentina and 194 (1096 cycles) in Venezuela. In total 389 (95.6%) subjects completed the six cycles of OC use.

Table 1. Demographic features (mean ± SD)

	Pill starters (n = 311)	*Pill switchers (n = 95)*	*Total (n = 407)*
Mean age (years)	25.3 ± 4.9	26.3 ± 4.7	25.5 ± 4.9
Age distribution (%)			
< 20 y	14.2	7.4	12.5
20–24 y	32.2	30.5	31.7
25–29 y	34.1	33.7	33.9
30–34 y	16.1	23.2	17.9
> 34 y	3.5	5.3	3.9
Menarche (age)	12.4 ± 1.2	12.6 ± 1.3	12.5 ± 1.2
Gravida	1.2 ± 1.4	1.5 ± 1.4	1.3 ± 1.4
Para	1.1 ± 1.3	1.4 ± 1.4	1.1 ± 1.3
Cycle length (days)	29.3 ± 3.0	28.3 ± 1.7	29.1 ± 2.8
Duration of withdrawal bleeding (days)	4.4 ± 1.3	3.7 ± 0.9	4.3 ± 1.2
Amount of withdrawal bleeding (score 1–3)	2.1 ± 0.5	1.9 ± 0.4	2.0 ± 0.5
Body weight (kg)	56.0 ± 6.7	56.4 ± 7.5	56.1 ± 6.9

Efficacy

None of the women became pregnant during the six cycles of treatment with Marvelon, indicating excellent contraceptive efficacy. Compliance throughout the study was good, with 142 cycles (6.0%) in which one or more tablets were forgotten. The majority of women who omitted pills were 'pill starters' (81.0%), and most of them missed only one tablet per cycle, mainly in cycle 1.

Table 2. Incidence and duration of menstrual/withdrawal bleeding before and during treatment

	Pill starters			*Pill switchers*		
Cycle	*n*	*Incidence*[a]	*Duration*[b]	*n*	*Incidence*[a]	*Duration*[b]
0	311	–	4.4 ± 1.3	95	–	3.7 ± 0.9
1	305	98.1	3.3 ± 0.8	95	100	3.4 ± 1.2
2	301	98.4	3.2 ± 0.8	92	97.9	3.2 ± 0.8
3	298	98.0	3.1 ± 0.7	90	95.7	3.2 ± 0.8
4	295	98.3	3.1 ± 0.7	92	98.9	3.1 ± 0.6
5	292	98.3	3.1 ± 0.7	92	100	3.0 ± 0.7
6	290	98.0	3.0 ± 0.6	91	98.9	3.0 ± 0.6

[a]Percent of women; [b]days ± SD

Cycle control

Overall, the study OC had a beneficial effect on cycle control. The occurrence of withdrawal bleeding in the tablet-free period was reported in 98.3% of the cycles with no statistically significant difference between the 'pill starters' and the 'pill switchers' groups. As presented in Table 2, in both groups, the duration of the withdrawal bleeding while using Marvelon was shorter than the bleeding before treatment.

In Figure 1, the incidence of irregular bleeding, consisting mainly of spotting, before and during study medication is shown. As expected, there was an initial increase in the rate of irregular bleeding, but, already in the second treatment cycle, the rate was lower than before treatment. Breakthrough bleeding was relatively consistent across all cycles. Overall, the incidence of spotting and breakthrough bleeding was low, with slightly higher incidences reported by subjects receiving an OC for the first time than by those who were switching from another prescription. Some subjects in both groups reported more bleeding episodes during the first months of treatment (Table 3).

Acne

In Table 4, the occurrence and severity of acne before and during the trial are presented. During the consecutive treatment cycles a progressive improvement of acne was observed, and no subjects presented with severe acne after three cycles of treatment. This reduction of acne severity from the baseline score was highly significant ($p = 0.0001$). After six treatment cycles, acne had completely disappeared in 47.1% of the women who had presented with acne at baseline.

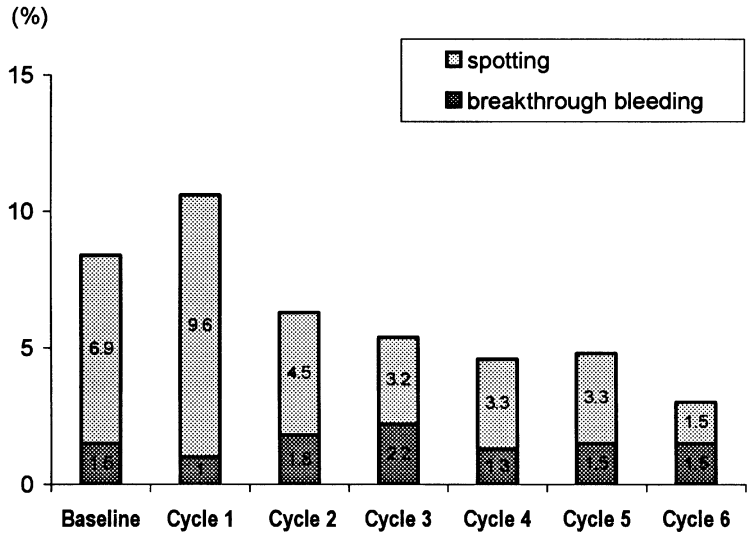

Figure 1. Incidence of total irregular bleeding (spotting and breakthrough bleeding) before and during treatment (% of women)

Table 3. Incidence of irregular bleeding before and during treatment (% of women)

	Absent		*Spotting*		*Breakthrough bleeding*		*More episodes*	
Cycle	*Pill starters*	*Pill switchers*	*Pill starters*	*Pill switchers*	*Pill starters*	*Pill switchers*	*Pill starters*	*Pill switchers*
0	92.0	90.5	6.4	8.4	1.6	1.1	–	–
1	85.9	90.5	10.9	5.3	1.0	1.1	2.3	3.2
2	92.2	94.7	4.6	4.3	2.0	0	1.3	1.1
3	94.1	95.7	3.6	2.1	2.3	1.1	0	1.1
4	94.3	98.9	4.3	0	1.3	1.1	0	0
5	94.6	96.7	3.4	2.2	1.7	1.1	0.3	0
6	95.6	100	2.0	0	2.0	0	0.3	0

Table 4. Presence and severity of acne before and during treatment (% of women)

	Acne score			
Cycle	*Absent*	*Mild*	*Moderate*	*Severe*
0	82.6	13.5	3.4	0.5
1	84.8	12.7	1.7	0.8
3	87.3	10.7	2.0	0
6	90.8	8.2	1.1	0

Table 5. Incidence of minor side-effects before and during treatment (% of women)

	Nausea		*Headache*		*Nervousness*		*Breast tenderness*	
Cycle	*Pill starters*	*Pill switchers*	*Pill starters*	*Pill switchers*	*Pill starters*	*Pill switchers*	*Pill starters*	*Pill switchers*
0	3.5	10.5	6.8	9.5	9.0	13.7	7.1	17.9
1	13.6	4.2	14.2	7.4	16.5	12.6	16.5	17.9
3	9.8	2.2	10.1	7.5	14.1	8.6	17.0	18.3
6	5.8	0	6.5	5.5	11.0	9.9	12.3	18.7

Side-effects

Marvelon was well tolerated by both 'pill starters' and 'pill switchers'. During the course of the study, no cases of deep venous thrombosis or other serious side-effects were observed and the overall incidence of minor side-effects during OC use was low. The frequency of the most commonly reported subjective side-effects (i.e. nausea, headache, nervousness and breast tenderness) is presented in Table 5. There were some differences between 'pill starters' and 'pill switchers'. Women of the 'pill starters' group reacted with an increased incidence of subjective side-effects in the first treatment cycle compared with pretreatment, whereas, in those switching from another preparation, the rate of occurrence had already decreased in the first cycle of use, except for breast tenderness (Table 5).

After six cycles of OC use, body weight was not affected in 93.8% of the participating women. A weight increase of >2 kg was reported in 5.1% of the women and, in 1.1%, a weight decrease of >2 kg had occurred. The changes in body weight were more pronounced in the group of women receiving an OC for the first time, as is

Table 6. Characteristics of body weight (kg) during the study

			Change in body weight (% of women)			
Group	*Cycle*	*n*	*Decrease > 2 kg*	*No change*	*Increase > 2 kg*	*Mean (SD)*
Pill starters	0	309	–	–	–	56.0 (6.7)
	1	307	1.6	98.0	0.3	56.0 (6.6)
	3	303	2.0	94.3	3.7	56.3 (6.7)
	6	289	0.4	94.0	5.7	56.5 (6.6)
Pill switchers	0	95	–	–	–	56.4 (7.5)
	1	94	0	100	0	56.4 (7.6)
	3	91	0	100	0	56.3 (7.3)
	6	91	3.3	93.4	3.3	56.4 (7.2)

shown in Table 6. Overall, a small but significant weight gain of 0.4 kg ($p < 0.001$) was found throughout the 6-month observation period. A small clinically non-relevant change in both systolic and diastolic blood pressure occurred after six cycles of treatment of 0.6 mmHg and 1.3 mmHg ($p < 0.001$), respectively (Figure 2). None of the subjects discontinued because of hypertension.

Eighteen women (4.4%) discontinued prematurely, of which 15 were 'pill starters' and 3 were 'pill switchers'. Reasons for early discontinuation were side-effects ($n = 7$), non-related medical reasons ($n = 5$), personal reasons ($n = 5$), and lost to follow-up ($n = 2$).

Discussion

The monophasic OC preparation containing 150 μg desogestrel plus 30 μg ethinyl estradiol was shown to provide reliable contraceptive efficacy, excellent cycle control, and a low incidence of side-effects during 2383 cycles of use in Latin-American women. A high degree of acceptance was evidenced by the high overall continuation rate for six cycles of 95.6%. The preparation was well tolerated, as indicated by the fact that only 7 out of 407 subjects (1.7%) discontinued prematurely because of side-effects. The frequency of missed pills was greatest in those women who were taking an OC for the first time. As expected, the incidence of intake errors fell rapidly throughout the course of the study. Despite the fact that pills were forgotten, no pregnancies occurred, confirming Marvelon's excellent contraceptive efficacy.

Major reasons for women to stop taking OCs are frequent irregular bleeding and heavy and/or prolonged withdrawal bleeding. Therefore, compliance will improve

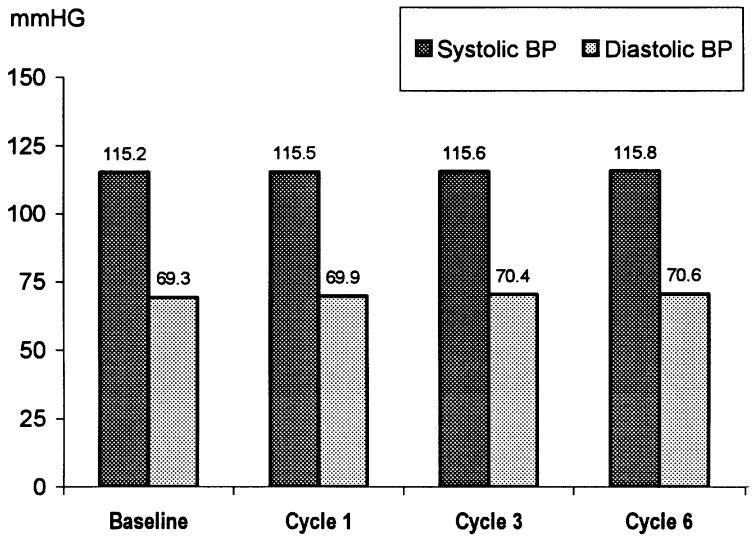

Figure 2. Systolic and diastolic blood pressure (mmHg) before and during treatment

when an OC provides good cycle control. With Marvelon, excellent cycle control was obtained and the incidence of irregular bleeding (spotting and breakthrough bleeding) was low. In accordance with the data obtained in previous OC trials [8], the rate of irregular bleeding was increased in the first cycle of use, to decrease again in subsequent cycles. In women switching from another OC preparation, a reduction in irregular bleeding was already observed in the first cycle of use. Moreover, the duration of the withdrawal bleeding was reduced with OC treatment.

Data from other studies generally indicate that the use of OCs is associated with an increased incidence of certain subjective side-effects, especially during the early months of pill use. In the present study, indeed, an increased incidence of nausea and headache in the first treatment cycle was reported by those women who had not previously used contraceptive steroids, whereas, in those who switched from another OC, the incidence of these side-effects was already lower in the first cycle compared with pretreatment levels.

From the current study as well as other studies [1,5,7,10], it can be concluded that combined OCs containing new-generation progestogens are beneficial in the treatment of hyperandrogenic skin disorders, such as acne vulgaris. It has been demonstrated that the monophasic desogestrel-containing combined OC induces an increase in sex-hormone-binding globulin levels, resulting in a reduction of free plasma testosterone concentrations, which, in turn, may lead to a significant improvement of pre-existing acne [7,8,10]. In our study, a significant improvement occurred within a few months of treatment, and, after six cycles of OC use, a complete remission of acne was found in almost 50% of the women presenting with acne at baseline.

Weight gain is an important concern of many women using OCs. After 6 cycles of treatment with Marvelon, a small increase in body weight of 0.4 kg was found. However, the fact that 93.8% of the participating women experienced no significant change in body weight and none of the women discontinued the study because of weight gain indicates that the effect on body weight is of no clinical relevance. This is in line with other trials, confirming the absence of any change in weight in the majority of women using the desogestrel/ethinyl estradiol preparation [2–6,10]. In those studies, occasional slight fluctuations in body weight were recorded, which were comparable with those found in non-pill users.

The safety of Marvelon, as assessed by changes in blood pressure, was confirmed by the absence of any premature discontinuations because of hypertension and the absence of any clinically relevant changes in blood pressure. This is in agreement with the data reported from previous OC trials, in which no or only small increases in mean blood pressure were observed, remaining within what is considered the normotensive range [1,8,11].

Conclusion

The consistently high contraceptive efficacy and the excellent profile regarding cycle control and acceptability of the monophasic desogestrel/ethinyl estradiol combination observed in other studies were confirmed in our study. Therefore, Marvelon can be considered a first-choice OC preparation in Latin-American women.

Acknowledgements

The authors acknowledge the contributions of Dr Monique op ten Berg, Mr Paul Geurts, Mrs Hanneke Nieuwenhuis, Dr Cecile Janssens and Dr Moki Vree (NV Organon, Oss, the Netherlands) in the design, data collection and reporting of the study. This study was financially supported by NV Organon, Oss, the Netherlands and was analyzed at the Department of Medical Statistics, University of Nijmegen, Nijmegen, the Netherlands.

The following investigators participated in the Argentinian part of this multicenter study: Dr Mario Comparato (Hospital Juan A. Fernandez, Buenos Aires), Dr Bautista Perez Ballester (Ceprim, Bahia Blanca), Dr Carlos Lopez (Instituto Modelo Privado de Capital, Cordoba), Dr Jesus Ernesto Olcese (Hospital Central de Capital, Mendoza), Dr German Bluvstein (Hospital Escuela de Capital, Corrientes), Dr Guillermo Focaccia (Hospital Escuela de Capital, Neuquen), and Dr Nestor Dron (Hospital Escuela, Universidad de La Plata, La Plata).

The following investigators participated in the Venezuelan part of this multicenter study: Dr Juan Yabur (Servicio de Ginecologia y Reproduccion Humana, Hospital Jose Ignacio Baldo, Caracas), Dr Ylayali Troconis (Servicia de Ginecologia, Hospital Vargas, Caracas), Dr Leo Acosta (Facultad de Medicina, Universidad Centro-Occidental Lisandro Alvarado, Barquisimeto), Dr Nelson Velasquez (Departemento

de Reproduccion Humana, Hospital Chiquinquira, Maracaibo), Mariela Bajares (Servicio de Ginecologia, Hospital Clinico Universitario, Caracas).

References

1. Newton JR. Classification and comparison of oral contraceptives containing new generation progestogens. Hum Reprod Update. 1995;1:231–63.
2. Rekers H. Multicenter trial of a monophasic oral contraceptive containing ethinyl estradiol and desogestrel. Acta Obstet Gynecol Scand. 1988;67:171–4.
3. Halbe HW, Cunha DC, Diaz J et al. Clinical experience in Brazil with a desogestrel-containing oral contraceptive. In: Halbe HW, Rekers H, eds. Oral Contraception into the 1990s. Carnforth: Parthenon Publishing Group; 1989:69–74.
4. Bruyniks N, Kovacs L, Rákóczi I. Multicenter study in Hungary with a 30 μg ethinylestradiol- and 150 μg desogestrel-containing monophasic oral contraceptive. Adv Contracept. 1994;10:175–85.
5. Koetsawang S, Charoenvisal C, Banharnsupawat L, Singhakovin S, Kaewsuk O, Punnahitanont S. Multicenter trial of two monophasic oral contraceptives containing 30 mcg ethinylestradiol and either desogestrel or gestodene in Thai women. Contraception. 1995;51:225–9.
6. Notelovitz M. Contraceptive efficacy and safety of a monophasic oral contraceptive containing 150 μg desogestrel and 30 μg ethinyl estradiol: United States clinical experience using a "Sunday start" approach. Fertil Steril. 1995;64:261–6.
7. Mango D, Ricci S, Manna P, Miggiano GAD, Serra GB. Clinical and hormonal effects of ethinylestradiol combined with gestodene and desogestrel in young women with acne vulgaris. Contraception. 1996;53:163–70.
8. Fotherby K. Twelve years of clinical experience with an oral contraceptive containing 30 μg ethinylestradiol and 150 μg desogestrel. Contraception. 1995;51:3–12.
9. Comparato M, Bluvstein G, Dron N et al. Estudio multicentrico sobre 1.278 ciclos, del anticonceptivo oral monofasico combinado etinilestradiol/desogestrel. Sinop Obs Gin. 1993;40:39–44.
10. Bilotta P, Favilli S. Clinical evaluation of a monophasic ethinylestradiol/desogestrel-containing oral contraceptive. Arzneimittelforschung. 1988;38:932–4.
11. Nichols M, Robinson G, Bounds W, Newman B, Guillebaud J. Effect of four combined oral contraceptives on blood pressure in the pill-free interval. Contraception. 1993;47:367–76.

Manuscript received 13 June 1997.
Accepted for publication 7 July 1997.

Resumé

Dans une étude multicentrique ouverte en Argentine (7 centres) et au Venezuela (5 centres), portant sur six cycles, on a évalué l'efficacité contraceptive, l'acceptabilité par le sujet (régulation du cycle, effets secondaires, contrôle de l'acné, gain pondéral) et la pression sanguine lors de l'administration d'un contraceptif monophasique contenant 30 μg d'éthinyl oestradiol et 150 μg de désogestrel (Marvelon). Sur les 407 femmes participant à l'étude, 389 (95,6%) ont terminé 6 cycles de traitement, produisant des données pour un total de 2383 cycles. Aucune grossesse n'est survenue dans le courant de l'étude, confirmant la grande fiabilité contraceptive du Marvelon. La régulation du cycle était excellente, la durée des écoulements sanguins diminuait durant les cycles de traitement consécutifs et l'apparition de microrragies et de flux sanguin était faible. La combinaison désogestrel/éthinyl oestradiol était bien tolérée et, dans la plupart des cas, l'incidence d'effets secondaires, qui était déjà faible lors du premier cycle de traitement, décroissait au cours des cycles successifs. Cette préparation s'est révélée utile dans une réduction de l'acné pré-existant, tandis qu'elle ne provoquait pas, du point de vue clinique, de changements importants de pression sanguine et de gain pondéral.

Le Marvelon a démontré que c'était un contraceptif oral utile, bien toléré et un excellent régulateur du cycle chez les femmes latino-américaines.

Resumen

La eficacia anticonceptiva, la aceptabilidad de las mujeres (control del ciclo, efectos secundarios, puntuación de acné y aumento de peso) y la tensión arterial de un anticonceptivo oral monofásico que contenía 30 μg de etinil estradiol y 150 μg de desogestrel (Marvelon) se evaluaron en un estudio abierto multicentro de 6 ciclos realizado en Argentina (7 centros) y Venezuela (5 centros). De las 407 mujeres participantes, 389 (95,6%) completaron seis ciclos de tratamiento, proporcionando datos relativos a un total de 2383 ciclos. No se registró ningún embarazo en el curso del estudio, hecho que confirmó la alta fiabilidad anticonceptiva de Marvelon. El control del ciclo fue excelente; la duración del sangrado por retiro disminuyó durante ciclos de tratamiento consecutivos y la incidencia de microrragia y sangrado por el tratamiento fue baja. La combinación de desogestrel/etinil estradiol fue bien tolerada y la incidencia de efectos secundarios, ya baja en el primer ciclo de tratamiento, disminuyó en la mayoría de los casos durante ciclos posteriores. La preparación fue eficaz para reducir el acné preexistente y no indujo cambios clínicamente pertinentes en la tensión arterial ni el aumento de peso.

Se demostró que Marvelon representaba un anticonceptivo oral eficaz, con buena tolerancia y excelente control del ciclo en mujeres latinoamericanas.