

# Clinical behavior of a cohort of adult women with facial acne treated with combined oral contraceptive: ethinylestradiol 20 µg/dienogest 2 mg

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**Abstract:** Acne vulgaris is the most common skin disease. It affects the young adult female population and generates great impact on physical and mental health. One of the treatments with good results for affected women is combined oral contraceptive pills (COCPs). The aim of this study was to determine the clinical effect of facial acne management with ethinylestradiol 20 µg/dienogest 2 mg in a cohort of Colombian adult women. A cohort of 120 female university students was followed for 12 months. These participants were enrolled in the Sexual and Reproductive Health Program of the Santiago de Cali University. This cohort admitted women between 18 and 30 years old who had chosen to start birth control with ethinylestradiol 20 µg/dienogest 2 mg COCPs, did not have contraindications to the use of COCPs, and had been diagnosed with acne. Monthly monitoring of facial acne lesion count was performed. Relative changes in facial lesion count were identified. At the end of follow-up, the percentage of reduction of lesions was 94% and 23% of women had a 100% reduction in acne lesions. In conclusion, the continued use of the ethinylestradiol 20 µg/dienogest 2 mg COCPs reduced inflammatory and non-inflammatory acne lesions in reproductive-age women between 18 and 30 years of age with no severe acne.

**Keywords:** skin diseases, acne vulgaris, reproductive control agents, contraceptive agents, female contraceptive agents, oral, hormonal

## Plain language summary

The study sought to measure the benefit of combined oral contraceptive therapy in acne, at concentrations which had not been studied in real-life conditions. Since acne is a disease of high prevalence and with a strong impact on the mental health of young people, this non-contraceptive benefit can be used as a treatment strategy for acne. University students who started contraceptive therapy with ethinylestradiol 20 µg/dienogest 2 mg and had mild-to-moderate acne were invited to participate in a follow-up study for 12 months. Each month, the contraceptive use was checked and the number of acne facial lesions was checked. At follow-up, the percentage of lesions reduction was 94% and 23% of women had a 100% reduction in acne lesions. It has been demonstrated in real-life conditions that for women of childbearing age with mild/moderate acne, in whom the use of combined oral contraceptive pills is not contraindicated and who wish to use them, continued use of ethinylestradiol 20 µg/2 mg dienogest is a beneficial alternative in the treatment of acne.

## Introduction

Acne vulgaris is the most common chronic inflammatory skin disease in adolescents and young adults. Prevalence reports of this condition range between 12% and 59%.<sup>1,2</sup> Approximately 80% of adult women have persistent acne, and approximately 20% have acne de novo, which appears between the ages of 21 and 25 years. Acne in adult

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women occurs mainly with facial lesions in mild and moderate forms of acne<sup>2</sup> and can have both physical and emotional consequences at medium and long term, such as the presence of scars, low self-esteem, depression, and anxiety – affecting women's quality of life.<sup>1</sup>

Acne is a disease of multifactorial origin, including factors such as follicular hyper-keratinization, *Propionibacterium acnes* colonization, increased sebum production, and mechanisms of innate or acquired inflammation.<sup>1,3</sup> From the hormonal point of view, androgens have a central role in the pathogenesis of the disease;<sup>4</sup> it is suggested that there is an increased sensitivity of hormone receptors expressed by sebocytes and keratinocytes as well as increased local androgen metabolism by enzymes.<sup>2,4</sup> In particular, women have different endogenous sources of androgens such as their ovaries, adrenal gland, and skin,<sup>5</sup> which permanently exposes them to the effects of androgens, which in turn may lead to persistent and very symptomatic typical acne lesions.

Understanding the pathophysiologic mechanism that operates in cases of female acne has led to proposing the use of combined oral contraceptive pills (COCPs), which have been used mainly as adjuvants,<sup>5–10</sup> in cases of papulopustular, nodular, and conglobate acne, in women diagnosed with hyperandrogenism, with menstrual cycle disorder.<sup>4</sup> These drugs have direct effects on androgen production and thus positive effects on the skin of women.<sup>4</sup> Several studies have shown the effect of COCPs in acne, even compared to antibiotics.<sup>6,11</sup> Specifically, progestogens have potent anti-androgenic activity and act by blocking androgen receptors in target organs, improving skin conditions mediated by androgen, such as skin spots and acne vulgaris action.

A large number of COCPs are available in Colombia, including ethinylestradiol 0.02 mg/dienogest 2 mg. Dienogest provides anti-androgenic properties useful in the treatment of symptoms of androgenization, seborrhea, hirsutism, endometriosis, and acne. In addition, low doses of estrogen, combined with different progestogens including dienogest, have a lower risk of developing adverse effects associated with this component.<sup>12–17</sup> Several clinical trials have documented the efficacy of this combination with percentages of improvement of 80% after six cycles of treatment and total response after 12 cycles;<sup>8,11,12</sup> however, it is important to document the effect of this treatment in a context of application in real-life conditions. Consequently, this study was developed with the aim of establishing the clinical effect of facial acne management with ethinylestradiol 20 µg/dienogest 2 mg, in a real-life cohort of Colombian adult women.

## Subjects and methods

An observational study was performed, following a cohort of female students between 18 and 30 years of age with a diagnosis of mild-to-moderate acne, whose treating physician prescribed ethinylestradiol 20 µg/dienogest 2 mg as birth control method. These women attended the Sexual and Reproductive Health Program of the Santiago de Cali University (Cali, Colombia).

A sequential convenience sampling was used, excluding women with a history of using other COCPs within 2 months prior to the start of this monitoring, patients in acne treatment with oral medications, overweight women, patients with a history of atopy or severe acne conglobata, and patients with the completion of gestation history within 2 previous months at study entry. The sample was calculated considering a decreased percentage of total facial acne lesions of 15%,<sup>6</sup> accuracy of the estimate of 95%, a 95% confidence, and a percentage of loss to follow-up of 20%. In this way, a final sample of 121 women was obtained. The protocol was approved by the ethics committee of the Santiago de Cali University, and all participants provided written informed consent. This study adhered to the principles of the Declaration of Helsinki and the National Ethical Framework: Resolution 008430 of 1993.

For inclusion of women in the cohort, the principal researcher, following the research protocol, invited to participate candidates who began their birth control with ethinylestradiol 20 µg/2 mg dienogest, after leaving birth control consultation with their treating physician. After explaining the information about the study and checking the inclusion and exclusion criteria, informed consent was obtained. Data such as demographics (age, ethnicity), personal history of hyperandrogenism, mental disorder, and family history with acne were collected. Tracking of acne lesions was made throughout a 12-month period, counting the number of inflammatory lesions (papules, pustules, and nodules) and comedones (both open and closed), in each of the face areas (forehead, chin, cheeks, and nose area). The counts were performed by a trained physician. In addition, patients were asked about the use of acne products, tobacco consumption, and side effects related to the treatment. To this end, an instrument designed by the research team, based on the relevant scientific literature,<sup>18–20</sup> was used.

For analysis, variables of interest were described according to their scale of measurement using frequencies or measures of central tendency and dispersion. Distribution behavior of quantitative variables (weight, height, body mass

index [BMI], and facial acne lesion count) was explored using the Shapiro–Wilks test.<sup>21</sup>

Reduction in acne lesions was evaluated using absolute and relative changes in facial lesion count of comedones, papules, pustules, and nodules and the sum of these at 6 and 12 months of follow-up. In addition, a bivariate analysis of the median relative difference by age group was performed by race, BMI, use of acne products, family history of acne and individual history of polycystic ovary, stress disorder or anxiety, and smoking; hypothesis test for the Wilcoxon test<sup>20</sup> was used. *p*-values <0.05 were considered significant. Analyses were performed using STATA 10.

## Results

A total of 120 women using ethinylestradiol 20 µg/dienogest 2 mg diagnosed with acne were recruited, and the percentage of nonparticipation was 12.4%. Follow-up median was 9 months (interquartile range [IQR]: 3–10). The percentage of loss to follow-up was 34.2% at 12 months (Figure 1). Most losses were voluntary retirements not related to either adverse events or the ethinylestradiol 20 µg/dienogest 2 mg taken, due to “not needing birth control” (two women), lack of time (two), travel (three), not interest (13), fear of taking pills (four), and family problems (one). On the other hand, four women were withdrawn having reached the improvement in acne lesions and only two due to no improvement. The median age of the study population was 21 years (IQR: 19–22). Regarding epidemiological and clinical characteristics that can affect the presence of acne lesions, it was found that 39% of participants were afro-descendants, 21% used non-prescribed topical presentations for acne, 12.5% had a history of estrogenic disease, and 22.5% had a history of smoking (Table 1). In addition, median weight was 57 kg, height 1.60 m, and BMI 22.2 kg/m<sup>2</sup> (Table 1).

As for the lesions associated with acne, the most frequently were open and closed comedones, papules were reported less frequently, and pustules and nodules were almost zero frequency. About 50% of women were diagnosed with 52 or more lesions at baseline, while at 6 months the range of lesions was between 6 and 27, and 4–29 lesions in the last month of follow-up (Table 2). The reduction in lesion counts appeared early in the follow-up (Figures 2 and 3). The reduction in the median was observed between start-up and the first month of use of ethinylestradiol/dienogest. After 6 months of follow-up, it was observed that no substantial changes in the median of lesions were presented, and it remained at low levels as those achieved in the first semester.

At least 50% of the population had decreases of at least 45 acne lesions up to the sixth month of follow-up, corresponding to 90% of the lesions from baseline. At the end of follow-up, the median of the relative difference increased by 3% (Table 3). Of the 74 women who attended the sixth-month follow-up appointment, 26% showed a reduction of 100% of lesions compared to their baseline at start-up and 23% showed a reduction of 90%–99%, 32% showed a reduction of 76%–89%, 16% showed a reduction of 50%–75%, and 3% showed a reduction between 30% and 49%. While at the end of follow-up of the 79 women who attended, 23% of them reduced all of the acne lesions. In 48% of women, lesions were reduced by 90%–99%, and in the remaining 28%, acne lesions were reduced by 50%–89% (Table 4).

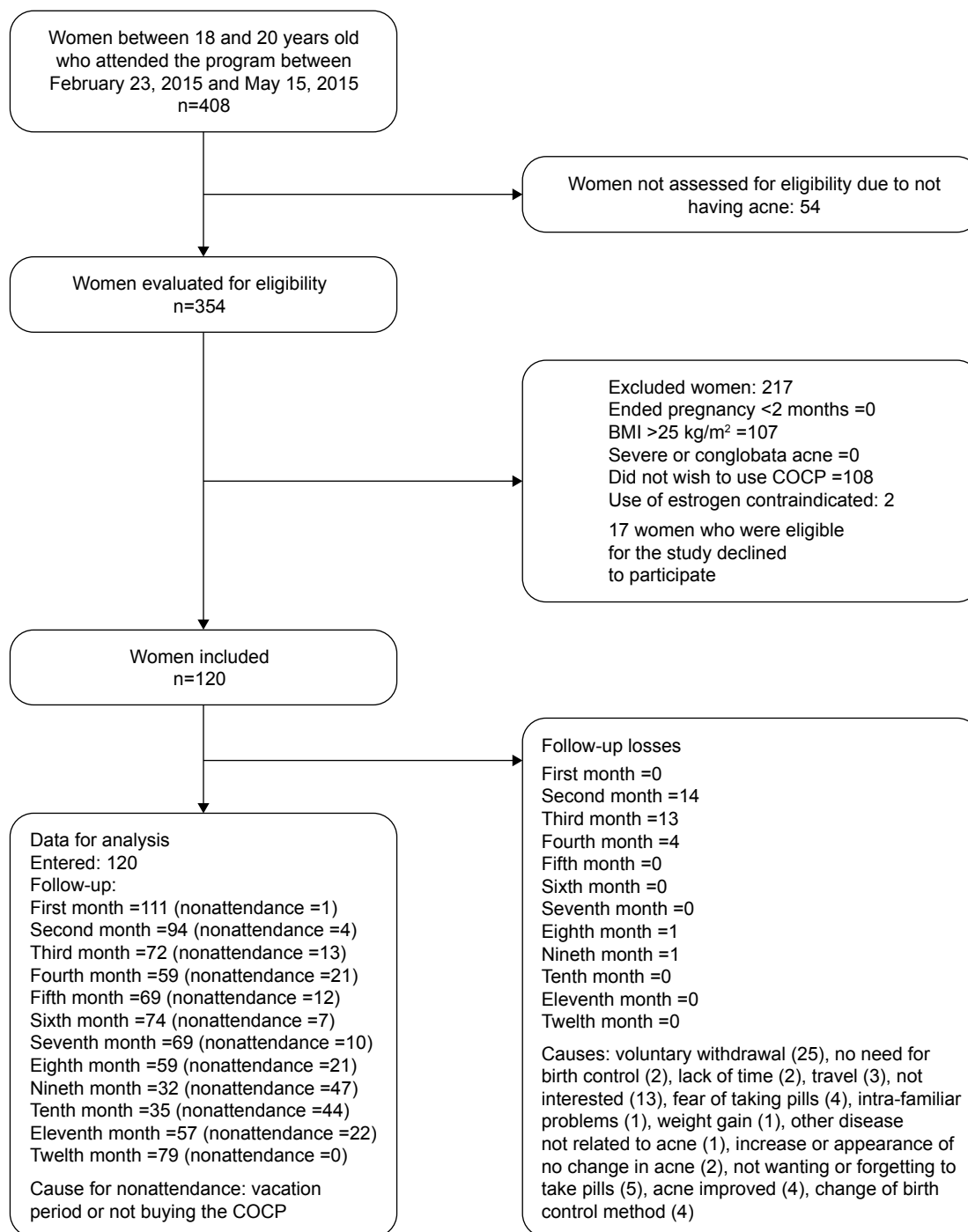
In a bivariate analysis, we found that the median relative difference in total acne lesions at 6 and 12 months of follow-up was greater than 80% for all groups. In the sixth month, the median relative difference was greater in women with no family history of acne compared to those without such a history, while at the end of follow-up the median relative difference was greater in non-African descendant women compared to that in African descendant. In addition, the data suggest that in women with no history of polycystic ovary and in those with a BMI of <20 kg/m<sup>2</sup> median relative difference was greater, but the findings were statistically significant (Table 5).

Regarding the adverse side effects, 24 women (20%) reported adverse events: eight had headaches, 15 women reported small breakthrough bleeding (spotting), and one woman reported weight gain.

## Discussion

This study showed statistically significant reductions in clinical symptoms regarding facial lesions of mild-to-moderate acne in women between 18 and 30 years old. This reduction was evident in the relative reduction in the total number of comedones, papules, and pustules. The results were 92% and 94% of lesion reduction at 6 months and at the end of follow-up, respectively. In addition, 80% of patients improved with a reduction of more than 75% at 6 months, with an increase of 12% at 12 months. Finally, 23% of women completed the follow-up without lesions.

These results are aligned to those described in an uncontrolled, Phase III, multicenter, clinical trial conducted in Poland, with ethinylestradiol 30 µg/dienogest 2 mg, in which women aged 18–35 years participated during 12-month follow-up. A total of 50 women with acne showed 80% improvement at 6 months, while at 12 months 54% showed



**Figure 1** Recruitment and follow-up flow diagram.

**Abbreviations:** BMI, body mass index; COCP, combined oral contraceptive pill.

improvement and 37% were cured.<sup>8</sup> Another multicenter, double-blind, randomized study, which included women between 16 and 45 years with mild-to-moderate acne, in which 525 patients received ethinylestradiol 30 µg/dienogest 2 mg, reported that the percentage of reduction in total lesions was  $-54.7\% \pm 26.3\%$  at 6 months and for inflammatory lesions was  $-64.6\% \pm 31.2\%$ ; the percentage of patients

with improvement was 90.2% at 6 months of follow-up and was superior to placebo.<sup>22</sup>

Other studies have similar results in the tendency of reducing lesions, although not to the same extent. In a Cochrane systematic review on the effectiveness of oral contraceptives in acne treatment, it was found that in 31 trials, contraceptives had an effect on the reduction in acne

**Table 1** Characteristics of the study population

Variables	At admission		Loss to follow-up	
	n=120	%	n=41	%
Age (years) <sup>a</sup>	21 (18–30)		20 (18–26)	
Race				
Non-African descendant	73	60.9	23	56.1
African descendant	47	39.1	18	43.9
Use of non-prescribed topical presentations for acne				
Yes	23	20.9	6	13.5
No	87	79.1	35	86.5
First-degree family history of acne				
Yes	78	65.0	24	58.5
No	42	35.0	17	41.5
Family history of vascular disease in the lower limbs				
Yes	66	55.5	23	56.1
No	53	44.5	18	43.9
Background estrogenic diseases (yes)	<b>15</b>	<b>12.5</b>	<b>2</b>	<b>4.9</b>
Hirsutism	1	0.8	0	–
Polycystic ovary	14	11.7	2	4.9
Mental disorders (yes)	<b>15</b>	<b>12.5</b>	<b>3</b>	<b>7.3</b>
Depression	2	1.6	0	–
Stress	10	8.3	3	7.3
Anxiety and stress	2	1.6	0	–
Depression and anxiety	1	0.8	0	–
Smoking history				
Yes	27	22.5	9	22.0
No	93	77.5	32	78.0
Current smoker				
No	26	96.3	41	100.0
Yes	1	3.7	0	0.0
Anthropometric mediated				
Weight (kg) <sup>a</sup>	57 (36–80)		55 (45–78)	
Height (m) <sup>a</sup>	1.60 (1.50–1.75)		1.60 (1.52–1.74)	
BMI (kg/m <sup>2</sup> ) <sup>a</sup>	22.2 (15.4–25.9)		22.5 (18.1–25.8)	

**Notes:** <sup>a</sup>Median (range). Values in bold indicate absolute and relative frequency of pathological antecedents in the total study population.

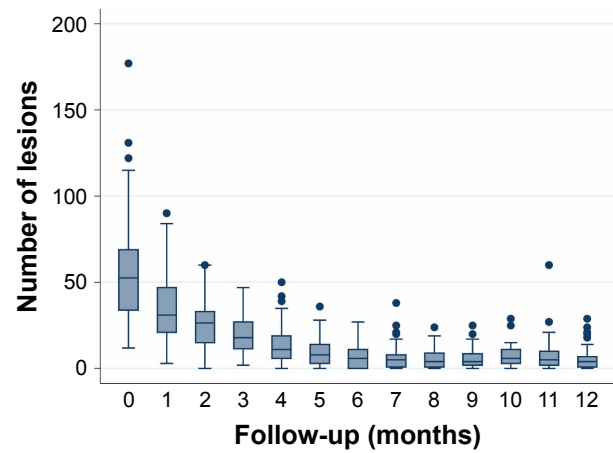
**Abbreviation:** BMI, body mass index.

lesions. Regarding dienogest, it was reported that the group using this compound reached a percentage of reduction in total lesions of –15.3 (95% CI –19.9 to –10.6) as for the inflammatory lesions.<sup>23</sup> Another study in women aged

**Table 2** Median and ranges of acne lesions in the study population

Follow-up (months)	Acne lesions				
	Comedones	Papules	Pustules	Nodules	Total
Baseline (n=120)					
Median	48	3	0	0	52.5
IQR	30–62	1.5–7.5	0–0	0–0	34–69
Range	6–160	0–32	0–5	0–3	9–177
6 (n=74)					
Median	5.5	0	0	0	6
IQR	0–10	0–0	0–0	0–0	0–11
Range	0–26	0–6	0–1	0–0	0–27
12 (n=79)					
Median	3	0	0	0	4
IQR	0–7	0–1	0–0	0–0	1–7
Range	0–20	0–9	0–2	0–1	0–29

**Abbreviation:** IQR, interquartile range.



**Figure 2** Distribution of the number of acne lesions in the study population by month of follow-up.

15–45 years with low doses of ethinylestradiol 20 µg and other progestogen (drospirenone 3 mg) also had an effect in reducing inflammatory and non-inflammatory lesions.<sup>24</sup> The ethinylestradiol dose of 20 µg was selected in combination with dienogest in this study.



**Figure 3** Photographs of the reduction in acne lesions.

**Table 3** Absolute and relative reduction in acne lesions in the study population during follow-up

Lesions	Baseline	Month		
	Median Lesions	1 Dif (%)	6 Dif (%)	12 Dif (%)
Comedones	48	-18 (37.8)	-41 (90.0)	-41 (94.2)
Papules	3	-2 (50.0)	-3 (100.0)	-3 (100.0)
Pustules	42	0 (100.0)	0 (100.0)	0 (100.0)
Nodules	0	0 (0.0)	0 (0.0)	0 (0.0)
Total lesions	52.5	-19 (40.3)	-45.5 (90.0)	-46 (93.2)

Note: Dif, difference.

Dienogest<sup>25</sup> has a significant anti-androgenic activity, which ameliorates the symptoms of acne vulgaris, hirsutism, seborrhea, alopecia, greasy skin, and hair. In addition, it inhibits ovulation, stabilizes the menstrual cycle and has anti-proliferative effects on the endometrium. As a combined oral contraceptive, dienogest/ethinylestradiol inhibits ovulation, improves menstrual cycle control, reduces the intensity and duration of menstrual bleeding, and improves dysmenorrhea. It is a well-tolerated product, which can induce adverse events such as breast pain, headache, intermenstrual bleeding, nausea, or vomit.<sup>25</sup> This study reported expected adverse events such as headache and intermenstrual bleeding, which was also reported as the most frequent in another study.<sup>22</sup>

In addition, the findings in the relative reduction in acne lesions in users of dienogest/ethinylestradiol are similar to those effects reported by other non-contraceptive drug used in acne treatment, such as isotretinoin. A study in patients with moderate-to-severe acne found that a 92% of women with moderate acne showed a reduction in lesions at sixth month.<sup>26</sup> In this study, the papule and pustule lesions reduced almost in total. However, this study was not intended to compare the COCP effects vs isotretinoin; because the participants included did not have severe acne, use of isotretinoin was not recommended.

**Table 4** Levels of relative reduction in acne lesions during follow-up

Relative reduction (%)	Follow-up	
	6 months, n=74 (%)	12 months, n=79 (%)
100	19 (25.7)	18 (22.8)
90-99	17 (23.0)	38 (48.1)
76-89	24 (32.4)	17 (21.5)
50-75	12 (16.2)	6 (7.6)
30-49	2 (2.7)	0 (0.0)
0-29	0 (0.0)	0 (0.0)

**Table 5** Median relative difference in total acne lesions at follow-up

Variables	Relative difference	
	6 months (n=74)	12 months (n=79)
Age (years)		
18-22	-89.7	-93.3
23-30	-89.8	-92.5
Race		
Non-African descendant	-90.8	-96.0*
African descendant	-86.6	-90.6
BMI (kg/m <sup>2</sup> )		
<20	-88.0	-96.9**
20-25	-90.6	-91.6
>25	-87.1	-92.9
Using non-prescribed product for acne		
No	-89.6	-93.2
Yes	-97.8	-93.4
Mental disorders (anxiety and stress)		
No	-89.5 <sup>†</sup>	-92.6
Yes	-97.8	-95.2
Polycystic ovary		
No	-90.4	-93.8 <sup>†</sup>
Yes	-87.5	-88.3
Family history of acne		
No	-94.3*	-94.2
Yes	-86.6	-92.0
Smoking history		
No	-95.4	-94.2
Yes	-88.3	-92.1
Attended contraception program >6 times		
No	-77.8	-90.1
Yes	-90.1	-93.3

Notes: \* $p < 0.05$ ; \*\* $p = 0.05-0.10$ ; <sup>†</sup> $p = 0.11-0.15$ .

Abbreviation: BMI, body mass index.

According to the guidelines for the management of acne vulgaris of the American Academy of Dermatology<sup>1</sup> and the European guide for the management of acne,<sup>27</sup> oral contraceptives are part of alternative treatment for women combined with other medicines for moderate acne, including papulopustular acne. However, this study shows evidence that women's oral contraceptive ethinylestradiol 20 µg/dienogest 2 mg may be considered for the treatment of mild and moderate comedonian and papulopustular acne or may be an alternative choice as an adjunct to topical treatment within the first line of treatment in women, as proposed by the Department of Family and Community Medicine at Hershey Medical Center and Mayo Clinic in the USA.<sup>28</sup>

Among the possible limitations of this study is that the percentage of loss to follow up was greater than 20%, while women who did not complete follow-up were similar to those who continued in the study (Table 1). Most losses were voluntary withdrawals; additionally, incomplete

tracking for all women, in particular those who were withdrawn because of improvement or no improvement, being more the “improved” group, may had an impact on an underestimation of the effect of COCPs in relative reduction in acne lesions. High attrition rates were also found in different studies.<sup>23</sup> In bivariate analysis, it was found that those women not being an afro-descendant and not having family history of acne are more likely to reduce lesions; however, different studies have demonstrated that there are no strong relationships between different age groups and family history acne.<sup>18</sup>

Another limitation was not having standardized the information about the topical products (self-prescribed) used for acne. However, bivariate analysis of reduced acne lesions and use of these products showed that the median of relative difference of lesions to the end of follow up was not different between users and nonusers of acne products. A strength of the study was tracking up to 12 months of oral contraceptive use; this identified that reducing lesions occurs mainly in the first 6 months and that in later periods the benefit is maintained. Further studies to estimate the probability and time to full or partial improvement of acne lesions and possible predictors are required.

## Conclusion

The continued use of COCPs, ethinylestradiol 20 µg/dienogest 2 mg, reduced inflammatory and non-inflammatory acne lesions in women in childbearing age with nonsevere acne, who participated in this study. For women with acne, in which this type of treatment is not contraindicated and who wish to use COCPs, ethinylestradiol 20 µg/dienogest 2 mg could be a beneficial alternative.

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The student appearing in Figure 3 has provided her written informed consent for this publication.

## Disclosure

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