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**Effect of oral contraceptive containing estradiol and nomegestrol acetate or ethynyl estradiol and chlormadinone acetate on primary dysmenorrhea.**

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**Conflict of interest**

All authors state explicitly that potential conflicts of interest don't exist.

All authors deny any financial relationship with biotechnology manufacturers, pharmaceutical companies and other commercial entities in relation to this original research study.

## Structured Abstract

**Objective:** To study the three cycles effect on primary dysmenorrhea of the monophasic 24/4 estradiol/nomegestrol acetate (E2/NOMAC) oral contraceptive and of a 21/7 ethinyl-estradiol/chlormadinone acetate (EE/CMA) association. The tolerability and the effect on metabolism and health-related quality of life of both preparations were also evaluated.

**Design:** Prospective observational cohort study.

**Setting:** Tertiary gynecologic center for pelvic pain.

**Patients:** Subjects with primary dysmenorrhea requiring an oral contraceptive, who spontaneously selected either E2/NOMAC (n=20) or EE/CMA (n=20).

**Main Outcome Measures:** Visual Analogue Scale (VAS) score for dysmenorrhea, Short Form-36 questionnaire for health-related quality of life, lipoproteins and days of menstrual bleeding (withdrawal bleeding during oral contraceptive).

**Results:** Mean age and BMI were similar between the two groups. The final analysis was performed on 34 women, 15 in E2/NOMAC and 19 in EE/CMA group. Compliance with treatment was significantly higher with EE/CMA (100%) than E2/NOMAC (75%) ( $p=0.038$ ). Both treatments significantly ( $p<0.0001$ ) reduced VAS of primary dysmenorrhea, similarly (E2/NOMAC by a mean of 74.7%, EE/CMA by a mean of 78.4%;  $p=0.973$ ). Only E2/NOMAC significantly increased SF-36 score ( $p=0.001$ ), both in physical ( $p=0.001$ ) and mental domains ( $p=0.004$ ). The mean number of days of menstrual bleeding was significantly reduced in E2/NOMAC group (from  $4.86\pm 1.20$  days to  $2.64\pm 1.59$  days,  $p=0.0005$  vs. baseline,  $p=0.007$  vs. EE/CMA group). BMI did not vary in either group. E2/NOMAC did not change lipoproteins and Apoproteins while EE/CMA increased total cholesterol ( $p=0.0114$ ), HDL-cholesterol ( $p=0.0008$ ), tryglicerides ( $p=0.002$ ), Apo-A1 ( $p=0.0006$ ) and Apo-B ( $p=0.008$ ) and a decrease of LDL/HDL ratio ( $p=0.024$ ).

## Conclusions

Both oral contraceptives reduced similarly dysmenorrhea, with E2/NOMAC also reducing withdrawal bleedings, and being neutral on lipid metabolism.

**Keywords:** primary dysmenorrhea, estradiol, ethinylestradiol, nomegestrol acetate, chlormadinone acetate, metabolism, side effects, quality of life, tolerability.

## **Main text**

### **Introduction**

#### *Background/Rationale*

Dysmenorrhea is a very common disease with a prevalence up to 90% of women in reproductive age[1]. It can be classified in, As the consequence of an absent or present underlying organic cause dysmenorrhea can be classified as primary or secondary, respectively. For women who wish contraception, combined oral contraceptives (COCs) are the preferential therapy for pain relief [2,3]. Among all COCs, the monophasic 21/7 regimen COC containing chlormadinone acetate (CMA) in a dosage of 2 mg combined with 30 mcg of ethinyl-estradiol (EE) seems to be one of the most effective preparation [2]. The effect of this particular preparation was widely demonstrated in large clinical trials, even when other hormonal contraceptives failed [5,6]. The relevant therapeutic effect has to be ascribed to CMA, which is capable to reduce prostaglandin synthesis by down-regulating the key enzyme cyclo-oxygenase 2 (COX-2)[4]. CMA also exerts partial glucocorticoid activity whose role in reducing dysmenorrhea [2], remains to be elucidated [4].

A new COC was recently introduced in the market, an association between 17 $\beta$  estradiol (E2) and norgestrel acetate (NOMAC) in a monophasic 24/4 regimen [7]. Recently, a pooled analyses of two large randomized, open-label studies reported that this preparation is associated with a significant reduction of menstrual pain and cramps when compared with a COC containing EE and drospirenone [8]. No other comparative data on dysmenorrhea is available between E2/NOMAC association and other COCs .

Main objective of this observational study is to verify the effect on primary dysmenorrhea of the monophasic 24/4 E2/NOMAC COC in comparison to that exerted by one of the most effective COC for the treatment of dysmenorrhea such as the monophasic 21/7 EE/CMA association. Secondary objectives of the study were to observe the effect on quality of life, tolerability, and metabolism of these two formulations.

## **Materials and methods**

This was a prospective observational mono-centric study, performed at a University Hospital service for chronic pelvic pain between January 2012 and June 2014. It was conducted in full accordance with the World Medical Association Declaration of Helsinki and it was approved by the Internal Review Board of our department,

Women suffering from menstrual pain from more than 12 months, of normal weight (BMI < 25), 18 to 35 years old, with no contraindication to the use of COC (WHO, 2009) [9], with regular menstrual cycles (cycle length between 26 and 30 days) and requiring an hormonal contraceptive were eligible for the study. Exclusion criteria were presumptive causes for secondary dysmenorrhea, demonstrated by a routine transvaginal scan of the pelvis (endometriosis/adenomyosis, fibroids, pelvic congestion syndrome, pelvic adhesions, etc.) or previous pelvic surgery (laparoscopy or laparotomy).

Counseling presenting the different hormonal contraceptives was performed to each woman, and those that spontaneously chose one of the two COCs under investigation, were enrolled into the study. Once enrolled each woman signed an informed consent for the use of her sensitive data. The COCs under investigation were a monophasic oral contraceptive containing 24 tablets of 1.5 mg E2 and 2.5 mg NOMAC + 4 placebo pills (Zoely®, Teva Italia, Milan, Italy) and a monophasic oral contraceptive containing 21 tablets of 30 µg EE and 2 mg CMA + 7 days of drug-free interval ((Lybella®, Alfa Wassermann Formenti, Milan, Italy). Each patient paid her own medicine as in real life condition.

The investigation consisted in two evaluations. Prior to treatment, during the early follicular phase of the menstrual cycle (3–5 days after spontaneous menstruation), anthropometric measures, a blood sample were collected. Intensity of dysmenorrhea as the “worst pain experienced during withdrawal bleeding days”, was evaluated by a 10 cm visual analogue scale (VAS), [10] and health related quality of life was evaluated by the Italian translation of the SF-36 questionnaire [11]. Height was measured barefoot and weight with the subject wearing light clothes without shoes. BMI (Kg/m<sup>2</sup>)

was calculated. All the measurements were repeated during the fourth cycle of COC administration, 3–5 days after withdrawal bleeding. During the 3 months women were requested to daily fill a diary reporting days of spotting and bleedings.

#### *Blood samples*

All blood samples were collected in the morning, after 12 h of fasting, into tubes placed on ice and immediately centrifuged. An aliquot of serum was immediately tested for glucose, and another aliquot was used for the determination of total cholesterol, HDL-cholesterol, total triglycerides, apoprotein-A1 (Apo-A1) and apoprotein-B (Apo-B).

Glucose was determined by enzymatic method (instrument Cobas c 501, Q3 Roche, Mannheim, Germany). Plasma total cholesterol and triglycerides were obtained by enzymatic colorimetric methods (instrument Cobas c 501, Roche), while HDL-cholesterol was measured by enzymatic colorimetric homogeneous methods (Instrument Cobas c 501, Roche). LDL-cholesterol levels were calculated by the Friedewald formula. Apo-A1 and Apo-B were measured by an immunonephelometric method Q3 (Instrument BN II, Siemens, München, Germany). All analyses were performed in the same laboratory.

#### *Data analysis*

Statistical analysis was performed using the statistical package StatView (version 5.01.98, SAS

Institute Inc, Cary, NC, USA). Data were analyzed by one of the authors (G. G.) who was blinded to the specific treatment of each woman. Intragroup comparison was performed by the t test for paired data or by the Wilcoxon signed-rank test for normal and non-normal distribution of data, respectively. For all analyses, the null hypothesis was rejected at a two-tailed p value <0.05. Results are expressed as the mean±standard deviation (SD).

#### Sample size determination

Sample dimension of the study group was calculated on possible menstrual pain VAS modification. A previous study showed COC-induced reduction of VAS score for menstrual pain of 4 points with a SD of 2 [12]. By setting type I error at 0.05 and type II error at 0.20, 4 subjects would have been necessary to document a significant variation within group. Similarly in order to evaluate non-inferiority of one treatment over the other we assumed that the reduction of VAS induced by either treatment was within 1 SD of the difference (i.e a value of 2). With these values a total sample size of 30 women was necessary to document a non-inferiority of one treatment vs. the other. Enrollment was closed when 40 women were enrolled, 20 for each group.

## **Results**

A total of 40 women were included in the study, equally divided 20 in E2/NOMAC and 20 in EE/CMA group. Mean age and BMI were similar between groups (Table 1). In the E2/NOMAC group 5 out of 20 (25%) women interrupted the treatment: 2 (10%) during the first cycle for continuous headache, 2 (10%) during the second cycle for bloating and increased appetite and 1 (5%) during the third cycle for occasional headache and bloating. One woman who initially requested EE/CMA did not start the treatment for lack of need of contraception. The final analysis was then performed on 34 women, 15 in the E2/NOMAC and 19 in EE/CMA group. During the first three cycles of treatment compliance with treatment was significantly greater with EE/CMA (100%) than E2/NOMAC (75%) ( $p=0.038$ ). Two women in E2/NOMAC group and one in EE/CMA experienced spotting during the first two cycles of treatment, that resolved in the third cycle.

### *Mean objectives*

Both treatments significantly ( $p<0.0001$ ) and similarly ( $p=0.973$ ) reduced VAS of menstrual pain (E2/NOMAC by a mean of 74.7%, EE/CMA by a mean of 78.4%) (Figure 1). Only E2/NOMAC significantly increased SF-36 score ( $p=0.001$ ), both in physical ( $p=0.001$ ) and mental domains ( $p=0.004$ ) (Table 1). The mean number of days of menstrual bleeding (withdrawal bleeding during COC treatment) did not change during EE/CMA but was significantly reduced by E2/NOMAC (from  $4.86\pm 1.20$  days to  $2.64\pm 1.59$  days,  $p=0.0005$  vs. baseline, and  $p=0.007$  vs. EE/CMA group) (Table1).

### *Secondary objectives*

With both treatments BMI did not change from baseline values (Table 1). The three cycles of treatment with E2/NOMAC did not change lipoprotein, tryglicerides, apoproteins and fasting glucose (Table 2). Conversely the three cycles of treatment with EE/CMA induced an increase of

total cholesterol (p=0.0114), HDL-cholesterol (p=0.0008), tryglicerides (p=0.002), Apo-A1 (p=0.0006) and Apo-B (p=0.008) and a decrease of LDL/HDL ratio (p=0.024), Lipid modifications were significant also vs. those induced by E2/NOMAC (Table 2).

## **Discussion**

### *Key results*

This observational study demonstrates that a monophasic oral contraceptive composed by 24 days of E2 and NOMAC is as effective as the monophasic 21 days association of EE/CMA in improving primary dysmenorrhea. This effect is associated with a reduction of days of menstrual bleeding only in subjects receiving E2/NOMAC. This pain improvement is associated with an increased quality of life particularly in those receiving E2/NOMAC. The effect of E2/NOMAC is neutral on weight and lipid metabolism, while EE/CMA increases total cholesterol, HDL-cholesterol, tryglicerides and apoproteins and decreases LDL/HDL ratio. The three-cycles compliance to treatment was major in subjects in treatment with EE/CMA.

### *Interpretation*

COCs, providing in general some relief from dysmenorrhea, are recommended as a first-line treatment option for women with primary dysmenorrhea who wish contraception. However, not all COC formulations are equally effective on this complaint.

EE/CMA seems one of the formulations providing a more pronounced relief of dysmenorrhea when compared with other hormonal contraceptive formulations [2,4-6]. Its efficacy is probably due to a direct effect of CMA on prostaglandin synthesis, by a down-regulation of cyclo-oxygenase 2 (COX-2) [2, 4] and a specific glucocorticoidal partial activity [2]. In one study [13], it was documented a EE/CMA is associated with a complete resolution of menstrual pain in 61.1% of switcher from other hormonal contraceptive formulations, especially in those women with frequent dysmenorrhea. In a prospective observational study carried out in 170 *healthy females, a progressive and significant reduction of mild and moderate dysmenorrhea was found in the EE/CMA group in comparison to EE/DRSP group* [14].

Extended regimen of COCs with a shorter hormone free interval (i.e.. 24/4- and 26/2-day regimens) were shown to be beneficial for menstrual cycle complaints, including menstrual pain [15]. In

general, a simple and shared hypothesis is that fewer days of menstrual bleeding might be associated with less dysmenorrheic pain.

It might be expected that E2/NOMAC with its shortened hormone free interval to 4 days would have a favorable effect on primary dysmenorrhea compared with an established COC used in a 21/7-day regimen. A potent anti-gonadotropin progestogen like NOMAC that can stabilize the endometrium combined with E2, is associated with a tolerable and acceptable bleeding profile and few symptoms attributable to the hormone-free interval, such as dysmenorrhea. Indeed, in the present study we showed that the length of menstrual bleeding is significantly shortened by E2/NOMAC.

Quality of life is associated with the intensity of pelvic pain: in particular it is inversely related to inter-menstrual pelvic pain but also, less stringently, to dysmenorrhea [10]. Accordingly the reduction of dysmenorrhea was associated with an improvement of health related quality of life that reached the significance in the E2/NOMAC group.

The effect of EE/CMA on lipoproteins was similar to what previously reported for this formulation, with an increase of HDL-cholesterol and triglycerides and a decrease of LDL/HDL-cholesterol [16,17].

E2/NOMAC was more neutral on lipid metabolism, with no modification of lipoproteins and apoproteins. These effects were in accordance with those reported in a previous larger randomized study where this formulation was compared to the EE/levonorgestrel association [18]. NOMAC does not give modification of lipoproteins also when given alone in a dose of 5 mg/day [19]. Lack of modification observed during E2/NOMAC may thus indicate the non-capability of the weak estrogen E2 to modify lipoprotein profile, as recently proposed for the other estradiol-based COC containing estradiol valerate and dienogest in a quadriphasic association [16].

### *Limitations*

One limitation of the study is the small sample of subjects included. Accordingly this can be considered a pilot study with preliminary results. The observational design is another important

concern of the study, with no randomization of subjects to the different treatment groups. However, no difference was found between the baseline characteristics of the women enrolled in the two groups and data report a situation of real life condition. The study was conducted in a single center in Caucasian women and the results cannot be generalized. For all these reason the results should be considered preliminary, but worthy to be explored in larger comparative investigations.

### *Conclusion*

The association of E2/NOMAC seems effective as the association of EE/CMA in reducing menstrual pain. This effect is associated with a greater reduction of menstrual bleeding and a reduced impact on lipid metabolism.

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**Tables MANCA LA VAS???? Due tabelle una per gli effetti uno per il metabolismo**

Table I Mean ( $\pm$ SD) parameters and scores of visual analogue scale for dysmenorrhea (VAS), and of the Short Form-36 questionnaire (SF-36) for health-related quality of life, observed in healthy women before and after 3 cycles of treatment with estradiol/nomegestrol acetate (E2/NOMAC; n=15) or ethinyl-estradiol and chlormadinone acetate (EE/CMA; n=19).

	E2/NOMAC (n=15)			EE/CMA (n=19)			p intergroup
	Before	During	P	Before	During	P	
Age yrs.	31.23 $\pm$ 6.93			31.07 $\pm$ 7.02			0.953
BMI	22.93 $\pm$ 4.28	19.65 $\pm$ 9.44	0.191	22.69 $\pm$ 3.69	22.93 $\pm$ 3.71	0.221	0.168
Menstrual bleeding length (n days)	4.86 $\pm$ 1.20	2.64 $\pm$ 1.59	0.0005	5.07 $\pm$ 1.07	4.57 $\pm$ 0.67	0.160	0.007
VAS Dysmenorrhea							
SF-36 total	68.52 $\pm$ 18.19	77.13 $\pm$ 12.81	0.001	68.60 $\pm$ 16.61	73.17 $\pm$ 21.13	0.416	0.523
SF-36 Physical	64.17 $\pm$ 22.30	73.91 $\pm$ 17.31	0.001	65.49 $\pm$ 17.79	76.16 $\pm$ 21.45	0.071	0.992
SF-36 Mental	71.18 $\pm$ 17.89	80.12 $\pm$ 11.09	0.004	66.80 $\pm$ 22.02	69.29 $\pm$ 23.71	0.706	0.420

Table 2. Mean ( $\pm$ SD) metabolic parameters observed in healthy women before and after 3 cycles of treatment with estradiol/nomegestrol acetate (E2/NOMAC; n=15) or ethinyl-estradiol and chlormadinone acetate (EE/CMA; n=19).

	E2/NOMAC (n=15)			EE/CMA (n=19)			p intergroup
	Before	During	P	Before	During	P	
T-Chol mmol/L	4.77 $\pm$ 0.44	4.59 $\pm$ 0.21	0.251	4.49 $\pm$ 0.65	5.06 $\pm$ 1.10	0.0114	0.006
HDL-C mmol/L	1.70 $\pm$ 0.44	1.60 $\pm$ 0.44	0.214	1.59 $\pm$ 0.29	1.92 $\pm$ 0.30	0.0008	0.0005
LDL-C mmol/L	2.90 $\pm$ 0.64	2.84 $\pm$ 0.36	0.650	2.74 $\pm$ 0.54	2.84 $\pm$ 0.91	0.545	0.194
LDL/HDL	1.70 $\pm$ 0.30	1.77 $\pm$ 0.45	0.547	1.72 $\pm$ 0.26	1.48 $\pm$ 0.42	0.024	0.031
T Chol/HDL	2.55 $\pm$ 0.72	2.87 $\pm$ 0.73	0.112	2.82 $\pm$ 0.34	2.63 $\pm$ 0.89	0.224	0.124
Triglycerides mmol/L	0.87 $\pm$ 0.28	0.75 $\pm$ 0.20	0.420	0.78 $\pm$ 0.32	1.48 $\pm$ 0.62	0.002	0.006
Apo-A1 g/dL	1.68 $\pm$ 0.18	1.57 $\pm$ 0.23	0.121	1.59 $\pm$ 0.23	2.07 $\pm$ 0.37	0.0006	0.002
Apo-B g/dL	0.84 $\pm$ 0.16	0.91 $\pm$ 0.13	0.436	0.65 $\pm$ 0.12	0.80 $\pm$ 0.24	0.008	0.321
Apo-A1/Apo-B	2.00 $\pm$ 0.37	1.72 $\pm$ 0.44	0.218	2.44 $\pm$ 0.40	2.59 $\pm$ 0.84	0.261	0.154
Fasting glucose mmol/L	4.88 $\pm$ 0.31	4.85 $\pm$ 0.63	0.881	5.09 $\pm$ 0.52	4.98 $\pm$ 0.54	0.274	0.616

## **Legend for Figures**

**Figure 1.** Intensity of primary dysmenorrhea expressed in visual analogic score in women before and after three cycles of treatment with E2/NOMAC or EE/CMA.

\*  $p < 0.0001$  vs. baseline

**Figure 2.** Length of menstrual bleeding expressed in number of days in women before and after three cycles of treatment with E2/NOMAC or EE/CMA.

\*  $p < 0.0001$  vs. baseline; \*\*  $p < 0.01$  vs. EE/CMA

Figure 1

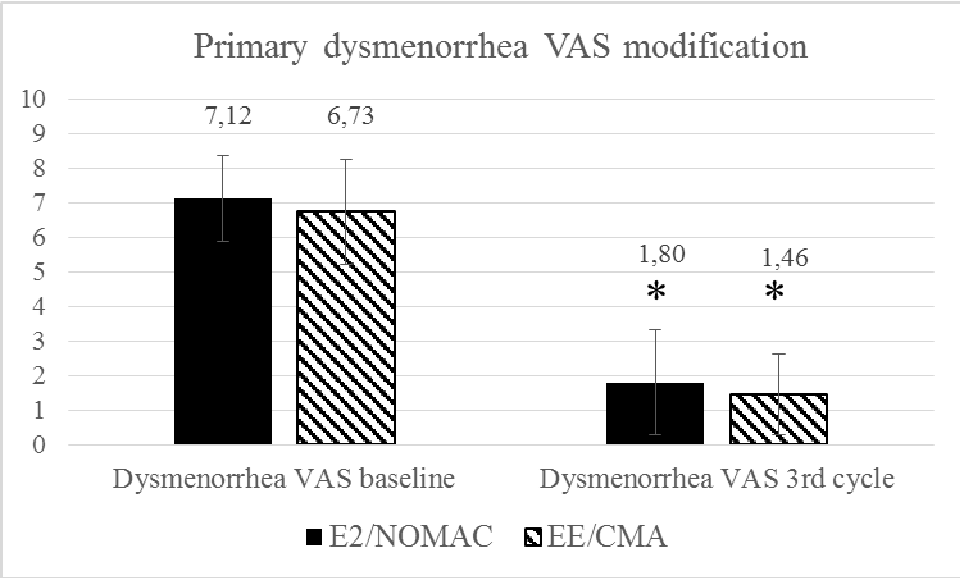


Figure 2

