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Comparative analysis of the effects of nomegestrol acetate/17β-estradiol and drospirenone/ethinylestradiol on premenstrual and menstrual symptoms and dysmenorrhea

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ABSTRACT

Objectives To compare premenstrual and menstrual symptoms in healthy women using nomegestrol acetate/17β-estradiol (NOMAC/E2) and drospirenone/ethinylestradiol (DRSP/EE) via the Moos Menstrual Distress Questionnaire Form C (MDQ-C).

Methods Women completed the MDQ-C at baseline and after completion of cycles 1, 3, 6 and 13, for the premenstrual (four days before most recent flow) and menstrual (most recent flow) phases in two randomized controlled trials. Treatment effects of NOMAC/E2 and DRSP/EE on the t-scores of eight MDQ-C symptom domains from 3522 women were examined, and the effects of both treatments on the score for cramps from 1779 women with moderate to severe cramps at baseline. Longitudinal data analysis methods were applied in both analyses.

Results NOMAC/E2 users experienced a significant improvement in Pain, Water Retention, Negative Affect, Impaired Concentration and Behaviour Change domain scores in the menstrual phase compared with DRSP/EE users (p ≤ 0.001 for all comparisons). However, Arousal (emotional and mental) scores worsened with NOMAC/E2 but not with DRSP/EE. Women with moderate to severe cramps experienced an improvement in the cramps score with NOMAC/E2 and DRSP/EE.

Conclusions NOMAC/E2 was effective in reducing most premenstrual and menstrual symptoms, and was associated with significantly greater improvements in many MDQ-C domain scores compared with DRSP/EE.

(ClinicalTrials.gov: NCT00413062 and NCT00511199).

KEYWORDS NOMAC/E2; DRSP/EE; MDQ; combined oral contraceptive; nomegestrol acetate; 17β-estradiol; drospirenone; ethinylestradiol
INTRODUCTION

Oral contraception remains a popular choice for birth control; new developments are focused on improvements in both efficacy and safety. Nomegestrol acetate/17β-estradiol is a recently developed monophasic combined oral contraceptive (COC) containing 1.5 mg of 17β-estradiol (E2) and 2.5 mg of the progestin nomegestrol acetate (NOMAC). Each 28-day package contains 24 days of hormones and four days of placebo tablets. E2 is bio-identical to endogenous estrogen but has less metabolic impact than synthetic ethinylestradiol (EE)1–3. EE has been shown to have effects on hepatic metabolism, including liver proteins, lipoproteins, acute phase reactants and coagulation factors2–4. In contrast, E2 induces little to no change in hepatic proteins5–7.

NOMAC is structurally similar to progesterone and exhibits 150% greater affinity for the progesterone receptor than progesterone itself8. The affinity of NOMAC for other steroidal receptors is extremely weak8. In humans, NOMAC treatment is associated with ovulation inhibition and suppression of estradiol, luteinising hormone and progesterone9.

Two randomised, one-year (13 cycle), open-label studies comparing a monophasic 24/4-day regimen of NOMAC/E2 with an established monophasic 21/7-day regimen COC, drospirenone/ethinylestradiol (DRSP/EE), have shown that NOMAC/E2 provided equivalent contraceptive efficacy, with shorter, lighter withdrawal bleeding as compared with monophasic DRSP/EE (3 mg/30 μg)9,10. This paper reports the findings from a pooled analysis of these two studies to compare the effects of NOMAC/E2 and DRSP/EE on premenstrual and menstrual symptoms, including the impact of shorter, lighter withdrawal bleeding9,10.

METHODS

Study design

This was a pooled analysis of two, one-year, randomised, open-label, multicentre studies (Merck Sharp & Dohme Corp., MK-8175A Protocol Numbers 05722 and 05724; ClinicalTrials.gov identifiers: NCT00413062 and NCT00511199) that compared the effectiveness of monophasic 24/4 NOMAC/E2 (2.5 mg/1.5 mg) and monophasic 21/7 DRSP/EE (3 mg/30 μg) in healthy, fertile women9,10. The primary aim of this analysis was to compare the effects of NOMAC/E2 and DRSP/EE on premenstrual and menstrual symptoms using the Moos Menstrual Distress Questionnaire Form C (MDQ-C)11.

Participants in the two studies were enrolled from 184 gynecological or general practices from 24 countries (Argentina, Australia, Belgium, Brazil, Canada, Chile, Czech Republic, Denmark, Finland, France, Germany, Hungary, Italy, Malaysia, Mexico, the Netherlands, Norway, Poland, Spain, Sweden, Switzerland, Thailand, USA, and the UK) between May 2006 and April 2008 (NCT00413062) and between June 2006 and July 2008 (NCT00511199). The study protocols were approved by independent ethics committees or Institutional Review Boards for the participating institutions, and were performed in accordance with Declaration of Helsinki and the International Conference on Harmonisation guidelines on good clinical practice. All eligible women provided written informed consent. In each study, participants were randomly allocated in a 3:1 ratio to either NOMAC/E2 or DRSP/EE for 13 consecutive cycles of 28 days. The randomisation procedures have been previously described9,10; randomisation was stratified by age group (≤35 years, >35 years).

Participants

Healthy, sexually active women (aged 18 to 50 years) with a body mass index between 17 and 35 kg/m² who did not plan to use barrier methods of contraception were included. Exclusion criteria have been previously published9,10 and included contraindications for contraceptive steroids, an abnormal Pap test, recent use of an injectable hormonal method of contraception and prohibited medications (e.g., phenytoin, barbiturates).

Treatments

One tablet of study drug was taken orally every day for 13 consecutive 28-day cycles. For each cycle, treatment consisted of either NOMAC/E2 (2.5 mg/1.5 mg) on days 1 to 24 and placebo tablets on days 25 to 28 or DRSP/EE (3 mg/30 μg) on days 1 to 21 and placebo tablets on days 22 to 28. NOMAC/E2 was supplied by N.V. Organon, the Netherlands (currently part of MSD) and DRSP/EE was purchased from Schering AG (currently Bayer Schering AG), Germany. DRSP/EE was re-blistered, with blister packaging designed...
in similarity to NOMAC/E2 packaging; this was performed by Aptuit Inc., USA for Canadian and US sites and Aptuit Ltd., UK for all other sites.

Women not using systemic hormonal contraceptives at enrollment were instructed to initiate study treatment on the first day of their next menstrual period. Women switching from another combined hormonal contraceptive (e.g., combined oral pill, patch or vaginal ring) started study medication within seven days of the last oral tablet or between day of removal and up to next planned patch or ring application. Women switching from a progestogen-only pill, implant or intrauterine system started immediately. Women were instructed to take any forgotten tablets as soon as they were remembered and to take subsequent tablets as scheduled.

**Measurements**

The effect of NOMAC/E2 and DRSP/EE on premenstrual and menstrual symptoms was compared using the Moos MDQ-C. The Moos MDQ-C is a standard 47-item, self-report inventory for measuring cyclical premenstrual, menstrual and intermenstrual symptoms. Forty-six of the 47 items are grouped into eight symptom domains (one item ‘increased appetite’ is not included); each domain comprises four to eight individual symptom items as follows: Pain (muscle stiffness, headache, cramps, backache, fatigue and general aches and pain), Water Retention (weight gain, skin blemish or disorder, painful or tender breasts and swelling), Autonomic Reactions (dizziness or faintness, cold sweats, nausea vomiting, and hot flashes), Negative Affect (loneliness, anxiety, mood swings, crying, irritability, tension, feeling sad or blue and restlessness), Impaired Concentration (insomnia, forgetfulness, confusion, poor judgment, difficulty concentrating, distractible, minor accidents and poor motor coordination), Behaviour Change (poor school or work performance, take naps or stay in bed, stay at home, avoid social activities and decreased efficiency), Arousal (affectionate, orderliness, excitement, feelings of well-being and bursts of energy or activity) and Control (feelings of suffocation, chest pains, ringing in the ears, heart pounding, numbness or tingling and blind spots or fuzzy vision).

The MDQ-C items are rated on a five-point scale (0 = no experience of symptoms; 1 = present, mild; 2 = present, moderate; 3 = present, strong; 4 = present, severe). The items in each domain are summed to create the domain scores. For all domains except Arousal, a higher score indicates more negative symptoms. Women completed the MDQ-C at baseline and after completion of cycles 1, 3, 6 and 13, rating symptoms for the most recent cycle during the premenstrual (four days before most recent flow), menstrual (most recent flow) and intermenstrual (the remainder of the cycle) phases. Data from the intermenstrual phase were not included in the present analysis.

**Statistical analyses**

The scores of the eight MDQ-C symptom domains at baseline (day of first study treatment intake) and at the end of cycles 1, 3, 6 and 13 for the premenstrual and menstrual phases were compared. The score for cramps from the MDQ-C Pain domain was analysed separately in women with moderate, strong, or severe cramps at baseline.

If a woman did not answer an individual item on any domain at a particular cycle and phase, the raw score for that domain was adjusted by calculating the mean score for the answered items and adding that number to the raw score. If a woman did not answer two or more items on any domain, that domain was not scored. To allow comparison of MDQ-C results within and across cycle phases and between women, the adjusted raw scores were rounded to the nearest whole number and converted to t-scores using standardised conversion values from the MDQ-C manual\(^1\).

A Mixed Model for Repeated Measures (MMRM)\(^ {12,13} \) method was performed as a longitudinal data analysis of the repeated domain scores (at baseline and cycles 1, 3, 6 and 13) from each participant. Classical statistical methods cannot utilise incomplete or missing data and consider repeated measures (t-scores) within participants as independent observations. In contrast, the MMRM method does not require complete data from all women and results in more appropriate estimates of the effect of treatment and their standard errors at each cycle.

Treatment effect (NOMAC/E2 vs. DRSP/EE) on t-scores, adjusted for baseline score, was estimated for each MDQ-C domain and menstrual phase using an MMRM. The model included fixed, categorical effects of treatment (NOMAC/E2, DRSP/EE), cycle (1, 3, 6 and 13), trial\(^ {9,10} \), treatment-by-cycle interaction, as
well as the fixed covariate of baseline score. Estimates of treatment differences (including two-sided 95% CIs and \( p \)-values) at each of the cycles and of the overall treatment difference (calculated as the [unweighted] average of the estimated treatment differences at cycles 1, 3, 6 and 13) were derived from this model. An unstructured covariance matrix was used to model the residual correlation among repeated \( t \)-scores within participants, and the Kenward-Roger approximation was used for the denominator degrees of freedom for the tests of fixed effects. The model was checked by a plot of the scaled residuals: the model fits the data well when the scaled residuals follow an approximate normal distribution with a mean around zero. Trial-by-treatment interaction was added to the model to check for the consistency of the treatment effects across the two trials.

Mean \( t \)-scores during treatment with NOMAC/E2 and DRSP/EE were estimated by symptom domain and phase using the same MMRM, but excluding 'trial' as a factor in the model. These were obtained from the model and calculated as the (unweighted) average of the least squares mean estimates of the \( t \)-scores of cycles 1, 3, 6 and 13. Fixed covariates for age class (\( \leq 35 \) years, \( > 35 \) years) and prior use of contraceptives (starters, switchers) were added to the model to estimate the mean \( t \)-scores during treatment stratified by these covariates.

Estimates of the treatment differences of the \( t \)-scores, adjusted for baseline score, were presented by symptom domain and phase (premenstrual, menstrual). Mean \( t \)-scores at baseline and estimates of the mean \( t \)-scores during treatment were presented by symptom domain, treatment group and phase, as well as by age class and by starters versus switchers of contraceptive use.

The effectiveness of NOMAC/E2 or DRSP/EE on the cramps score (from the MDQ-C Pain domain) was separately analysed in women who had a moderate to severe score for cramps at baseline. The mean score for cramps at the different time points (baseline, cycles 1, 3, 6 and 13) was presented by treatment group and phase. Treatment effects on the odds of improvement from baseline of the score for cramps at cycles 1, 3, 6 and 13 was estimated using a generalised linear mixed model (GLMM) for repeated binary responses\(^1\). Improvement (yes/no) was defined as a negative cramps score for the change from baseline. The model included the same fixed effects as in the MMRM model, except for the baseline score, and was applied to the cramps scores in the premenstrual and menstrual phases. An unstructured covariance matrix was applied to model the residual correlation among repeated measures (cramp scores), and the Satterthwaite approximation was used for the denominator degrees of freedom for the tests of fixed effects in the model. The logit link was used in the model to derive odds ratio (OR) estimates of the treatment effect, two-sided 95% CIs and associated \( p \)-values. A \( p \)-value of 0.05 was considered statistically significant.

All statistical analyses were performed using SAS\textsuperscript{®} version 9.3, using the SAS\textsuperscript{®} procedures MIXED for the MMRM model and GLIMMIX for the GLMM model\textsuperscript{15}.

**R E S U L T S**

**Participants**

A total of 3522 women were included in the MDQ-C symptom domains analysis; 2631 using NOMAC/E2 and 891 using DRSP/EE. Baseline characteristics are summarised in Table 1. Women were well-matched with regard to demographic and clinical characteristics, and prior medication use. The majority of women enrolled were switching from another contraceptive method (66.1% of the NOMAC/E2 users and 65.1% of the DRSP/EE users) as opposed to being new starters. Most of the women had used a COC as their last contraceptive method (64.8% of the NOMAC/E2 users and 62.5% of the DRSP/EE users) as opposed to being new starters. Most of the women had used a COC as their last contraceptive method (64.8% of the NOMAC/E2 users and 62.5% of the DRSP/EE users). The mean exposure to NOMAC/E2 and DRSP/EE was 10.4 and 10.7 cycles per woman, respectively.

A total of 1779 women who had a moderate to severe score for cramps at baseline were included in the MDQ-C cramps item analysis; 1342 treated with NOMAC/E2 and 437 treated with DRSP/EE. The baseline characteristics of these patients are summarised in Table 1.

**Effectiveness of NOMAC/E2 and DRSP/EE on premenstrual and menstrual MDQ-C symptoms**

The mean \( t \)-scores at baseline and during treatment (average of the mean of the \( t \)-scores at cycles 1, 3, 6 and 13) and the estimated treatment difference (NOMAC/E2 – DRSP/EE) on the change from baseline are presented by MDQ-C symptom domains and phase.
in Figure 1. Treatment estimates for the Autonomic Reactions and Control domains were not determined because the scaled residuals of the MMRM showed a strong deviation from normality for these two domains in both phases, which indicates that treatment estimates from this model for these domains might be biased.

In the menstrual phase, women using NOMAC/E2 experienced a reduction from baseline in six out of the eight symptom domain scores, including Pain (mean t-score was 55.7 at baseline vs. 51.2 during treatment), Water Retention (54.3 vs. 50.7), Negative Affect (54.3 vs. 51.1), Impaired Concentration (53.9 vs. 51.2), Behaviour Change (54.1 vs. 51.6) and Arousal (53.9 vs. 51.2). Women using DRSP/EE experienced less reduction in Water Retention, Pain, Negative Affect, Impaired Concentration and Arousal domain scores than women treated with NOMAC/E2 (Figure 1). The reductions in mean t-scores for the premenstrual phase are comparable to those for the menstrual phase for both NOMAC/E2 and DRSP/EE.

The estimated treatment difference (95% CI) in t-score between NOMAC/E2 and DRSP/EE for the MDQ-C symptom domains during the menstrual
phase significantly favoured NOMAC/E2 for Pain (−3.9 [−5.0 to −2.7]), Water Retention (−2.2 [−3.3 to −1.1]), Negative Affect (−2.1 [−3.2 to −0.9]), Impaired Concentration (−2.4 [−3.4 to −1.3]), and Behaviour Change (−2.1 [−3.1 to −1.0]) (all \( p < 0.001 \)) (Figure 1). Similar but smaller benefits were observed for NOMAC/E2 in the premenstrual phase. There was a significant reduction (i.e., worsening) in Arousal scores with NOMAC/E2 in the menstrual (−2.9 [−4.0 to −1.9]) and premenstrual (−2.1 [−3.2 to −1.1]) phases compared with DRSP/EE (both \( p < 0.0001 \)).

The mean \( t \)-scores stratified by prior use of contraceptives (starters, switchers) and by age (≤35 or

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**Figure 1** Mean \( t \)-scores at baseline and during treatment, and estimated treatment differences for Menstrual Distress Questionnaire Form-C (MDQ-C) domain symptoms measured during the premenstrual (A) and menstrual (B) phases in women using nomegestrol acetate/17\( \beta \)-estradiol (NOMAC/E2) or drospirenone/ethinylestradiol (DRSP/EE). Higher mean \( t \)-scores indicate more negative symptoms (except Arousal); negative treatment differences are in favour of NOMAC/E2 (except Arousal). *Unweighted mean of the estimated treatment differences adjusted for baseline at cycles 1, 3, 6 and 13. The estimates were derived from a Mixed Model for Repeated Measures (MMRM) of the MDQ-C domain scores at cycles 1, 3, 6 and 13. The model included factors for baseline domain score, trial (Mansour et al., 2011; Westhoff et al., 2012), treatment (NOMAC/E2, DRSP/EE), cycle (1, 3, 6 and 13) and treatment-by-cycle interaction. Cycle was included as a categorical variable. Treatment estimates for the Autonomic Reactions and Control domains were not determined because the scaled residuals of the MMRM showed a strong deviation from normality for these two domains in both phases (which indicates that treatment estimates from this model might be biased); †\( p \)-value of test of no treatment difference. ND: not determined.
>35 years) are presented in Table 2 and Table 3, respectively. Starters had higher (i.e., worse) baseline scores (except for Arousal), resulting in starters being generally more responsive than switchers for most domains in the premenstrual and menstrual phases. Arousal, however, was equally reduced for both starters and switchers in the NOMAC/E2 group but not the DRSP/EE group; in this group, the change in Arousal was numerically greater for switchers than starters. NOMAC/E2 reduced all menstrual phase domain scores in both the starter and switcher groups. In contrast, DRSP/EE had little effect on menstrual phase domain scores with the exception of Pain and Water Retention in the starter group. The Control domain scores were stable across groups and contraception methods as expected.

Compared to the older cohort, women aged ≤35 years tended to have higher baseline scores on almost all domain scores during both the premenstrual and menstrual phases and experienced greater changes on all domain scores (except Arousal) in both groups. Of note, women aged >35 years who were treated with DRSP/EE, experienced an increase (worsening) in the domain scores across both the premenstrual and menstrual phases, with the exception of an improvement in Arousal during both phases and an improvement in Negative Affect during the premenstrual phase. In contrast, women aged >35 years treated with NOMAC/E2 reported improvements in all domains except for the Autonomic Reactions and Behaviour Change domains in the menstrual phase.

### Table 2 Mean t-score at baseline and during treatment for starters and switchers, by Menstrual Distress Questionnaire Form-C domain, phase and treatment group.

<table>
<thead>
<tr>
<th></th>
<th>NOMAC/E2</th>
<th>DRSP/EE</th>
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<tbody>
<tr>
<td></td>
<td>Starter (n = 891)</td>
<td>Switcher (n = 1740)</td>
</tr>
<tr>
<td></td>
<td>At baseline During treatment</td>
<td>At baseline During treatment</td>
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<tr>
<td><strong>Premenstrual phase, mean t-score†</strong></td>
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<td></td>
</tr>
<tr>
<td>Pain</td>
<td>57.9</td>
<td>53.5</td>
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<tr>
<td>Water Retention</td>
<td>60.2</td>
<td>52.5</td>
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<tr>
<td>Autonomic Reactions</td>
<td>53.3</td>
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<tr>
<td>Negative Affect</td>
<td>57.8</td>
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<td>Impaired Concentration</td>
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<tr>
<td>Behaviour Change</td>
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<td>55.5</td>
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<tr>
<td>Arousal</td>
<td>59.5</td>
<td>55.7</td>
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<tr>
<td>Control</td>
<td>54.3</td>
<td>54.8</td>
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<td><strong>Menstrual phase, mean t-score†</strong></td>
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<tr>
<td>Pain</td>
<td>58.6</td>
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<td>Water Retention</td>
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<tr>
<td>Control</td>
<td>51.7</td>
<td>52.1</td>
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DRSP/EE: drospirenone/ethinylestradiol; n: number of women at baseline; NOMAC/E2: nomegestrol acetate/17β-estradiol.

*Use (switcher) or no use (starter) of a hormonal contraceptive method in the two months before the start of treatment.

†The mean t-score during treatment is the average of the mean t-scores of cycles 1, 3, 6 and 13. A higher mean t-score indicates more negative symptoms, except for Arousal where a higher mean t-score indicates less negative symptoms.
Effectiveness of NOMAC/E2 and DRSP/EE on premenstrual and menstrual cramps

The mean scores for cramps at baseline and cycles 1, 3, 6 and 13 in women using either NOMAC/E2 or DRSP/EE are shown in Figure 2. Women with moderate to severe cramps at baseline experienced an improvement with NOMAC/E2 or DRSP/EE at all cycles during the premenstrual and menstrual phases (Figure 2). The NOMAC/E2 versus DRSP/EE OR for improvement from baseline was >1 at cycles 1, 3 and 6 in the premenstrual phase and at cycle 1 in the menstrual phase (all p < 0.05). The OR in cycle 1 of the menstrual phase was 1.41 (p = 0.02), which indicates that the odds of improvement in cramps score was 1.41 times more likely with NOMAC/E2 than DRSP/EE.

Table 3 Mean t-score at baseline and during treatment for women aged ≤35 or >35 years, by Menstrual Distress Questionnaire Form-C domain, cycle phase and treatment group.

<table>
<thead>
<tr>
<th></th>
<th>NOMAC/E2 ≤35 years (n = 2220)</th>
<th>NOMAC/E2 &gt;35 years (n = 411)</th>
<th>DRSP/EE ≤35 years (n = 751)</th>
<th>DRSP/EE &gt;35 years (n = 140)</th>
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<td>At baseline</td>
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DRSP/EE: drospirenone/ethinylestradiol; n: number of women at baseline; NOMAC/E2: nomegestrol acetate/17β-estradiol.
*The mean t-score during treatment is the average of the mean t-scores of cycles 1, 3, 6 and 13. A higher mean t-score indicates more negative symptoms, except for Arousal where a higher mean t-score indicates less negative symptoms.

**DISCUSSION**

In this analysis of two open-label, one-year, randomised twin studies in more than 3500 healthy, fertile women, NOMAC/E2 users reported an improvement in the Pain, Water Retention, Negative Affect, Impaired Concentration and Behaviour Change MDQ-C domain scores during the premenstrual and menstrual phases. Women using DRSP/EE also experienced a reduction, albeit smaller, in Pain, Water Retention, Negative Affect and Impaired Concentration domain scores. The estimated treatment differences significantly favoured NOMAC/E2 for Pain, Water Retention, Negative Affect and Impaired Concentration domain scores during both premenstrual and menstrual phases. However, there was a significant worsening of Arousal domain scores with NOMAC/E2 during the menstrual and premenstrual...
phases compared with DRSP/EE. Switchers from other hormonal contraceptives showed lower baseline domain scores than starters, and their treatment responses were generally smaller. Women >35 years treated with DRSP/EE experienced less favourable results than NOMAC/E2 across most domain scores during both the premenstrual and menstrual phases. The analysis also showed that NOMAC/E2 and DRSP/EE were beneficial in improving the cramps item score; the benefits were consistent across the cycles, and were significantly greater for NOMAC/E2 than DRSP/EE during the premenstrual phase of most cycles, and the menstrual phase in cycle 1.

The differences in the premenstrual and menstrual MDQ-C symptom reductions reported by women using either NOMAC/E2 or DRSP/EE may be associated with a number of factors. The common denominator in peri-menstrual complaints is the fluctuation in hormone levels, which may give rise to a variety of abnormal physical, endocrinological, neurological and psychological responses. In regimens like DRSP/EE with EE, a steep drop in estrogen is typically seen at the beginning of the hormone-free interval with discontinuation of EE\textsuperscript{16}. However, with NOMAC-E2 in which the administered estrogen is the same as the endogenous estrogen, the initial drop associated with the start of the hormone-free interval is compensated for by the simultaneous resumption of endogenous E\textsubscript{2} production\textsuperscript{17,18}. Endogenous E\textsubscript{2} shows more cyclic fluctuation than with NOMAC-E2, i.e., with lower levels during the active treatment phase and a steep increase during the hormone-free interval when ovarian activity resumes. Additionally, the half-life of NOMAC (∼46 hours) is approximately 50% longer than of DRSP (∼30 hours), which may provide for more constant progestagen levels\textsuperscript{16,18}. Overall, the more stable hormonal changes result in less variation in FSH levels, follicular diameter and endometrial thickness, as observed with NOMAC/E2 as compared to DRSP/EE\textsuperscript{17}.

Figure 2 Mean scores at baseline and at cycles 1, 3, 6 and 13, and estimated treatment effects on cramps score measured during the premenstrual (A) and menstrual (B) phases in women (with moderate to severe cramps at baseline) using nomegestrol acetate/17\textbeta-estradiol (NOMAC/E2) or drospirenone/ethinylestradiol (DRSP/EE). A lower mean score indicates improvement. An odds ratio (OR) > 1 indicates higher probability of improvement with NOMAC/E2. *Based on a Generalised Linear Mixed Model for the improvement from baseline (yes/no) of the scores for cramps at cycles 1, 3, 6 and 13. Factors included in the model were trial (Mansour et al., 2011\textsuperscript{9}; Westhoff et al., 2012\textsuperscript{10}), treatment (NOMAC/E2, DRSP/EE), cycle (1, 3, 6 and 13) and treatment-by-cycle interaction. Cycle was included as a categorical variable. The model was applied to the cramps scores in the premenstrual and menstrual phases, respectively; †p-value of test of no treatment difference. N: number of subjects.
In this particular study, the shorter length of the hormone-free interval with NOMAC/E2 (4 days) vs DRSP/EE (7 days) potentially contributes to more hormonal stability and the clinical effects observed. Women who switch from a DRSP-EE 21/7 regimen to a continuous DRSP/EE regimen experience a substantial decrease in physical and emotional scores (measured by the Penn Daily Symptom Report [DSR 17]) and lose cyclic variation in symptoms. These types of changes are also seen in a COC containing DRSP and 20 μg EE in a 24/4 regimen (Yaz®), which has been approved for treatment of the emotional and physical symptoms of premenstrual dysphoric disorder (PMDD). Although direct comparisons are not available, the shortening of the hormone-free interval, and possibly the lowering of the EE dose to 20 μg, may have caused Yaz® to be more effective than Yasmin® in treating peri-menstrual symptoms.

In addition, the nature of the progestagen and estrogen administered may contribute to differential effects. Women on COCs containing EE and a 19-nortestosterone derivative (norethisterone, levonorgestrel, desogestrel, norgestimate) and who switch to DRSP-EE, all in a 21/7 regimen, show a decrease in physical and emotional scores as measured by the Penn Daily Symptom Report (DSR 17), and especially a reduction in the peak scores reached three to four days after the start of the hormone-free interval. The apparent efficacy of DRSP/EE as compared to COCs containing a 19-nortestosterone derivative as the progestagen has been attributed to the antimineralocorticoid properties of DRSP, leading to less fluid retention and associated potential clinical effects (blood pressure, weight gain, breast tenderness, skin blemish, swelling). In addition to endocrinologic effects, COCs may have differential effects on the serotonergic and GABA neurotransmitter systems, and on neuropeptides such as β-endorphins, which have been suggested to be involved in the neurological and psychological peri-menstrual complaints.

The favorable result for NOMAC/E2 with respect to menstrual cramping scores may also be related to the differences in vaginal bleeding pattern, with NOMAC/E2 being associated with shorter, lighter withdrawal bleeding compared with DRSP/EE. Again, this difference in bleeding patterns may, in part, be attributable to the difference in dosing regimens, as similar results were reported in studies comparing NOMAC/E2 administered in a 24/4 and a 21/7 regimen and in two twin studies that compared the effects of DRSP/EE (3 mg/30 μg) in a 21/7 regimen to DRSP/EE (3 mg/20 μg) in a 24/4 regimen. However, in two other studies that compared DRSP/EE (3 mg/20 μg) used in a 24/4 regimen with desogestrel/EE (150 μg/20 μg) in a 21/7 regimen over 7 treatment cycles, the incidence of scheduled/unscheduled bleeding was comparable, suggesting that other factors may also play a role, including the effect of different agents on the endometrium itself.

One strength of the data reviewed is the large number of women with data available, suggesting an overall benefit on peri-menstrual complaints associated with use of the NOMAC/E2 2.5/1.5 mg COC in a 24/4 regimen as compared to DRSP-EE 3 mg/30 μg in a 21/7 regimen. However, the studies were not designed to demonstrate such differences. The MDQ-C questionnaire was provided to subjects in order to identify potential non-contraceptive benefits, and there were no specific enrollment criteria related to peri-menstrual complaints. Moreover, the treatments differed in too many aspects to allow for a proper mechanistic explanation of the differences observed, notably the differences in both the progestagen and estrogen component, as well as the treatment regimen. Although the findings are clinically relevant with regard to symptom control, the analyses do have a number of limitations. The MDQ-C is subject to criticism primarily associated with the recall periods. A participant’s ability to recall symptoms over the different phases of their most recent menstrual flow may be limited. However, the fact that different domain scores showed more change during the premenstrual phase (e.g., Water Retention) than in the menstrual phase appears to at least partially eliminate a concern over the recall periods. There may also be some instability in the MDQ, resulting in some symptoms being perceived as more important than others, although it is widely regarded as accurately representing the general structure of the menstrual cycle. In addition, there are no published thresholds with the MDQ determining clinical relevance. The MDQ manual suggests scores between 45 and 55 to be considered ‘average’, with each further five-point deviation from average being labelled as ‘slightly below/above’, ‘below/above’, ‘much below/above’ and ‘very much below/above’, respectively. Scores below 35 or above 65 are ‘much below’ or ‘much above’ average, respectively, and possibly clinically relevant. Not unexpectedly, the populations enrolled in the studies were ‘slightly above average’ at baseline. This follows on
from the enrolment criteria, which required women ‘in good physical and mental health’.

In conclusion, this pooled analysis showed that NOMAC/E2 was associated with improvements in most negative menstrual symptoms as assessed by MDQ-C, and in premenstrual Pain, Water Retention, Negative Affect and Impaired Concentration, the domains that are considered key features of the premenstrual syndrome\textsuperscript{26}. However, NOMAC/E2 was associated with a worsening of the Arousal domain during both the premenstrual and menstrual phases compared with DRSP/EE. NOMAC/E2 and DRSP/EE were also beneficial in reducing premenstrual and menstrual cramps. Cramps are an important clinical issue, and one of the major symptoms of menstrual distress. Overall, these findings indicate that NOMAC/E2 might be associated with a number of advantages particularly in women who experience premenstrual and menstrual symptoms, and is a suitable COC choice for new users or in women switching from different methods of contraception irrespective of age.

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\textbf{Author Contributions}

Conceived, designed or planned the study: TK; Collected or assembled the data: TK; Performed or supervised analyses: TK and HW; Provision of study materials of patients: IS-P; Interpreted the results; wrote sections of the initial draft or provided suggestions for revision; and reviewed and approved final version: all authors.


