Comparison of the pharmacologic and clinical profiles of new combined oral contraceptives containing estradiol

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Abstract: Three estradiol (E2)-containing oral contraceptives, estradiol valerate/cyproterone acetate (E2V/CPA, Femilar®), estradiol valerate/dienogest (E2V/DNG, Qlaira®/Natazia™), and estradiol/nomegestrol acetate (E2/NOMAC; Zoely®), have received approval for use in general practice. Only Finnish women currently have access to all three E2-based formulations. E2/NOMAC is currently approved only in Europe, while E2V/DNG is approved globally. To assist clinicians counseling women considering use of one of these formulations, we conducted a review of the published information about the current E2-containing oral contraceptives.

Introduction

Over the last 50 years, refinements in the formulation of combined oral contraceptives (COCs) have focused on improving their tolerability and safety. Primary modifications include a reduced ethinylestradiol (EE) dose and incorporation of new progestins with improved selectivity profiles which are closer in function to natural progesterone. Drospirenone (DRSP), dienogest (DNG), and nomegestrol acetate (NOMAC) are the most recent progestins introduced to the market, and products containing nestorone and trimestreare in development.

Although the contraceptive effects of COCs are mainly achieved through progestin alone, estrogen remains an important component because its inclusion enhances contraceptive efficacy and helps regulate bleeding. While the type of progestin and dosing regimen used may affect overall cycle control, COCs with lower EE doses tend to have poorer cycle control (ie, unscheduled bleeding and/
Early attempts to develop $E_2$-containing oral contraceptives as alternatives to EE-based formulations showed that $E_2$-containing formulations could achieve effective inhibition of ovulation and contraception. However, these early formulations were associated with unacceptable bleeding patterns and, thus, were suspended from further development.\textsuperscript{17-21} The bleeding problems associated with these earlier attempts to incorporate $E_2$ into an oral contraceptive might be explained, in part, by the activity of 17$\beta$-estradiol dehydrogenase. This enzyme rapidly converts $E_2$ (but not EE) into estrone ($E_1$),\textsuperscript{22,23} an estrogen with only weak estrogenic activity that is unable to maintain stable endometrial proliferation.\textsuperscript{23} The rate of transformation of $E_2$ to its metabolites may be influenced by some progestins;\textsuperscript{13} consequently, progestins with minimal impact on $E_1$ metabolism and endometrial stroma stability may improve cycle stability with $E_2$-based oral contraceptives.\textsuperscript{24}

To date, only three $E_2$-containing oral contraceptives have received regulatory approval for use in general practice. These include estradiol valerate/cyproterone acetate (E, V/CPA; Femilar\textsuperscript{®}, Bayer Oy, Turku, Finland), estradiol valerate/dienogest ($E_2$/V/DNG; Qlaira\textsuperscript{®}/Natazia\textsuperscript{TM}, Bayer HealthCare Pharmaceuticals, Berlin, Germany), and estradiol/nomegestrol acetate ($E_2$/NOMAC; Zoely\textsuperscript{®}; Theramex Srl, Milan, Italy). Clinicians and other family planning providers need informed guidance when counseling their patients about $E_2$-containing oral contraceptives, because a number of factors may influence women’s choice. As new data have become available, this comprehensive review seeks to compare and contrast the pharmacologic and clinical profiles of $E_2$-containing oral contraceptives.

**Methods**

A systematic literature search was conducted using Ovid to search both MEDLINE and EMBASE simultaneously for clinical studies published up to February 20, 2013 on the three marketed $E_2$-containing COCs ($E_2$/V/DNG, $E_2$/NOMAC, and $E_2$/V/CPA). The search strategy combined free text terms relevant to oral contraception and estradiol as follows: (beta estradiol OR beta estradiol OR $E_2$, OR natural estradiol OR natural estradiol) AND contracept* (where* is a wild character). The titles and abstracts from the electronic searches were initially assessed for relevant articles published in English. In addition, the reference lists of pertinent review articles identified were also examined for relevant studies not captured by the electronic search. Studies evaluating the pharmacologic and clinical profiles...
of these E2-containing COCs were chosen for inclusion in this review.

**Approved formulations and regimens**

E2V/CPA is a biphasic preparation taken in a 21/7 cycle regimen (E2V 1 mg/CPA 1 mg on days 1–10, E2V 2 mg/CPA 2 mg on days 11–21, and a 7-day pill-free interval). The rationale for the biphasic E2V/CPA regimen has not been discussed in the literature, but phasic regimens are generally used in order to optimize control of bleeding.

E2V/DNG is taken in a 26/2 cycle, with E2V 3 mg on days 1–2, E2V 2 mg/DNG 2 mg on days 3–7, E2V 2 mg/DNG 3 mg on days 8–24, E2V 1 mg on days 25–26, and placebo on days 27–28. This specific regimen was established as the lowest effective dose of E2V combined with DNG for efficient ovulation inhibition while maintaining acceptable bleeding control.25,26 The regimen for E2V/DNG was designed to provide phased delivery of hormones with estrogen dominance early in the cycle and progestin dominance from the mid-to-late part of the cycle. Early estrogenic dominance is thought to allow for initial endometrial proliferation and upregulation of progesterone receptors; this enhances sensitivity to mid-cyclic progestin action, leading to endometrial stroma stability at the end of the cycle, thereby resulting in predictable bleeding.27 The rationale for estradiol alone towards the end of the cycle and the short hormone-free interval is to ensure that overall estradiol levels remain relatively stable throughout each cycle (including the hormone-free interval).22

E2/NOMAC is a monophasic preparation taken over a cycle of 24/4 days (E2 1.5 mg/NOMAC 2.5 mg on days 1–24 and placebo on days 25–28). The 2.5 mg dose of NOMAC was established as the optimum dose needed for ovulation inhibition. The 1.5 mg E2 dose was selected based on the dose used in estrogen replacement therapy established to provide adequate estrogen levels for prevention of osteoporosis in postmenopausal women.28 The rationale behind the 24/4 regimen for E2/NOMAC is based, in part, on the greater ovarian suppression achieved relative to the conventional 21/7 regime, which may result in a greater contraceptive margin and a shorter duration of withdrawal bleeding (compared with traditional 21/7 regimen oral contraceptives), as well as decreased hormonal fluctuations (particularly for E2) and associated hormone withdrawal symptoms.29 The bleeding control achieved with E2/NOMAC has been hypothesized to be due to the ability of NOMAC to maintain endometrial stability through its minimal impact on endometrial E2 metabolism, which ensures sufficient E2 levels in the endometrium and thus prevents endometrial breakdown.24,30

The absolute bioavailability of E2 following oral E2/NOMAC administration was estimated to range between 1% and 5%,31 and that following oral E2V/DNG administration to be about 3%–6%.32 E2V is rapidly hydrolyzed and converted to 17β-estradiol (E2) during absorption in the gastrointestinal tract following oral administration (1 mg of

![Figure 1 Estradiol serum concentration-time curves following single oral doses of micronized E2 (2 mg) and E2V (2 mg). Data obtained from postmenopausal women.](https://www.dovepress.com/)

**Note:** Data used to create the figure taken with permission from Timmer CJ, Geurts TB. Bioequivalence assessment of three different estradiol formulations in postmenopausal women in an open, randomized, single-dose, 3-way cross-over study. *Eur J Drug Metab Pharmacokinet*. 1999;24:47–53.33

**Abbreviations:** E2, estradiol; E2V, estradiol valerate; h, hours.
E₂V contains 0.76 mg of E₂. The E₂ pharmacokinetic profile following oral micronized E₂ (1.5 mg) appears to be similar to that following oral E₂V (2 mg, Figure 1).

**Indications and pivotal studies for approved E₂-containing COCs**

E₂V/CPA is available in Finland only and indicated for women ≥40 years and for women aged 35–40 years for whom an oral contraceptive containing EE is not appropriate. The pivotal registration study for E₂V/CPA was an open-label trial that recruited 288 Finnish women aged 30–49 (mean 39.3 ± 3.4) years and was conducted over thirteen 28-day cycles.

E₂V/DNG is available globally and is indicated for contraception and for the treatment of heavy menstrual bleeding in “women without organic pathology who desire oral contraception”. The pivotal registration studies for the contraception indication included two open-label, non-comparative efficacy trials, one undertaken in Europe and the other in the US and Canada. The European study enrolled 1,377 women aged 18–50 years and was conducted over twenty 28-day cycles. The US and Canadian study enrolled 499 women aged 18–35 years, and although initially planned for 13 cycles, was later extended to 28 cycles. This latter study, although undertaken to assess contraceptive efficacy, cycle control, and safety of E₂V/DNG, was not powered for a separate Pearl Index calculation. The pivotal registration studies for the treatment of heavy menstrual bleeding indication included two similarly designed, randomized placebo-controlled studies, one undertaken in Europe and Australia (n=231) and the other in the US and Canada (n=190).

E₂/V/CPA is available in Europe, Australia, and some South American countries, and is indicated for contraception. There were two pivotal registration studies for E₂/V/CPA, one conducted in Europe, Asia, and Australia and the other in the US. Both studies were randomized open-label, comparative trials that recruited women aged 18–50 years, of whom 3,323 were randomized to receive E₂/V/CPA and 1,110 to EE/DRSP (30 μg/3 mg; Yasmin®, Bayer HealthCare Pharmaceuticals) for 13 cycles.

**Clinical profiles**

**Pharmacodynamic effects**

The pharmacodynamic effects of E₂V/CPA, E₂V/DNG, and E₂/NOMAC, as well as the individual progestin components (CPA, DNG, and NOMAC, respectively), have been well documented. In essence, the main contraceptive effects of these combined formulations are due to the progestin component; this is also the case with other COCs containing EE.

CPA 1 mg daily appears sufficient to inhibit ovulation. A dose-ranging study of CPA (0.125–1.00 mg daily) in healthy women aged 20–28 years (n=12) showed that CPA 1 mg inhibited ovulation (as determined by daily measurements of luteinizing hormone, follicle-stimulating hormone, E₂, and progesterone) in all women assessed (n=5). Concomitant effects of CPA on the endometrium and cervical mucus were not reported in this study.

The ovulation-inhibiting effects of DNG were assessed in a dose-ranging (0.5 mg–3 mg DNG daily) study in healthy women aged 18–35 years (n=102) using the Hoogland score, which determines ovarian activity based on largest follicular size and highest serum hormone levels. Dose-dependent ovulation-inhibiting effects were observed across the doses tested. Ovulation was suppressed in all women taking 2 mg (n=20) or 3 mg (n=23) of DNG daily. In addition, endometrial thickness was reduced compared with pretreatment. DNG also induced moderate suppression of endogenous E₂ production.

The contraceptive effects of NOMAC have also been assessed in a dose-ranging (1.25–5 mg NOMAC daily) study in 13 healthy women. In this study, pituitary-ovarian function was determined by measuring E₂, follicle-stimulating hormone, and luteinizing hormone levels. Ovulation was inhibited in all women across the doses of NOMAC. In a separate study of 16 normally cycling women assessing the effects of NOMAC (2.5 mg or 5 mg daily) on mid-cycle cervical mucus, the changes observed were similar to those induced by progesterone during the luteal phase. In a more recent study, 2.5 mg of NOMAC was again shown to inhibit ovulation and decrease cervical mucus scores (ie, indicative of increased hostility to sperm penetration) in healthy women aged 18–35 years (n=9). These data support cervical mucus inhibition as a secondary contraceptive mechanism.

The approved formulations of E₂V/CPA, E₂V/DNG, and E₂/V/CPA all consistently inhibit ovulation in ≥95% of women. However, studies with E₂V/CPA were performed in small samples of women with a mean age of 39 (range 30–49) years, and as such may overestimate the rate of ovulation inhibition in “more fertile” younger women. In addition, the contraceptive effects of E₂V/CPA achieved through alteration in cervical mucus and the endometrium have not, to our knowledge, been reported. E₂V/DNG has been shown to have suppressive effects on endometrial growth and cervical mucus as assessed by transvaginal ultrasound in healthy women aged 18–35 years (n=100); mean...
maximal endometrial thickness decreased from 10.1 mm at baseline to 6.5 mm during cycle 3. Although treatment was associated with a reduction in the ultrasound appearance of cervical mucus, the quality of mucus was not assessed.46 Similar changes in cervical mucus and the endometrium were observed with E₂/NOMAC in healthy women aged 18–35 years (n=32); mean maximum endometrial thickness was reduced from 9.9 mm at screening to 4.9 mm in cycle 6. In this study, cervical mucus, assessed using the Insler cervical mucus score, decreased from a mean maximum of 8.9 at screening to 2.3 during the first treatment cycle (with lower scores indicating poor likelihood of sperm penetration).47

**Contraceptive efficacy**

The approved E₂/V/CPA, E₂/V/DNG, and E₂/NOMAC formulations appear to have similar contraceptive efficacy profiles (Table 1).30,34–36,39 The net pregnancy rate with E₂/V/CPA was reported to be 0.4% over 12 months in Finnish women (n=288) aged 30–49 years; one pregnancy occurred in 2,800 cycles of exposure, equating to a Pearl Index of 0.46.44 Again this may be an overestimation of the contraceptive efficacy of E₂/V/CPA in younger more fertile women. In addition, this lone study would be insufficient to meet current recommendations for regulatory approval of a new hormonal contraceptive in Europe (“for any new contraceptive, at least 400 women should have completed one year of treatment”).49

The contraceptive efficacy of E₂/V/DNG was established in two open-label, noncomparative studies, one conducted in Europe and the other in North America, in over 1,850 women aged 18–50 years.35,36 In the European study (conducted in Austria, Germany, and Spain), the Pearl Index at 20 cycles of treatment was reported to be 0.73 in women aged 18–50 years and 0.94 in women aged 18–35 years (n=998).35 The second study conducted in North America recruited women aged 18–35 years (n=490) and reported a Pearl Index of 1.64 at one year; however, this study was not sufficiently powered for a stand-alone contraceptive efficacy calculation.

The contraceptive efficacy of E₂/NOMAC was established in two randomized, open-label, comparative studies (compared with EE 30 µg/DRSP 3 mg [Yasmin]), one conducted in Europe, Asia, and Australia,46 and the other in the US, Canada, Argentina, Brazil, Chile, and Mexico,46 in over 3,250 women aged 18–50 years. The study conducted in Europe, Asia, and Australia reported a Pearl Index of 0.31 in women aged 18–50 years, and a Pearl Index of 0.38 in women aged 18–35 years (n=1,315). The other E₂/NOMAC efficacy study reported a Pearl Index at one year of 1.13 in women aged 18–50 years, with a corresponding Pearl Index of 1.27 in women aged 18–35 years (n=1,375).

Of note, the Pearl indices reported at one year from the E₂/V/DNG and E₂/NOMAC studies that included study centers in the US were slightly higher than for the similar studies conducted elsewhere. This is a well recognized phenomenon in contraceptive research, and may, in part, be due to differences in compliance rates and/or recruitment practices.50 Indeed, residential poverty level, an indirect measure of individual income, was shown to be the strongest predictor of noncompliance in a US oral contraceptive clinical trial.51 Nonetheless, the one-year Pearl indices for the approved E₂-containing oral contraceptives are consistent with those reported for recently approved low-dose EE-containing formulations (Pearl indices 0–1.6).50

**Bleeding profile**

A direct comparison of bleeding profile between oral contraceptive formulations, especially by cycle, is difficult due to the lack of uniform definitions and results across studies.52

### Table 1 Summary of published studies reporting contraceptive efficacy of estradiol-containing oral contraceptives

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Study location</th>
<th>Treatment duration</th>
<th>Age group, years</th>
<th>n</th>
<th>Exposure</th>
<th>Pregnancies (n)</th>
<th>Pearl Index</th>
<th>Upper 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>E₂/V/CPA44</td>
<td>Finland</td>
<td>1 year</td>
<td>30–49</td>
<td>288</td>
<td>2,800 cycles</td>
<td>1</td>
<td>0.46</td>
<td></td>
</tr>
<tr>
<td>E₂/V/DNG45</td>
<td>Austria, Germany, Spain</td>
<td>20 cycles</td>
<td>18–50</td>
<td>1,377</td>
<td>23,368 cycles</td>
<td>13</td>
<td>0.73</td>
<td>1.24</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>18–35</td>
<td>998</td>
<td>16,608 cycles</td>
<td>12</td>
<td>0.94</td>
<td>1.65</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;35–50</td>
<td>379</td>
<td>6,760 cycles</td>
<td>1</td>
<td>0.19</td>
<td></td>
</tr>
<tr>
<td>E₂/V/DNG46</td>
<td>US, Canada</td>
<td>1 year</td>
<td>18–35</td>
<td>490</td>
<td>3,969 cycles</td>
<td>5</td>
<td>1.64</td>
<td>3.82</td>
</tr>
<tr>
<td>E₂/NOMAC48</td>
<td>Europe, Asia, Australia</td>
<td>1 year</td>
<td>18–50</td>
<td>1,587</td>
<td>1,293 woman-years</td>
<td>4</td>
<td>0.31</td>
<td>0.79</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>18–35</td>
<td>1,315</td>
<td>1,058 woman-years</td>
<td>4</td>
<td>0.38</td>
<td>0.97</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;35–50</td>
<td>272</td>
<td>235 woman-years</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>E₂/NOMAC49</td>
<td>US, Canada, Argentina, Brazil, Chile, Mexico</td>
<td>1 year</td>
<td>18–50</td>
<td>1,634</td>
<td>1,146 woman-years</td>
<td>13</td>
<td>1.13</td>
<td>1.94</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>18–35</td>
<td>1,375</td>
<td>946 woman-years</td>
<td>12</td>
<td>1.27</td>
<td>2.22</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;35–50</td>
<td>259</td>
<td>235 woman-years</td>
<td>1</td>
<td>0.43</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** CI, confidence interval; CPA, cyproterone acetate; E₂V, estradiol valerate; DNG, dienogest; NOMAC, nomegestrol acetate; E₂, estradiol.
Although the World Health Organization has made recommendations for the analysis of menstrual patterns, these have not been uniformly adopted. Nonetheless, irrespective of definitions used, studies that assessed bleeding profiles associated with E₂V/CPA, E₂V/DNG, and E₂/NOMAC consistently suggest that these oral contraceptives are associated with shorter, lighter bleeding versus comparator EE-containing pills or baseline.²⁷,³⁰,³⁴,³⁶,³⁹,⁴¹

Table 2 summarizes the number of uterine bleeding days using 90-day and 91-day reference periods observed in the randomized controlled trials with E₂V/DNG and E₂/NOMAC compared with EE/levonorgestrel (EE 20 µg/LNG 100 µg, Miranova®, Bayer HealthCare Pharmaceuticals) and EE/DRSP (Yasmin), respectively.²⁷,³⁰,³⁹ The study with E₂V/DNG and EE/LNG was conducted over seven 28-day cycles in centers across Germany, the Czech Republic, and France, and reported uterine bleeding data from 399 women aged 18–50 years in both treatment groups.²⁷ These studies demonstrated statistically significant and/or clinically meaningful reductions in bleeding/spotting days with E₂V/DNG and E₂/NOMAC compared with the comparator EE-based oral contraceptives.²⁷,³⁰,³⁹ There are no available bleeding data with E₂V/CPA where the data are reported by reference period.

The data reported by cycle with both E₂V/DNG and E₂/NOMAC are also consistent with reduced bleeding (or an absence of bleeding) relative to the comparator EE-based formulations. For example, the rate of absence of withdrawal bleeding (mean over cycles 1–7) was 19.4% (range 16.8%–22.3%) in women treated with E₂V/DNG compared with 7.7% (range 6.2%–10.5%) in women treated with EE/LNG.²⁷ In the open-label North American E₂V/DNG study, the rate of absent withdrawal bleeding occurred in a mean 23.5% of women through cycles 1–12 (range 17% and 32%).³⁶ For E₂/NOMAC, in the study conducted in Europe, Asia, and Australia, 30% of women had at least one absence of withdrawal bleeding during cycles 2–4. Moreover, a progressive increase in the incidence of absent withdrawal bleeding from 22% to 31% occurred in cycles 4–12, indicating a tendency towards absent withdrawal bleeding with continued use.³⁰ In the comparator EE/DRSP formulation group, the incidence of absent withdrawal bleeding was relatively stable, ranging from 3% to 6%. A similar trend towards absent withdrawal bleeding with continued use (approximately 18%–34%) was also observed with E₂/NOMAC, but not with EE/DRSP (approximately 4%–9%), in the study conducted in North and South America.³⁹

### Table 2

<table>
<thead>
<tr>
<th>Study</th>
<th>Formulation</th>
<th>Reference period</th>
<th>Bleeding/spotting days (n)</th>
<th>Spotting days (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahrendt et al⁴</td>
<td>E₂V/DNG</td>
<td>R1 R2 R3 R4 R5</td>
<td>17.3⁵ 13.4⁶ 11.5 9.7 7</td>
<td>- 9.0 8.0 7.5 6.5</td>
</tr>
<tr>
<td>Mansour et al³</td>
<td>E₂V/DNG</td>
<td>R1 R2 R3 R4 R5</td>
<td>21.5 15.9 14.5 11.0 10.5</td>
<td>- 9.0 8.0 7.5 6.5</td>
</tr>
<tr>
<td>Wescheff et al³</td>
<td>E₂V/DNG</td>
<td>R1 R2 R3 R4 R5</td>
<td>- - - - -</td>
<td>- - - - -</td>
</tr>
<tr>
<td>Ahrendt et al⁴</td>
<td>E₂V/DNG</td>
<td>R1 R2 R3 R4 R5</td>
<td>- - - - -</td>
<td>- - - - -</td>
</tr>
</tbody>
</table>

Notes: Data estimated from published graphs; *P<0.001 versus comparator; †90-day reference period used; ‡91-day reference period used; EE/DRSP (Yasmin), nomegestrol acetate + drospirenone; LNG, levonorgestrel.
Intracyclic bleeding was reported to occur in approximately 14% of women receiving E\textsubscript{2}V/DNG (ranging from 10.5% to 18.6%) over cycles 1–7 compared with approximately 12% of women receiving the comparator EE/LNG formulation (ranging from 9.9% to 17.1%).\textsuperscript{27} In the open-label, North American E\textsubscript{2}V/DNG study, intracyclic bleeding ranged from 28.8% to 11.2% during cycles 2–13, with the data generally indicative of a tendency to less intracyclic bleeding with continued use.\textsuperscript{36} For E\textsubscript{2}/NOMAC, in the study conducted in Europe, Asia, and Australia, intracyclic bleeding progressively decreased with continued E\textsubscript{2}/NOMAC use from about 34% to 14% (through cycles 1–13); a similar trend was observed with the comparator EE/DRSP (28% to 13% through cycles 1–13).\textsuperscript{30} A similar trend towards progressively decreased intracyclic bleeding with continued E\textsubscript{2}/NOMAC use (from about 31% to 16% through cycles 1–13) was also observed in the study conducted in North and South America.\textsuperscript{19}

The overall bleeding profile associated with E\textsubscript{2}V/CPA is less well characterized compared with the other two approved E\textsubscript{2}-based formulations. In the pivotal, open-label, noncomparative study in Finnish women, intracyclic bleeding occurred in 33% of E\textsubscript{2}V/CPA users (mainly spotting) at 3 months, decreasing to 22% at 6 months and 24% at 12 months.\textsuperscript{34} Much lower rates of intracyclic bleeding were reported with E\textsubscript{2}V/CPA (n=26) in a second study (0%–15%), which was a randomized double-blind trial including biphasic E\textsubscript{2}V/norethisterone, but it is not clear from the report whether the incidence of spotting (20%–40%) included intracyclic bleeding.\textsuperscript{41} Using the comparator E\textsubscript{2}V/norethisterone (n=24), intracyclic bleeding occurred in 6%–42% of women (highest during the second cycle). Absent bleeding with E\textsubscript{2}V/CPA ranged between 5% and 19% (versus 6%–25% in the comparator group). The mean number of bleeding/spotting days per cycle decreased from 5.0 ± 1 days in the pretreatment cycle to 3.8 ± 3 days by cycle 12. In contrast, the number of bleeding/spotting days per cycle remained relatively stable with the comparator E\textsubscript{2}V/norethisterone (between 4.9 ± 1.2 days to 5.2 ± 2.5 days).

Hemostasis, lipid, and carbohydrate metabolism, and other parameters

Generally, E\textsubscript{2} and E\textsubscript{1} at equimolar doses are expected to have similar influences on hemostasis, lipids, and carbohydrate metabolism parameters, but less than those observed with EE. However, surrogate indices of hemostasis, lipids, and carbohydrate metabolism, or any other surrogate marker, cannot be translated into meaningful clinical outcomes, and the risk of cardiovascular events in users of oral contraceptives containing E\textsubscript{2} or E\textsubscript{1} needs to be established in large-scale, post-marketing, prospective, Phase IV cohort studies. Indeed, two large international active surveillance studies, i.e., the International Active Surveillance Study-Safety of Contraceptives: Role of Estrogens (INAS SCORE)\textsuperscript{53} and the Choice of estrogen and long-term investigation of nomegestrol acetate–International Active Surveillance Study (INAS-CELINA)\textsuperscript{44} are currently underway to investigate the occurrence of adverse cardiovascular events within a 5-year period in COC users (including E\textsubscript{2}V/DNG and E\textsubscript{2}/NOMAC, respectively). To the best of our knowledge, no such active surveillance studies have been undertaken or are planned for the E\textsubscript{2}V/CPA oral contraceptive.

The impact of E\textsubscript{2}V/DNG and E\textsubscript{2}/NOMAC on hemostatic parameters over three cycles.\textsuperscript{41} Both total cholesterol and high-density lipoprotein cholesterol were reported to decrease (by 9% and 5%, respectively) relative to baseline over 13 cycles in one study,\textsuperscript{41} but no significant changes were reported in total cholesterol or high-density lipoprotein cholesterol in the pivotal Finnish study.\textsuperscript{41} In the latter study, serum triglyceride levels increased >20% over 13 cycles.\textsuperscript{34}

The effect of E\textsubscript{2}V/DNG and E\textsubscript{2}/NOMAC on hemostatic and lipid parameters relative to EE-based oral contraceptive comparators is summarized in Table 3; both formulations appear to have less influence on these parameters than the EE-based formulations.\textsuperscript{61–64} However, it is important to keep in mind that none of these potential surrogate markers of venous thromboembolism risk have ever been validated. Estrogens influence both thrombotic and fibrinolytic pathways, and the net effect on hemostasis is difficult to predict.\textsuperscript{65} High-density lipoprotein cholesterol and low-density lipoprotein cholesterol were reported to increase and decrease, respectively, with both E\textsubscript{2}V/DNG and E\textsubscript{2}/NOMAC during up to seven cycles of treatment. The overall changes relative to baseline in these parameters were <10% for E\textsubscript{2}V/DNG.
Table 3 Changes from baseline in hemostatic, lipid, and carbohydrate metabolism indices

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Junge et al61,62</th>
<th>Klipping et al63,64</th>
<th>Agren et al48</th>
<th>Gaussem et al65</th>
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<tbody>
<tr>
<td></td>
<td>(7 cycles)</td>
<td>(3 cycles)</td>
<td>(6 cycles)</td>
<td>(3 cycles)</td>
</tr>
<tr>
<td>Hemostasis</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Prothrombin fragment I + 2</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
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<tr>
<td>D-dimer</td>
<td>++</td>
<td>++</td>
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<tr>
<td>Fibrinogen</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>NR</td>
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<td>Factor VII activity</td>
<td>+</td>
<td>+</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td>Factor VIII activity</td>
<td>=</td>
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<tr>
<td>Antithrombin III activity</td>
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<tr>
<td>Protein C activity</td>
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<td>+</td>
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<tr>
<td>APC sensitivity</td>
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<td>=</td>
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<tr>
<td>PAI-1 antigen ratio (aPTT)</td>
<td>NR</td>
<td>NR</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td>PAI-1 antigen activity</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>PAI-1 activity</td>
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<td>Lipid</td>
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<tr>
<td>Total cholesterol</td>
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<td>=</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>High-density lipoprotein</td>
<td>=</td>
<td>=</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Low-density lipoprotein</td>
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<td>=</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Triglycerides</td>
<td>++</td>
<td>++</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Notes: †intravariability change; ‡nAPC-r, Rosing's activated protein C resistance normalized ratio; ‡factor VIa or VIIa; =, no change (<10% change); +, ≥10% increase; –, ≥10% decrease; ++, ≥20% increase; –, ≥20% decrease; +++, ≥50% increase; –, ≥50% decrease.

Abbreviations: APC, activated protein C; aPTT, activated partial thromboplastin time; NR, not reported; PAI-1, plasminogen activator inhibitor type 1; E2, estradiol valerate; DNG, dienogest; NOMAC, nomegestrol acetate; EE, ethinylestradiol; LNG, levonorgestrel.

and <2% for E2/NOMAC.61,63 Total cholesterol increased with both E2/V/DNG and E2/NOMAC, but by ≤5% relative to baseline. Mean increases in endogenous thrombin potential-based activated protein C sensitivity ratios from baseline to cycle 3 were significantly lower with E2/V/DNG (0.09 versus 0.56, P<0.001) and E2/NOMAC (0.20 versus 0.46, P<0.01) than with EE/LNG (EE 30 µg/LNG 150 µg; Microgynon®, Bayer HealthCare Pharmaceuticals) or EE/LNG (EE 20 µg/LNG 100 µg; Miranova) comparators, respectively.62,64 Additionally, insulin and glucose remained relatively unaffected by E2/V/DNG and E2/NOMAC during oral glucose tolerance tests.61,63

The available data across four separate randomized trials seem to suggest that increases in sex hormone binding globulin (SHBG) with both E2/V/DNG and E2/NOMAC are more or less in the same range;61-64 however, increases in SHBG with the EE-based comparators in these studies were more inconsistent. In general, it would be expected that EE increases SHBG levels to a greater extent than E2.10 In COCs, the extent of an EE-induced (or E2-induced) SHBG increase may be attenuated by inclusion of a progestin with androgenic activity.10 Of note, the progestins used in the three approved E2-containing oral contraceptives do not have any androgenic activity,46 and as such are not expected to attenuate the limited estrogen-induced SHBG increase with the E2-containing oral contraceptives.

Safety and tolerability

The relevance of nonspecific adverse events with oral contraceptives reported outside randomized placebo-controlled trials has been questioned because the limited level 1 evidence suggests that these nonspecific events may not occur significantly more often with oral contraceptives and that they may simply reflect their background prevalence in the population.67 With this in mind, the adverse events reported in the E2/V/CPA, E2/V/DNG, or E2/NOMAC studies with ≥250 patients receiving one of the three oral contraceptives that were judged to be treatment-related were in general typical of those reported with EE-based oral contraceptives.27,30,35,36,39 Results from the randomized comparator studies of E2/V/DNG and E2/NOMAC show a similar distribution of adverse events. In the only placebo-controlled studies, where E2/V/DNG was used to manage heavy menstrual bleeding in North America and in Europe/Australia, breast pain and irregular bleeding were more common in women receiving E2/V/DNG, while headache was more commonly reported with placebo (Table 4).37,38 For E2/V/CPA (n=288) in the Finnish study, adverse events reported after 6 months included breast tenderness (9.4%), edema (8.5%),
Common adverse events (in alphabetical order) in subjects treated with estradiol valerate/dienogest or placebo in two randomized trials

<table>
<thead>
<tr>
<th>Adverse events, n (%)</th>
<th>E₂V/DNG (n=264)</th>
<th>Placebo (n=147)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acne</td>
<td>11 (4.2)</td>
<td>3 (2.0)</td>
</tr>
<tr>
<td>Back pain</td>
<td>6 (2.3)</td>
<td>7 (4.8)</td>
</tr>
<tr>
<td>Breast pain</td>
<td>13 (4.9)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Breast tenderness</td>
<td>10 (3.8)</td>
<td>4 (3.7)</td>
</tr>
<tr>
<td>Headache</td>
<td>26 (9.8)</td>
<td>21 (14.2)</td>
</tr>
<tr>
<td>Metrorrhagia</td>
<td>14 (5.3)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>21 (8.0)</td>
<td>4 (6.8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>13 (4.9)</td>
<td>7 (4.7)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5 (1.9)</td>
<td>6 (4.1)</td>
</tr>
</tbody>
</table>

Notes: Adapted with permission from Fraser IS, Rämer T, Parke S, et al. Effective treatment of heavy and/or prolonged menstrual bleeding with an oral contraceptive containing estradiol valerate and dienogest: a randomized, double-blind Phase III trial. Hum Reprod. 2011;26:2698–2708. Adapted with permission from Lippincott Williams & Wilkins/Wolters Kluwer Health: Obstet Gynecol. Jensen JT, Parke S, Mellinger U, Machlitt A, Fraser IS. Effective treatment of heavy menstrual bleeding with estradiol valerate and dienogest: a randomized controlled trial. 2011;117:777–787. Copyright © 2011. Promotional and commercial use of the material in print, digital or mobile device format is prohibited without the permission from the publisher Lippincott Williams & Wilkins. Please contact journalpermissions@ww.com for further information.

Abbreviations: E₂V, estradiol valerate; DNG, dienogest.

headache (6.6%), and depression (4.2%), decreasing to 7.7%, 5.5%, 4.4%, and 2.7%, respectively, by 12 months.

Discontinuations due to adverse events during up to 20 cycles of treatment with E₂V/DNG were reported to be up to 14%,27,35,36 with discontinuations due to bleeding problems ranging up to 5% over the first year of use.6 Similar discontinuation rates were documented for E₂/NOMAC, with up to 18% discontinuating due to adverse events over one year and up to 5% due to bleeding problems.6,39 For E₂V/CPA, 16% of women discontinued due to adverse events typically related to hormone use (“edema, breast tenderness, headache, weight change, and mood changes”) over one year and 9% due to menstrual problems.34

The effects of E₂/NOMAC (n=56) on bone mineral density were compared with those of EE/LNG (EE 30 µg/LNG 150 µg; Microgynon, n=54) in women aged 20–35 years over 2 years in a randomized controlled trial.86 No clinically relevant effects on bone mineral density were observed during this time with E₂/NOMAC or with the EE/LNG oral contraceptive comparator. In the absence of data on the effects of E₂V/DNG or E₂V/CPA on bone mineral density, it might be postulated that because similar doses of E₂ are used relative to E₂/NOMAC, the effects on bone density would be similar.

Other indications and benefits

The choice between the E₂V/CPA, E₂V/DNG, and E₂/NOMAC formulations is currently restricted by regional availability; so far, only Finnish women have access to all three E₂-based formulations. Elsewhere, women have either the option of E₂V/DNG or E₂/NOMAC (eg, Europe) or E₂V/DNG (eg, the US) alone as the only available E₂-based formulations.

Several studies have been conducted with E₂V/DNG to assess additional health benefits. No studies assessing additional health benefits associated with the other two E₂-based formulations have been published. E₂V/DNG has been shown to profoundly reduce menstrual blood loss in women with objectively confirmed heavy menstrual bleeding without organic pathology in two randomized, placebo-controlled, double-blind studies, one conducted in the US and Canada and the other in Europe and Australia.37,38 These studies led to the approval of E₂V/DNG for the treatment of heavy menstrual bleeding, a unique indication for this oral contraceptive formulation. The effect is rapid, with the greatest reduction in menstrual blood loss achieved by the first withdrawal bleed after treatment initiation and maintained with no loss of effect with continued treatment. Moreover, the observed reduction in menstrual blood loss with E₂V/DNG (median 88% reduction after seven cycles of treatment) appears to approach that achieved with the LNG-releasing intrauterine system.69 Overall, 64% of women with excessive menstrual blood loss receiving E₂V/DNG met the study criteria for treatment success (defined as menstrual blood loss <80 mL and a ≥50% reduction from baseline) compared with only 12% with placebo.70 Secondary endpoints in the two randomized studies included the impact of treatment with E₂V/DNG on heavy menstrual bleeding-related impairment of work productivity (presenteeism) and activities of daily living.71,72 These studies showed that E₂V/DNG had a consistent positive impact on work productivity and activities of daily living in women with heavy menstrual bleeding, and that these improvements could be translated into a reduction in the monetary burden associated with this condition.

Two more randomized, double-blind, active-controlled studies, one conducted in North America and the other in Western Europe, Thailand, Australia, and Mexico, were undertaken to assess the effect of E₂V/DNG on hormone withdrawal-associated symptoms (principally headache or pelvic pain) in women (n=414, across both studies) who experienced these symptoms with other COCs taken in the traditional 21/7 regimen.73,74 Switching to E₂V/DNG was shown to reduce the severity of these symptoms to a greater extent than switching to comparator triphasic EE/norgestimate (Ortho Tri-Cyclen® Lo, Ortho-McNeil-Janssen Pharmaceuticals Inc, Raritan, NJ, USA; n=204) or a monophasic EE/LNG (Microgynon; n=218).
A multicenter, double-blind, randomized study was conducted in Europe and Asia/Pacific to determine the effect of E$_2$ V/DNG (n=92) on oral contraceptive-related sexual dysfunction using EE/LNG (Microgynon, n=99) as a comparator. Among women reporting baseline sexual dysfunction while using an oral contraceptive, switching to either E$_2$ V/DNG or EE/LNG resulted in similar improvements in desire and arousal, a reduction in associated distress, and decreased vaginal symptoms. A study from Italy also suggested some benefit on sexual function with E$_2$ V/DNG (n=57), but the open-label noncomparative nature of this study provides no reference for the observed changes, making it impossible to draw conclusions from these results.

**Conclusion**

In summary, E$_2$ V/DNG, E$_2$/NOMAC, and E$_2$ V/CPA are all effective oral contraceptives. The contraceptive effectiveness of E$_2$ V/CPA was, however, assessed in women with a mean age of 39 years, and as such may not be directly generalizable to younger more fertile women. Although direct comparability between the studies is difficult, the available data suggest that E$_2$ V/DNG and E$_2$/NOMAC may have better bleeding profiles than E$_2$ V/CPA. Currently, E$_2$ V/DNG is the only oral contraceptive approved for the treatment of heavy menstrual bleeding. Emerging data suggest that E$_2$ V/DNG may be a good alternative to other COCs taken in the conventional 21/7 regimen for women susceptible to hormone-associated withdrawal symptoms, but there is insufficient evidence to conclude whether the effect is due to the components of the formulation or the dosage regimen. Both E$_2$ V/DNG and E$_2$/NOMAC generally have minimal influence on hemostatic, lipid, and carbohydrate metabolism parameters, or induce less change in these parameters than EE-based oral contraceptives. Whether these differences can translate into meaningful clinically important outcomes (specifically cardiovascular events) needs to be established in future large-scale prospective studies.

**Disclosure**

Jeffrey T Jensen has received payments for consulting and giving talks for Bayer HealthCare Pharmaceuticals, a company that may have a commercial interest in the results of this research and technology. This potential conflict of interest has been reviewed and managed by Oregon Health and Science University. Jeffrey T Jensen is also a consultant and speaker for Merck Sharp & Dohme, a consultant for HRA Pharma and Agile Pharmaceuticals, and has received research funding from Abbott Pharmaceuticals, Bayer HealthCare, Warner Chilcott, the Population Council, and the National Institutes of Health. Johannes Bitzer has participated in advisory boards for Bayer HealthCare Pharmaceuticals, Merck Sharp & Dohme, Lilly, Solvay Pharma, and Boehringer Ingelheim, and has lectured at meetings supported by Bayer HealthCare Pharmaceuticals, Merck Sharp & Dohme, Lilly, Solvay Pharma, and Boehringer Ingelheim. Marco Serrani is an employee of Bayer HealthCare Pharmaceuticals, the manufacturer of E$_2$ V/DNG. Richard Glover and Latoya M Mitchell of inScience Communications, Springer Healthcare, provided writing assistance during development of this manuscript. This assistance was funded by Bayer HealthCare Pharmaceuticals.

**References**


