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REVIEW

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

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Abstract: Three estradiol (E_2)-containing oral contraceptives, estradiol valerate/cyproterone acetate (E_2V/CPA, Femilar®), estradiol valerate/dienogest (E_2V/DNG, Qlaira®/Natazia™), and estradiol/nomegestrol acetate (E_2/NOMAC; Zoely®), have received approval for use in general practice. Only Finnish women currently have access to all three E_2-based formulations. E_2/NOMAC is currently approved only in Europe, while E_2V/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 E_2-containing oral contraceptives. A literature search was conducted using the Ovid interface and a combination of free search terms relevant to estradiol and oral contraception to identify suitable articles for inclusion in this review. The available data show that E_2V/DNG, E_2/NOMAC, and E_2V/CPA are all effective oral contraceptives. While direct comparisons are lacking, indirect evidence suggests that E_2V/DNG and E_2/NOMAC may have better bleeding profiles than E_2V/CPA. E_2V/DNG is also approved for the treatment of heavy menstrual bleeding. Both E_2V/DNG and E_2/NOMAC have minimal influence on hemostatic, lipid, and carbohydrate metabolism parameters, or induce less change in these parameters relative to ethinylestradiol-based oral contraceptives. However, the predictive value of these surrogate parameters is a matter of debate, and whether these differences can be translated into meaningful clinical outcomes needs to be established in large-scale, post-marketing, prospective, Phase IV cohort studies. Future studies are required to determine whether E_2-based oral contraceptives confer additional benefits compared with those of ethinylestradiol-based COCs.

Keywords: estradiol valerate, dienogest, nomegestrol acetate, cyproterone acetate

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.[1] Drospirenone (DRSP), dienogest (DNG), and nomegestrol acetate (NOMAC) are the most recent progestins introduced to the market, and products containing nestorone and trimegestone are 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,[2] COCs with lower EE doses tend to have poorer cycle control (ie, unscheduled bleeding and/

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or spotting) relative to formulations with the same progestin and a higher EE dose.[2–4] Very low-dose EE products administered in a 24/4 and 26/2 regimen (15 μg in combination with gestodene 60 μg,[5] and 10 μg in combination with norethindrone acetate 1 mg,[6] respectively) have been approved. Although EE 15 μg/gestodene 60 μg appears to have acceptable cycle control and tolerability,[7,8] no data are available for EE 10 μg/norethindrone acetate 1 mg. Although the reduction of the EE dose to less than 50 μg has greatly improved the cardiovascular safety profile of combined pills, the benefit of dose reduction to 20 μg or lower has not been definitively established.[9] Even with modern "low-dose" EE formulations, factors related to hepatic and carbohydrate metabolism, as well as hemostasis, may be maintained at an upregulated level. Biological potency of estrogens depends on ligand-receptor interactions plus the rate of absorption, distribution, metabolism, and elimination. For EE, both its receptor binding affinity and its biological potency with regard to various clinical and metabolic parameters are usually greater than with estradiol (E_2).[10,11] Reliance on the use of EE in COCs has largely been due to its higher oral bioavailability (38%–48%) compared with other estrogens.[10] Inclusion of a 17α-ethinyl group on estradiol greatly enhances oral activity due to inhibition of hepatic metabolism, in particular, reduced metabolism to weaker estrogens. Oral EE is completely and rapidly absorbed in the gastrointestinal tract, undergoing oxidation to yield free hydroxylated and methylated active metabolites plus sulfate and glucuronide conjugates during first-pass metabolism in the gut and liver.[12] In contrast, oral E_2 is completely absorbed in the gastrointestinal tract and undergoes extensive metabolism to less potent estrone and estrone sulfate during the absorption process and in the liver.[13] As a result, oral bioavailability of estradiol is typically only about 3%–6%.[12]

The higher intrinsic estrogenic activity of EE combined with the reduced degradation and active metabolites results in more pronounced effects on hepatic metabolism and hemostatic changes relative to E_2. More simply put, oral EE activates the liver through both a first-pass effect and recirculation of EE, while hepatic activation of oral E_2 occurs predominantly through first pass. For this reason, even non-oral routes of EE administration result in dose-related effects on hepatic globulins.[14] It has been hypothesized that using oral E_2 might reduce the relative impact on the hepatic and hemostatic effects and adverse events associated with EE, given that activation by recirculation does not occur.[15,16]

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.[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 17β-estradiol dehydrogenase. This enzyme rapidly converts E_2 (but not EE) into estrone (E_1),[22,23] an estrogen with only weak estrogenic activity that is unable to maintain stable endometrial proliferation.[23] The rate of transformation of E_2 to its metabolites may be influenced by some progestins;[13] consequently, progestins with minimal impact on E_2 metabolism and endometrial stroma stability may improve cycle stability with E_2-based oral contraceptives.[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_2V/CPA; Femilar®, Bayer Oy, Turku, Finland), estradiol valerate/dienogest (E_2V/DNG; Qlaira®/Natazia™, Bayer HealthCare Pharmaceuticals, Berlin, Germany), and estradiol/nomegestrol acetate (E_2/NOMAC; Zoely®; 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_2V/DNG, E_2/NOMAC, and E_2V/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 contracep* (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 E_2-containing COCs were chosen for inclusion in this review.

Approved formulations and regimens

E_2V/CPA is a biphasic preparation taken in a 21/7 cycle regimen (E_2V 1 mg/CPA 1 mg on days 1–10, E_2V 2 mg/CPA 2 mg on days 11–21, and a 7-day pill-free interval). The rationale for the biphasic E_2V/CPA regimen has not been discussed in the literature, but phasic regimens are generally used in order to optimize control of bleeding.

E_2V/DNG is taken in a 26/2 cycle, with E_2V 3 mg on days 1–2, E_2V 2 mg/DNG 2 mg on days 3–7, E_2V 2 mg/DNG 3 mg on days 8–24, E_2V 1 mg on days 25–26, and placebo on days 27–28. This specific regimen was established as the lowest effective dose of E_2V combined with DNG for efficient ovulation inhibition while maintaining acceptable bleeding control.[25,26] The regimen for E_2V/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]

E_2/NOMAC is a monophasic preparation taken over a cycle of 24/4 days (E_2 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 E_2 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 E_2/NOMAC is based, in part, on the greater ovarian suppression achieved relative to the conventional 21/7 regimen, 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 E_2) and associated hormone withdrawal symptoms.[29] The bleeding control achieved with E_2/NOMAC has been hypothesized to be due to the ability of NOMAC to maintain endometrial stability through its minimal impact on endometrial E_2 metabolism, which ensures sufficient E_2 levels in the endometrium and thus prevents endometrial breakdown.[24,30]

The absolute bioavailability of E_2 following oral E_2/NOMAC administration was estimated to range between 1% and 5%,[31] and that following oral E_2V/DNG administration to be about 3%–6%.[32] E_2V is rapidly hydrolyzed and converted to 17β-estradiol (E_2) during absorption in the gastrointestinal tract following oral administration (1 mg of

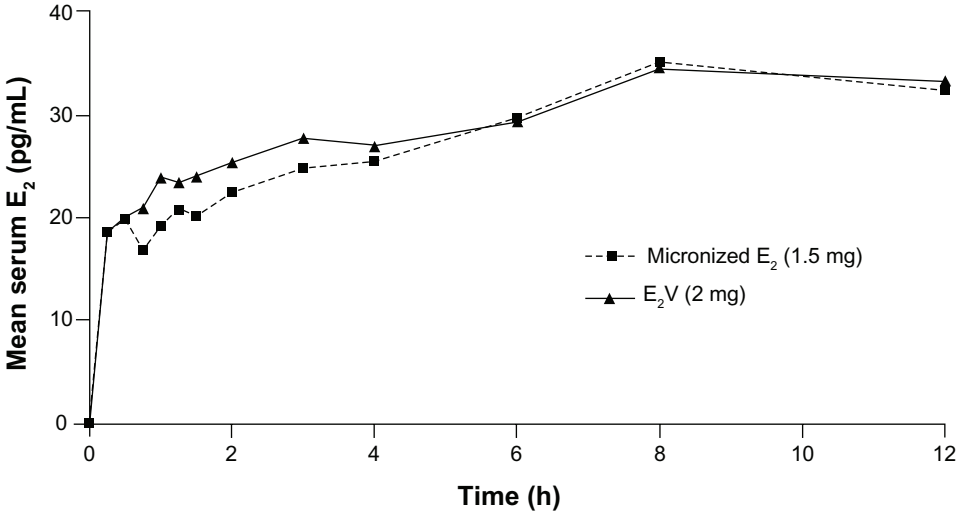

Figure 1 Estradiol serum concentration-time curves following single oral doses of micronized E_2 (2 mg) and E_2V (2 mg). Data obtained from postmenopausal women.
Note: Data used to create the figure taken with permission from Timmer CJ, Geurts TB. Bioequivalence assessment of three different estradiol 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: E_2, estradiol; E_2V, estradiol valerate; h, hours.

E_2V contains 0.76 mg of E_2).[23] The E_2 pharmacokinetic profile following oral micronized E_2 (1.5 mg) appears to be similar to that following oral E_2V (2 mg, Figure 1).[33]

Indications and pivotal studies for approved E_2-containing COCs

E_2V/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 E_2V/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.[34]

E_2V/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, noncomparative efficacy trials, one undertaken in Europe and the other in the US and Canada.[35,36] The European study enrolled 1,377 women aged 18–50 years and was conducted over twenty 28-day cycles.[35] 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.[36] This latter study, although undertaken to assess contraceptive efficacy, cycle control, and safety of E_2V/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).[37,38]

E_2/NOMAC is available in Europe, Australia, and some South American countries, and is indicated for contraception. There were two pivotal registration studies for E_2/NOMAC, one conducted in Europe, Asia, and Australia[30] and the other in the US.[39] Both studies were randomized open-label, comparative trials that recruited women aged 18–50 years, of whom 3,323 were randomized to receive E_2/NOMAC 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 E_2V/CPA, E_2V/DNG, and E_2/NOMAC, as well as the individual progestin components (CPA, DNG, and NOMAC, respectively), have been well documented.[26,34,40–43] 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.[44]

CPA 1 mg daily appears sufficient to inhibit ovulation.[43] 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, E_2, and progesterone) in all women assessed (n=5).[43] 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.[42] 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 E_2 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 E_2, follicle-stimulating hormone, and luteinizing hormone levels.[45] 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.[46] 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).[40] These data support cervical mucus inhibition as a secondary contraceptive mechanism.

The approved formulations of E_2V/CPA, E_2V/DNG, and E_2/NOMAC all consistently inhibit ovulation in ≥95% of women.[26,34,40,41,47] However, studies with E_2V/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.[34,41] In addition, the contraceptive effects of E_2V/CPA achieved through alteration in cervical mucus and the endometrium have not, to our knowledge, been reported. E_2V/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.[48] Similar changes in cervical mucus and the endometrium were observed with E_2/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 E_2V/CPA, E_2V/DNG, and E_2/NOMAC formulations appear to have similar contraceptive efficacy profiles (Table 1).[30,34–36,39] The net pregnancy rate with E_2V/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.[34] Again this may be an overestimation of the contraceptive efficacy of E_2V/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 E_2V/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 E_2/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,[30] and the other in the US, Canada, Argentina, Brazil, Chile, and Mexico,[39] 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 E_2/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 E_2V/DNG and E_2/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 E_2-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

Formulation	Study location	Treatment duration	Age group, years	n	Exposure	Pregnancies (n)	Pearl Index	Upper 95% CI
E_2V/CPA[34]	Finland	1 year	30–49	288	2,800 cycles	1	0.46	
E_2V/DNG[35]	Austria,	20 cycles	18–50	1,377	23,368 cycles	13	0.73	1.24
	Germany,		18–35	998	16,608 cycles	12	0.94	1.65
	Spain		>35–50	379	6,760 cycles	1	0.19	
E_2V/DNG[36]	US, Canada	1 year	18–35	490	3,969 cycles	5	1.64	3.82
E_2/NOMAC[30]	Europe, Asia,	1 year	18–50	1,587	1,293 woman-years	4	0.31	0.79
	Australia		18–35	1,315	1,058 woman-years	4	0.38	0.97
			>35–50	272	235 woman-years	0	0	
E_2/NOMAC[39]	US, Canada,	1 year	18–50	1,634	1,146 woman-years	13	1.13	1.94
	Argentina, Brazil,		18–35	1,375	946 woman-years	12	1.27	2.22
	Chile, Mexico		>35–50	259	235 woman-years	1	0.43	

Abbreviations: CI, confidence interval; CPA, cyproterone acetate; E_2V, estradiol valerate; DNG, dienogest; NOMAC, nomegestrol acetate; E_2, 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 E_2V/CPA, E_2V/DNG, and E_2/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 E_2V/DNG and E_2/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 E_2V/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 E_2V/DNG and E_2/NOMAC compared with the comparator EE-based oral contraceptives.[27,30,39] There are no available bleeding data with E_2V/CPA where the data are reported by reference period.

The data reported by cycle with both E_2V/DNG and E_2/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 E_2V/DNG compared with 7.7% (range 6.2%–10.5%) in women treated with EE/LNG.[27] In the open-label North American E_2V/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 E_2/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 E_2/NOMAC, but not with EE/DRSP (approximately 4%–9%), in the study conducted in North and South America.[39]

Table 2 Number of bleeding/spotting days associated with E_2V/DNG and E_2/NOMAC in randomized comparator studies (data displayed as means)

Study	Ahrendt et al[27,‡]							Mansour et al[30,#,‡]							Westhoff et al[39,‡]						
Formulation	E_2V/DNG				EE/LNG			E_2/NOMAC				EE/DRSP			E_2/NOMAC				EE/DRSP		
Reference period	R1	R2	R3	R4	R1	R2	R3	R4	R1	R2	R3	R4	R1	R2	R3	R4	R1	R2	R3	R4	R1	R2	R3	R4
Bleeding/spotting days (n)	17.3*	13.4*	–	–	21.5	15.9	–	–	15.0	12.5	11.0	10.5	18.5	16.5	16.0	19.5	14.8*	–	–	9.5*	17.7	–	–	19.3
Spotting days (n)	–	–	–	–	–	–	–	–	9.0	8.0	7	6.5	8.0	7.0	6.5	7.0	8.9	–	–	5.4	7.9	–	–	7.7

Notes: #Data estimated from published graphs; ‡91-day reference period used; *$p<0.001$ versus comparator; †90-day reference period used.
Abbreviations: E_2V, estradiol valerate; DNG, dienogest; NOMAC, nomegestrol acetate; DRSP, drospirenone; LNG, levonorgestrel; EE, ethinylestradiol.

Intracyclic bleeding was reported to occur in approximately 14% of women receiving E_2V/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% to17.1%).[27] In the open-label, North American E_2V/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.[36] For E_2/NOMAC, in the study conducted in Europe, Asia, and Australia, intracyclic bleeding progressively decreased with continued E_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).[30] A similar trend towards progressively decreased intracyclic bleeding with continued E_2/NOMAC use (from about 31% to 16% through cycles 1–13) was also observed in the study conducted in North and South America.[39]

The overall bleeding profile associated with E_2V/CPA is less well characterized compared with the other two approved E_2-based formulations. In the pivotal, open-label, noncomparative study in Finnish women, intracyclic bleeding occurred in 33% of E_2V/CPA users (mainly spotting) at 3 months, decreasing to 22% at 6 months and 24% at 12 months.[34] Much lower rates of intracyclic bleeding were reported with E_2V/CPA (n=26) in a second study (0%–15%),which was a randomized double-blind trial including biphasic E_2V/norethisterone, but it is not clear from the report whether the incidence of spotting (20%–40%) included intracyclic bleeding.[41] Using the comparator E_2V/norethisterone (n=24), intracyclic bleeding occurred in 6%–42% of women (highest during the second cycle). Absent bleeding with E_2V/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 ± 3.3 days by cycle 12. In contrast, the number of bleeding/spotting days per cycle remained relatively stable with the comparator E_2V/norethisterone (between 4.9 ± 1.2 days to 5.2 ± 2.5 days).

Hemostasis, lipid, and carbohydrate metabolism, and other parameters

Generally, E_2 and E_2V 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_2 or E_2V needs to be established in large-scale, post-marketing, prospective, Phase IV cohort studies. Indeed, two large international active surveillance studies, ie, the International Active Surveillance Study-Safety of Contraceptives: Role of Estrogens (INAS SCORE)[53] and the Choice of estrogen and long-term investigation of nomegestrol acetate–International Active Surveillance Study (INAS-CELINA)[54] are currently underway to investigate the occurrence of adverse cardiovascular events within a 5-year period in COC users (including E_2V/DNG and E_2/NOMAC, respectively). To the best of our knowledge, no such active surveillance studies have been undertaken or are planned for the E_2V/CPA oral contraceptive.

Large prospective cohort studies have the best ability to assess uncommon adverse outcomes like venous thrombosis, because their design allows for collection of baseline information on important confounders, such as obesity and age.[55–57] Recently published database studies have suggested that oral contraceptives containing CPA, desogestrel, or DRSP in combination with EE are associated with an elevated risk of venous thrombosis compared with LNG pills.[58,59] However, a large prospective Phase IV study similar in design to the INAS-CELINA and INAS-SCORE studies did not demonstrate an increase in risk for deep vein thrombosis with these progestins.[60]

E_2V/CPA appears to have minimal influence on hemostatic parameters over three cycles.[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,[41] but no significant changes were reported in total cholesterol or high-density lipoprotein cholesterol in the pivotal Finnish study.[34] In the latter study, serum triglyceride levels increased >20% over 13 cycles.[34]

The impact of E_2V/DNG and E_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.[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.[65] High-density lipoprotein cholesterol and low-density lipoprotein cholesterol were reported to increase and decrease, respectively, with both E_2V/DNG and E_2/NOMAC during up to seven cycles of treatment. The overall changes relative to baseline in these parameters were <10% for E_2V/DNG

Table 3 Changes from baseline in hemostatic, lipid, and carbohydrate metabolism indices

	Junge et al[61,#] (7 cycles)		Klipping et al[62,#] (3 cycles)		Agren et al[63] (6 cycles)		Gaussem et al[64] (3 cycles)	
Formulation	**E_2V/DNG**	**EE/LNG**	**E_2V/DNG**	**EE/LNG**	**E_2/NOMAC**	**EE/LNG**	**E_2/NOMAC**	**EE/LNG**
Hemostasis								
Prothrombin fragment 1 + 2	=	+++	=	++	=	+	=	+
D-dimer	=	+++	++	+++	=	=	– –	+
Fibrinogen	=	++	+	++	NR	NR	=	+
Factor VII activity	+	++	=	=	=$^{\Phi}$	+$^{\Phi}$	NR	NR
Factor VIII activity	=	=	=	=	=	=	=	=
Antithrombin III activity	=	=	=	=	=	=	=	=
Protein C activity	=	+	=	=	=‡	=‡	NR	NR
APC sensitivity ratio (aPTT)	=	=	=	=	=	=	NR	NR
APC sensitivity ratio	NR	NR	=$^{¥}$	++$^{¥}$	+++	+++	++$^{¥}$	++$^{¥}$
PAI-1 antigen	–	– –	NR	NR	NR	NR	– –	– – –
PAI-1 activity	=	=	NR	NR	NR	NR	NR	NR
Lipid								
Total cholesterol	=	=	NR	NR	=	=	NR	NR
High-density lipoprotein	=	=	NR	NR	=	–	NR	NR
Low-density lipoprotein	=	=	NR	NR	=	=	NR	NR
Triglycerides	++	++	NR	NR	=	+	NR	NR

Notes: #Intraindividual change; ¥nAPC-r, Rosing's activated protein C resistance normalized ratio; $^{\Phi}$factor V11a or VIIc; =, 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; E_2V, estradiol valerate; DNG, dienogest; NOMAC, nomegestrol acetate; EE, ethinylestradiol; LNG, levonorgestrel.

and <2% for E_2/NOMAC.[61,63] Total cholesterol increased with both E_2V/DNG and E_2/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 E_2V/DNG (0.09 versus 0.56, $P<0.001$) and E_2/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 E_2V/DNG and E_2/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 E_2V/DNG and E_2/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 E_2.[10] In COCs, the extent of an EE-induced (or E_2-induced) SHBG increase may be attenuated by inclusion of a progestin with androgenic activity.[10] Of note, the progestins used in the three approved E_2-containing oral contraceptives do not have any androgenic activity,[66] and as such are not expected to attenuate the limited estrogen-induced SHBG increase with the E_2-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 I 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 E_2V/CPA, E_2V/DNG, or E_2/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 E_2V/DNG and E_2/NOMAC show a similar distribution of adverse events. In the only placebo-controlled studies, where E_2V/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 E_2V/DNG, while headache was more commonly reported with placebo (Table 4).[37,38] For E_2V/CPA (n=288) in the Finnish study, adverse events reported after 6 months included breast tenderness (9.4%), edema (8.5%),

Table 4 Common adverse events (in alphabetical order) in subjects treated with estradiol valerate/dienogest or placebo in two randomized trials

Adverse events, n (%)	E_2V/DNG (n=264)	Placebo (n=147)
Subject-reported events		
Acne	11 (4.2)	3 (2.0)
Back pain	6 (2.3)	7 (4.8)
Breast pain	13 (4.9)	0 (0.0)
Breast tenderness	10 (3.8)	4 (3.7)
Headache	26 (9.8)	21 (14.2)
Metrorrhagia	14 (5.3)	1 (0.7)
Nasopharyngitis	21 (8.0)	4 (6.8)
Nausea	13 (4.9)	7 (4.7)
Vomiting	5 (1.9)	6 (4.1)

Notes: Adapted with permission from Fraser IS, Römer 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.[37] 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.[38]

Abbreviations: E_2V, 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.[34]

Discontinuations due to adverse events during up to 20 cycles of treatment with E_2V/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.[36] Similar discontinuation rates were documented for E_2/NOMAC, with up to 18% discontinuing due to adverse events over one year and up to 5% due to bleeding problems.[30,39] For E_2V/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 E_2/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.[68] No clinically relevant effects on bone mineral density were observed during this time with E_2/NOMAC or with the EE/LNG oral contraceptive comparator. In the absence of data on the effects of E_2V/DNG or E_2VCPA on bone mineral density, it might be postulated that because similar doses of E_2 are used relative to E_2/NOMAC, the effects on bone density would be similar.

Other indications and benefits

The choice between the E_2V/CPA, E_2V/DNG, and E_2/NOMAC formulations is currently restricted by regional availability; so far, only Finnish women have access to all three E_2-based formulations. Elsewhere, women have either the option of E_2V/DNG or E_2/NOMAC (eg, Europe) or E_2V/DNG (eg, the US) alone as the only available E_2-based formulations.

Several studies have been conducted with E_2V/DNG to assess additional health benefits. No studies assessing additional health benefits associated with the other two E_2-based formulations have been published. E_2V/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 E_2V/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 E_2V/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 E_2V/DNG met the study criteria for treatment success (defined as menstrual blood loss $<$80 mL and a $\geq$50% reduction from baseline) compared with only 12% with placebo.[70] Secondary endpoints in the two randomized studies included the impact of treatment with E_2V/DNG on heavy menstrual bleeding-related impairment of work productivity (presenteeism) and activities of daily living.[71,72] These studies showed that E_2V/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 E_2V/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 E_2V/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_2V/DNG (n=92) on oral contraceptive-related sexual dysfunction using EE/LNG (Microgynon, n=99) as a comparator.[75] Among women reporting baseline sexual dysfunction while using an oral contraceptive, switching to either E_2V/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_2V/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.[76]

Conclusion

In summary, E_2V/DNG, E_2/NOMAC, and E_2V/CPA are all effective oral contraceptives. The contraceptive effectiveness of E_2V/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_2V/DNG and E_2/NOMAC may have better bleeding profiles than E_2V/CPA. Currently, E_2V/DNG is the only oral contraceptive approved for the treatment of heavy menstrual bleeding. Emerging data suggest that E_2V/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 dosing regimen. Both E_2V/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

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