Changing convention in combination oral contraceptives: estradiol and nomegestrol acetate in a monophasic 24/4 regimen

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ABSTRACT

Initial oral contraceptive regimens were characterised by high doses of ethinylestradiol (EE) and a progestogen in a 21-day regimen that either included seven additional hormone-free tablets or simply the 21 days of combination hormonal tablets. These regimens were developed to ensure high contraceptive effectiveness, regular and predictable withdrawal bleeding episodes to mimic a menstrual cycle, and minimal unscheduled vaginal bleeding. However, these regimens were associated with adverse tolerability and safety issues resulting from the dose and characteristics of their hormonal components. Attempts to ameliorate these adverse issues included the development of lower-dose EE regimens, the incorporation of new progestogens, multiphasic regimens, and reduced hormone-free interval regimens. However, the EE component has remained a constant until the recent approval of combination oral contraceptives with an estrogen component other than EE. The development and introduction of an estradiol-based oral contraceptive regimen is presented in this review.

INTRODUCTION

The introduction of oral contraceptives in the 1960s represents one of the great advances in women's health, impacting women and society from a medical, social and political viewpoint. While the overall health benefits of contraception and oral contraception have been well documented,¹ there is still considerable debate concerning the role of oral contraceptives and contraception in general in our societies, involving the safety of contraceptives, the responsibilities of governments to provide contraception, and even whether the use of contraception should be permitted. It is surprising that these

Key message points

- This review introduces a new combined oral contraceptive (COC) containing estradiol (E2) in a 24/4 monophasic regimen in combination with nomegestrol acetate (NOMAC).
- This is the first monophasic COC regimen with E2 that has been made available for contraceptive use.
- This regimen has been shown to be effective and well tolerated due to its unique separate and combined pharmacological characteristics of E2 and NOMAC.

debates continue today, with more than 50 years having passed since the initial introduction of the 'Pill.'²

Initial oral contraceptives were characterised by high doses of ethinylestradiol (EE) and a progestogen usually derived from 19-nortestosterone in a 21-day regimen that either included 21 combined hormonal tablets or the 21 tablets plus an additional seven hormone-free tablets in a pill pack to encourage daily use. These regimens were developed to ensure high contraceptive effectiveness, regular and predictable withdrawal bleeding episodes to mimic a menstrual cycle, and minimal unscheduled vaginal bleeding. However, the early use of high doses of EE was associated with a marked increased risk for adverse venous and arterial events, and the early progestational agents were associated with a variety of adverse effects, most notably androgenic side effects and cycle control problems.²

Attempts to ameliorate these issues included the development of lower-dose EE regimens, the introduction of new progestogens, the development of multiphasic regimens involving the progestogen and EE components, and reduced hormone-free interval regimens. However, the EE component has remained a constant in these regimens until now, and even the lowest doses of EE are associated with a variety of safety and tolerability issues, including an increased risk for venous thromboembolic events, unscheduled bleeding and spotting, and missed withdrawal bleeding episodes. One option for reducing the risks associated with estrogencontaining oral contraception is to develop a combination pill using estradiol (E2) rather than EE, with the premise that E2, a naturally occurring estrogen, would be associated with a reduced impact on haemostatic factors and improved tolerability.³

Initial attempts at incorporating E2 into oral contraceptive regimens started in the 1990s. A variety of E2 doses (1–4 mg) and combinations with a variety of progestogens (e.g. norethisterone, desogestrel) were evaluated and generally showed sufficient ovulation inhibition and an acceptable level of contraceptive efficacy.^{4 5} However, none of these regimens were ever developed into commercially available contraceptive regimens because of their generally unacceptable bleeding profiles.⁶

Recently, an oral contraceptive pill containing estradiol valerate (E2V) and dienogest in a multiphasic (four-phasic) regimen characterised by an estrogenic 'step-down' and a progestogenic 'step-up' dosing approach with 26 days of hormonal tablets and only a 2-day hormone-free interval⁷ (Qlaira[®], Natazia[®]; Bayer Pharmaceutical, Berlin, Germany) was approved and introduced in several countries. The estrogen component of this oral contraceptive is E2V, a prodrug in which the valerate side-chain of the molecule is rapidly cleaved to form 17 β -estradiol and valeric acid.

This paper will review the recent introduction of another E2-based combination oral contraceptive in which the E2 component is delivered with 1.5 mg E2 and the progestogen is 2.5 mg nomegestrol acetate (NOMAC) in a monophasic regimen of 24 continuous days of active drug administration followed by four hormone-free days (four tablets of inert ingredients in the pill pack).

PHARMACOLOGY: ESTRADIOL (E2)

The estradiol component found in oral contraceptives and menopausal therapies is chemically identical to endogenous 17 β -estradiol (E2), the most potent of the endogenous estrogens that include estrone (E1), estriol (E3) and estetrol (E4).⁸ However, EE and a closely related compound mestranol, which is metabolised to EE after oral ingestion, were first used in combination oral contraceptives because of their considerably better oral bioavailability compared with E2.⁶ Oral bioavailability of EE is 55% to 80% compared with 2% to 5% for E2.⁵ Different approaches have been undertaken to overcome the relatively low bioavailability of E2, including micronisation and esterification.⁵ Indeed, the aforementioned fourphasic oral contraceptive features E2V as its estrogenic component; E2V is the valerate ester of E2, which is rapidly metabolised to E2 after oral ingestion.

The estrogenic effects and pharmacokinetic profile of E2V and E2 are comparable because E2V is rapidly converted to E2 in the gut and liver.9 The E2 component is then further metabolised to estrone and estrone sulfate, compounds that are considerably less estrogenic than the metabolites that result from the oral ingestion of EE. One milligram of E2V is equivalent to 0.76 mg of 17β-estradiol; however, the biological effect of a 2 mg daily dose of E2V is similar to that of EE 20 µg with regard to its effect on the hypothalamic-pituitary-ovarian axis and resultant effects on the ovaries and endometrium.¹⁰ Indeed, it is this production of less estrogenic metabolites by E2 compared with those produced by EE metabolism that is probably responsible for the reduced impact of oral E2 on metabolic and hepatic parameters compared with EE. Examples of this include a more favourable effect of E2 on lipids and a reduced effect on the synthesis of hepatic proteins, including sex hormone-binding globulin and angiotensinogen compared to EE.^{11 12}

Of considerable interest to those seeking to develop new contraceptives that have a more salutary safety profile is the apparent reduced impact of E2 on markers of hemostasis compared to EE.¹³ While there is currently no direct clinical evidence to support the consideration that E2-based oral contraceptives have a lower risk for thromboembolic events than pills containing EE, the development of a combination oral contraceptive with a reduced risk of thromboembolic events compared with EE-containing pills would clearly be of great interest, assuming the effectiveness and overall tolerability of such E2-based pills were comparable to the EE-containing oral regimens. However, a direct clinical comparison is not yet possible, owing to differences in the metabolism of the two orally active estrogenic compounds and the lack of head-to-head clinical trials.¹⁰

PHARMACOLOGY: NOMEGESTROL ACETATE (NOMAC)

NOMAC is structurally similar to and derived from 19-norprogesterone, in contrast to the majority of orally active contraceptive progestogens that are derived from 19-nortestosterone. NOMAC is a potent and highly selective agonist at the progesterone receptor with little to no binding to other steroid receptors, including the estrogen and glucocorticoid receptors.¹⁴ NOMAC has been shown to have greater anti-estrogenic activity than many commonly used progestogens in combination oral

contraceptive regimens, as well as mild anti-androgenic effects, all of which have important implications for the use of this progestogen in an E2-based oral contraceptive regimen.¹⁵ ¹⁶ In addition, NOMAC has been shown to have an antiproliferative effect on breast cell lines, in contrast to other commonly used oral progestogens, such as gestodene and norgestrel.¹⁵ Indeed, the characteristics of NOMAC, including its antiproliferative effect, anti-estrogenic activity, and ability to reduce accumulation of intracellular estrone, make for a progestogen that could prevent endometrial breakdown and thus make NOMAC a far better progestogen candidate to be combined with E2 rather than the progestogens that were previously combined with E2 and found to be associated with poor cycle control.¹⁵

Oral bioavailability of NOMAC is approximately 63%, with approximately 98% bound to albumin. Maximum serum concentration (C_{max}) after a single oral dose of 3.75 mg NOMAC was achieved at approximately 3 hours with a half-life of approximately 50 hours being reported.¹⁵ ¹⁷ NOMAC and its metabolites are mostly excreted by the gastrointestinal tract, with some excretion occurring in urine. Food intake does not appear to alter the pharmacokinetic profile of NOMAC.¹⁷

CONTRACEPTIVE CHARACTERISTICS

The addition of an estrogenic component to the oral contraceptive pill was initially undertaken to obtain a more predictable bleeding profile and create regular cyclic bleeding profiles. While a reduction in the daily dose of EE did reduce the risk of thromboembolic events compared with higher-dose pill regimens, such adverse outcomes remain a major concern among clinicians and patients, even though the risk of thromboembolic events among users of combination oral contraceptives is considerably less than that observed among pregnant and postpartum women.¹⁸ One potential solution would be the use of a less potent estrogenic molecule with a shorter half-life than EE. E2 was evaluated in several studies at different doses and with several different progestogens; all studies demonstrated acceptable ovulation inhibition but, as expected, the weaker and shorter-acting E2 was associated with an adverse bleeding profile that precluded the clinical development of any of the putative regimens.5

NOMAC has been used as a progestogen therapy in menopausal management and as a progestogen-only contraceptive.¹⁹ Barbosa and colleagues evaluated a single-rod subdermal contraceptive implant (Uniplant[®]; Thermex, Bahia, Brazil) containing 55 mg NOMAC and found that while 20% of cycles were ovulatory among the 20 volunteers using the implant for 1 year, the inhibitory effect on follicular growth and endometrial vascularisation would make for an effective non-oral contraceptive method.¹⁹ With regard to its effectiveness in an oral progestogen-only

regimen, an early study by Bazin and colleagues showed oral doses of 1.25, 2.5 and 5.0 mg once-daily to be highly effective in inhibiting ovulation.²⁰ In this same study, the evaluation of serum E2, follicle stimulating hormone (FSH), luteinising hormone and progesterone levels showed that its inhibition of ovulation was the result of its effect on the hypothalamicpituitary axis and its subsequent action on the ovary, suggestive of a potentially useful oral progestogenic agent for contraception. In addition, a later study by Chretien and Dubois²¹ showed that 2.5 and 5.0 mg daily doses of NOMAC resulted in a contraceptive effect on cervical mucus, providing a second mechanism for its contraceptive effectiveness as a progestogenonly contraceptive.

E2/NOMAC COMBINATION ORAL CONTRACEPTION

The development of an E2-based oral contraceptive regimen was limited by the inability of the tested regimens to deliver a tolerable bleeding profile.⁵ However, a potent antigonadotropin progestogen that could stabilise the endometrium would be a good candidate progestogen to be combined with E2 in an oral contraceptive regimen, potentially resulting in not only an effective contraceptive but also a more tolerable E2-based regimen than those evaluated previously. Because NOMAC is an orally active antigonadotropic progestogen with unique antiproliferative activity and without estrogenic activity, it clearly is an ideal candidate to consider for an E2-based oral contraceptive regimen.¹⁵

Chabbert-Buffet et al.²² evaluated 41 normal-cycling women with several doses of NOMAC in combination with 1.5 mg E2 or alone and found that 2.5 mg NOMAC was the optimal dose to inhibit ovulation and follicular maturation. In addition, the combination of 2.5 mg NOMAC with 1.5 mg E2 showed a reinforcement of the antigonadotropic effect, most probably as result of the inhibitory effect of E2 on FSH. After that, Christin-Maitre and colleagues²³ compared the 1.5 mg E2/2.5 mg NOMAC in a 21/7 and 24/4 regimen and found that while neither regimen was associated with anovulation, the 24/4 regimen was associated with greater inhibition of follicular growth and a shorter duration of withdrawal bleeding, suggesting that the 24/4 regimen of E2/NOMAC would be associated with a greater margin of contraceptive effectiveness and a more tolerable and acceptable bleeding profile with fewer symptoms attributable to the hormone-free interval and acute hormone withdrawal. More recently, Gerrits and colleagues showed that the 1.5 mg E2/ 2.5 mg NOMAC administered for 24 days has a pharmacokinetic profile consistent with once-daily dosing,²⁴ With the dosing and regimen studies complete, a comparative study of the impact of 1.5 mg E2/2.5 mg NOMAC 24/4 (Zoely[®], Merck & Co., Inc, Whitehouse Station, NJ, USA) on ovulation to that of a popular oral contraceptive regimen containing 30 µg EE/3 mg

drospirenone (DRSP) (Yasmin[®], Bayer Pharmaceuticals, Berlin, Germany) was undertaken.²⁵ Duijkers and colleagues found that no ovulations occurred among the 48 women randomised (2 E2/NOMAC:1 EE/DRSP) to one of the two regimens and that the suppressive effect of E2/NOMAC, as evaluated by ultrasound measurement of follicular diameter, was similar to that observed with users of EE/DRSP. With these supportive outcomes from small clinical studies, a Phase 3 study could now be undertaken to assess the contraceptive effectiveness and tolerability of E2/NOMAC.

Mansour et al.²⁶ compared E2/NOMAC in a 24/4 regimen to 30 µg EE/3 mg DRSP in a 21/7 regimen in a randomised, open-label trial that featured a 3:1 randomisation ratio of E2/NOMAC to EE/DRSP for 13 consecutive cycles of 28 days in healthy, sexually active women aged 18-50 years from Europe, Asia and Australia. The study recruited 2152 women; 1613 were randomised to E2/NOMAC and 539 to EE/DRSP. Calculated Pearl indices, evaluated in women aged 18-35 years, were 0.38 and 0.81 for E2/ NOMAC and EE/DRSP, respectively. Scheduled withdrawal bleeding was estimated to be generally shorter and lighter among women using E2/NOMAC; however, users of E2/NOMAC reported a higher frequency of missed withdrawal bleeding episodes than those women using EE/DRSP. Users of E2/NOMAC had fewer bleeding days per reference period (91 days) and had a similar rate of unscheduled bleeding as users of EE/DRSP, which declined over the course of the study for both cohorts. Acne was also evaluated in this study; improvements were observed in both study cohorts, although greater improvement was observed among women using the EE/DRSP regimen compared with the E2/NOMAC regimen.

Mansour *et al.* found E2/NOMAC to be a highly effective oral contraceptive characterised by shorter and lighter withdrawal bleeds and a higher likelihood of absent withdrawal bleeding episodes than the comparator EE/DRSP 21/7 regimen, although both regimens were characterised by similar unscheduled bleeding profiles, demonstrating the more acceptable bleeding profile achieved with NOMAC compared to earlier E2 formulations.

A further assessment of the clinical impact of E2/ NOMAC was undertaken by Agren *et al.* in two papers published in December 2011. Both papers reported on a study comparing E2/NOMAC 24/4 to a monophasic $30 \ \mu g \ EE/150 \ \mu g$ levonorgestrel (LNG) 21/7 oral contraceptive regimen. One paper reported on the two regimens with regard to their impact on hemostasis parameters, lipid profile and carbohydrate metabolism and found that E2/NOMAC had less impact on haemostatic parameters than EE/LNG.¹² Lipids were essentially unchanged among E2/NOMAC users compared with decreases in high-density lipoprotein cholesterol and slight increases in low-density lipoprotein cholesterol and triglycerides among EE/LNG users. Finally, E2/NOMAC resulted in negligible changes in carbohydrate metabolic parameters, whereas EE/LNG users were characterised by increases in four of five parameters for carbohydrate metabolism [area under the curve over 3 hours (AUC₃) for glucose, incremental AUC₃ for glucose, AUC₃ for insulin, and incremental AUC₃ for insulin]. The fifth parameter, glycosylated hemoglobin (HbA1c), was unchanged in both cohorts. The second paper from the same group reported the impact of the two contraceptive regimens on other physiological parameters and found that E2/NOMAC had significantly less impact on markers of adrenal and thyroid function and less impact on androgen and androgen precursors.²⁷ However, the paper reported that while users of both regimens were found to have a drop in androgens and androgen precursors, users of EE/LNG were characterised by more pronounced decreases than users of E2/NOMAC, an interesting finding given the anti-androgenic character of NOMAC. In another comparative study of the E2/NOMAC regimen with an EE/LNG comparator (30 µg/150 µg), Sørdal and colleagues²⁸ found no clinically relevant effect on bone mineral density among E2/NOMAC users and no significant difference in the bone mineral density of women using the two regimens after 26 cycles.

Most recently, the results of a randomised, open-label, comparative multicentre trial performed in several countries, including the USA, of 2281 women randomised in a 3:1 ratio to E2/NOMAC and EE 30 μ g/DRSP 3 mg 21/7 were published.²⁹ This study and the clinical outcomes were comparable to those of the Mansour *et al.*²⁶ study, with E2/NOMAC users characterised by shorter and lighter withdrawal bleeds and a higher frequency of missed withdrawal bleeds than users of EE/DRSP. Unscheduled bleeding rates were similar between the two cohorts. Also similar to the Mansour *et al.* study, both cohorts were characterised by a reduction in acne scores, with users of EE/DRSP showing a greater improvement than users of E2/NOMAC.

CONCLUSIONS

The aforementioned studies clearly demonstrate that 1.5 mg E2/2.5 mg NOMAC 24/4 is an effective and generally well-tolerated combination oral contraceptive; however, these studies do not address whether this pill regimen is safer, especially with regard to thromboembolic events, than EE-based pill regimens. While there is some evidence from studies of surrogate markers that indicate that E2-based pills may have a reduced impact on the clotting mechanism, only extensive follow-up clinical studies will give us any meaningful information on the actual safety profile of E2/NOMAC and other E2-based oral contraceptives. For now, any woman who cannot use EE-based pills based on personal or family medical histories or laboratory testing results should not use E2-based pills. In other words, any contraindication

to the use of an EE-based pill is, for now, a contraindication to the use of an E2-based pill.

The development of an E2-based combination oral contraceptive with an acceptable bleeding profile seemed to be a Herculean task based on the relatively short half-life of E2 (compared with EE) and its consistent association with adverse bleeding profiles in clinical studies. However, the ability to combine E2 with a novel progestogen characterised not only by a strong inhibition of ovulation but also with a unique antiproliferative effect that helps stabilise the endometrium has resulted in the development of a highly effective combination oral contraceptive with a tolerability profile that appears to be acceptable to a wide demographic of women seeking safe, reliable, effective and reversible contraception. While the last two decades of oral contraception development have mostly witnessed the lowering of EE doses, the recent introductions of E2/NOMAC and an E2V-based oral contraceptive demonstrate the feasibility of using E2 in lieu of EE in an oral contraceptive pill regimen. Further studies will be needed to determine whether such E2-based pills have a better safety profile than EE-based pills.

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