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Estradiol Valerate Combined with Dienogest: a New Concept Contraceptive Pill for Women With a Heavy Menstrual Bleeding

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Estradiol Valerate Combined with Dienogest: a New Concept Contraceptive Pill for Women With Heavy Menstrual Bleeding*

I. Sundström Poromaa

■ Introduction

In order to improve tolerability and safety, the development of a combined oral contraceptive containing estradiol has been the Holy Grail of pharmaceutical research and development for decades. Finally, in 2009 the first contraceptive pill containing estradiol in combination with dienogest (E_2V/DNG ; Qlaira®) became available across Europe and spread globally. Although the safety of an estradiol-containing oral contraceptive in terms of venous thromboembolism remains to be proven by future studies, this new concept pill is an important addition to our contraceptive repertoire.

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Historically, the main problem with estradiol-containing oral contraceptives (combined with progestogens such as norethisterone acetate, desogestrel or cyproterone acetate) was the lack of sufficient cycle control. Although reliable contraceptive efficacy was achieved in clinical trials, the high incidence of bleeding irregularities rendered these preparations unsuitable for general use. In clinical trials of estradiol-containing contraceptive pills, the number of women who reported spotting varied between 20% and 54%, and breakthrough bleeding occurred in 25–39% of women. The discontinuation rates for bleeding irregularities varied between 10% and 42% [1–7], or were cited as the main reason for discontinuation [8].

Clearly, an important step towards acceptable cycle control in estradiol-con-

taining pills has been the development of new progestogens. Dienogest was chosen because of prior extensive experience with it and because of its pronounced effect on the endometrium [9, 10]. Another important step for improving cycle control is the dynamic four-phasic dosing regimen. Hence, the E_2V/DNG treatment cycle consists of an estradiol step-down and a progestogen step-up over 26 days to ensure estrogen dominance in the early part of the cycle and progestogen dominance in the mid-to late part of the cycle. Together with 2 placebo days, this results in a treatment cycle of 28 days.

From the user's point of view, apart from the differences in design of the treatment cycle, E_2V/DNG offers reliable contraceptive efficacy and cycle control comparable to that of ethinylestradiol- (EE-) containing pills [11–14]. However, the new preparation promises additional benefits to those available with existing combined oral contraceptives, especially for women with heavy menstrual bleeding.

■ Contraceptive Efficacy

Data on the contraceptive efficacy of the new E_2V/DNG combination have been derived from three large-scale clinical trials conducted in Europe and North America [12–14]. A total of 2266 women were included in the trials. The Pearl index and adverse events included in the European summary of product characteristics are based on pooled analyses of these three pivotal studies. Accordingly, the Pearl index for method failure in women aged 18–35 years was 0.51 (approximately 10.0% [12]). The most frequent adverse events (upper limit of 95% CI: 0.97) and the Pearl index for

potentially related to the study drug included breast method plus user failure was 1.01 (upper limit of 95% pain, headache and acne. Overall, almost 80% of CI: 1.59, including incorrect or non-use of the women were either satisfied or very satisfied with the method). Adverse reactions were reported by approximately new pill [12, 13].

■ Added Benefits of E_2V/DNG

The potential use of E_2V/DNG in women with heavy menstrual bleeding was suggested by the positive results of a cycle control study. In a randomized double-blind study E_2V/DNG was compared with low-dose EE (20 µg) and levonorgestrel (EE/LNG), with bleeding pattern and cycle control as the main outcome measures [12]. Overall, 798 women between 18 and 50 years of age were randomized to seven cycles of E_2V/DNG or EE/LNG (399 in each treatment group). The primary efficacy endpoints included the number of bleeding/spotting days, the number and length of bleeding/spotting episodes, and the incidence and characteristics of withdrawal and intra-cyclic bleeding during two 90-day reference periods.

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Overall, the number of bleeding/spotting days during both 90-day reference intervals was significantly lower among E_2V/DNG users (17.3 ± 10.4 vs 21.5 ± 8.6 in EE/LNG users, first reference period). Similarly, significantly fewer bleeding/spotting episodes were reported by E_2V/DNG users than by EE/LNG users (3.7 ± 1.4 vs 4.1 ± 0.9 , first

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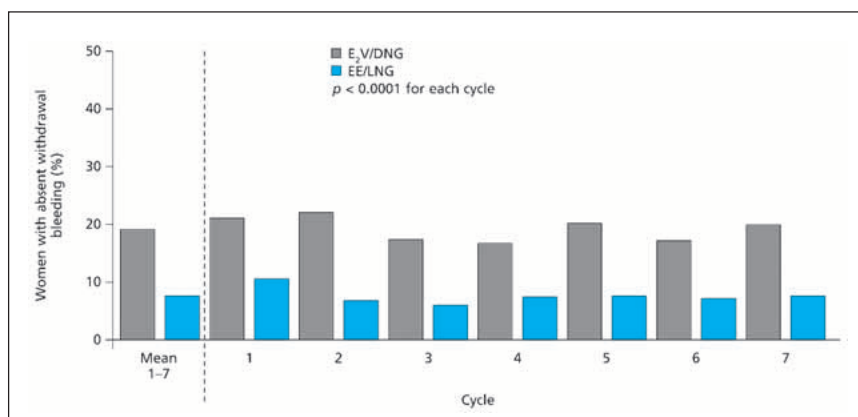


Figure 1. The proportion of women with absent withdrawal bleeding per cycle was 16.8–22.3% with E₂V/DNG and 6.2–10.5% with EE/LNG. The mean proportion of women who experienced no scheduled withdrawal bleeding (mean over 1–7 cycles) was 19.4% in the E₂V/DNG group and 7.7% in the EE/LNG group. In all 7 cycles of treatment, scheduled withdrawal bleeding was absent in significantly more women in the E₂V/DNG group ($p < 0.0001$). Adapted from [12].

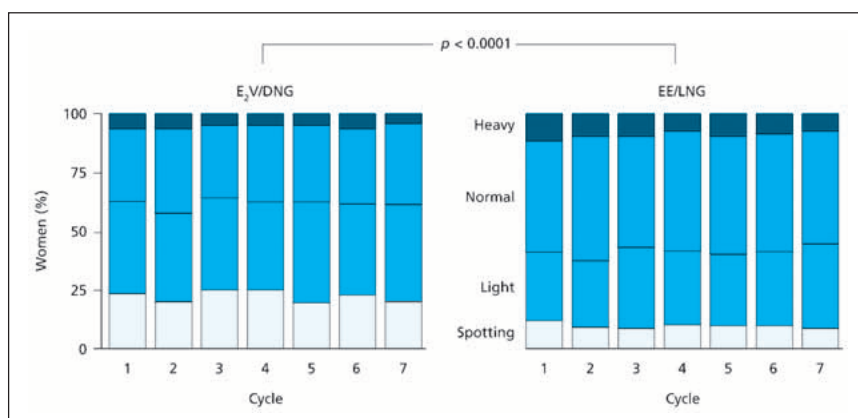


Figure 2. A greater proportion of women who received E₂V/DNG vs. EE/LNG deemed the maximum intensity of withdrawal bleeding to be spotting or light: mean score 3.2–3.3 per cycle (median 3 [light bleeding]) vs. mean score 3.6 (median 4 [normal bleeding]), respectively. The maximum intensity of withdrawal bleeding was significantly different in women in the E₂V/DNG group ($p < 0.0001$). Adapted from [12].

reference period). More women on E₂V/DNG reported absence of scheduled withdrawal bleeding. The mean proportion of women who experienced absent withdrawal bleeding with E₂V/DNG was 19.4%, whereas the corresponding number in women treated with EE/LNG was 7.7% (Fig. 1). Furthermore, scheduled withdrawal bleeding was significantly shorter and lighter in women treated with E₂V/DNG than in EE/LNG users. The median length of withdrawal bleeding was 4.0 days (range 4.1–4.7 days) in E₂V/DNG users compared with 5.0 days (range 5.0–5.2 days) in EE/LNG users. In addition, the intensity of withdrawal bleeding differed between treatments. A greater proportion of E₂V/DNG users experienced spotting or light bleeding relative to those who received EE/LNG (Fig. 2). The incidence of intracyclic bleeding during the entire treatment period did

not differ between groups. Intracyclic bleeding occurred in 14% (range 10.5–18.6%) of women treated with E₂V/DNG and in 12% (range 9.9–17.1%) of women on EE/LNG. Furthermore, in this trial there were no discontinuations due to bleeding disturbances in either treatment group.

■ E₂V/DNG for the Treatment of Heavy Menstrual Bleeding

The excellent bleeding profile of E₂V/DNG prompted two multicentre double-blind randomized placebo-controlled trials to study its effect on heavy and/or prolonged menstrual bleeding without organic cause [15, 16]. The two trials (Europe/Australia and US/Canada) had identical designs and analysis plans, which may ultimately allow for pooling of data.

According to the study protocols of both trials, women with complaints of heavy and/or prolonged menstrual bleeding underwent a 90-day run-in period to confirm the presence of heavy menstrual bleeding (at least two episodes each with a blood loss volume of at least 80 ml), prolonged bleeding (at least two episodes lasting at least 8 days) and/or frequent bleeding (more than five bleeding episodes with at least 20 bleeding days overall). The bleeding data were rigorously collected by electronic daily bleeding diaries and collection of sanitary items. The total menstrual blood loss volume from the sanitary products was calculated by the alkaline haematin method. Eligible women were subsequently randomized in a 2:1 ratio to either E₂V/DNG or placebo for six treatment cycles. The European study randomized 231 women and the North American study 190 women.

Both studies indicated that women treated with E₂V/DNG had a significantly greater reduction in mean menstrual blood loss compared with placebo users. E₂V/DNG users in the North American study had a mean blood loss reduction of –353 ml during the 90-day efficacy period, whereas the corresponding reduction for placebo users was –130 ml [15]. Similarly, the European study reported a significant difference in the adjusted mean difference of menstrual blood loss of –373 ml [16]. The marked decline in mean blood loss was already apparent from cycle 2 and was accompanied by significant improvements in haemoglobin and ferritin concentrations [15, 16].

“The marked decline in mean blood loss was already apparent from cycle 2 and was accompanied by significant improvements in haemoglobin and ferritin concentrations.”

■ Conclusion

Although the safety of an estradiol-containing oral contraceptive in terms of venous thromboembolism remains to be proven by future studies, the concept of an estradiol-containing contraceptive pill is an important addition to our contraceptive repertoire. This first of a new class oral contraceptive may be especially useful in women with heavy menstrual bleeding.

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