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Pituitary, ovarian and additional contraceptive effects of an estradiol-based combined oral contraceptive: results of a randomized, open-label study

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Abstract

Background: The estrogen step-down/progestogen step-up 28-day estradiol valerate/dienogest (E_2V/DNG) oral contraceptive effectively inhibits ovulation; however, limited data are available regarding its effects on estradiol (E_2), progesterone, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) or its additional extraovarian contraceptive effects.
Study Design: In this secondary analysis, 100 women received 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 for one treatment cycle. Measures included the presence/absence of cervical mucus; endometrial thickness; and serum E_2, progesterone, and gonadotropin levels.
Results: E_2, progesterone, LH and FSH levels did not exhibit the typical ovulatory increase and remained relatively stable during the cycle. E_2V/DNG reduced mean maximal endometrial thickness and proportion of women with visible cervical mucus. All parameters returned to pretreatment levels during the posttreatment cycle.
Conclusion: E_2V/DNG provides extraovarian contraceptive effects (reducing endometrial thickness and cervical mucus production) in addition to inhibiting ovulation, assuring contraceptive efficacy.

Keywords: Cervical mucus; Dienogest; Endometrial thickness; Estradiol valerate; Ovarian

1. Introduction

Since their introduction in the 1960s, oral contraceptives (OCs) have been a widely used method of birth control; however, for some women, treatment-related adverse events have proven to be problematic. Efforts to improve the tolerability of OCs have included the replacement of ethinylestradiol (EE) with 17β-estradiol (E_2). While the E_2-containing regimens have provided effective contraception [1–4], factors such as bleeding irregularities and suboptimal cycle control [1–3] have limited acceptability of such formulations.

To address the cycle control issues previously observed with E_2-containing regimens, a novel estradiol-based OC comprising estradiol valerate and dienogest (E_2V/DNG) in a dynamic estrogen step-down/progestogen step-up dosing regimen has been developed and is currently available in the majority of countries in Europe, the United States, Australia and Latin America. This formulation is the first widely available OC to deliver E_2 rather than EE. Data from a recent clinical trial in 1391 women show that E_2V/DNG is an effective and well-tolerated OC [5].

The primary mode of action of combined OCs is prevention of ovulation via inhibition of follicular development [as reflected by marked reductions in the levels of the gonadotropins follicle-stimulating hormone (FSH) and luteinizing hormone (LH), in addition to E_2 and progesterone levels, via a negative feedback mechanism], with secondary impacts on endometrial receptivity and the cervical mucus, as reviewed by Riviera et al. in 1999 [6]. It has previously

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been shown that the combined OC comprising E_2V/DNG provides efficient ovulation inhibition [7]. Indeed, large phase III studies have shown that E_2V/DNG provides reliable contraceptive efficacy in women aged 18–50 years, with an overall Pearl Index of 0.79 [8]. However, there is limited information available with regard to the effects on hormone levels and the additional extraovarian contraceptive effects. This paper, therefore, reports the effects of E_2V/DNG on levels of E_2, progesterone, and gonadotropins; endometrial thickness; and the presence/absence of cervical mucus visibility using data from an ovulation inhibition study [7].

2. Methods

2.1. Study participants

Healthy women aged 18–35 years (smokers not older than 30 years) were eligible for inclusion in this prospective, randomized, open-label study. The primary objective was to determine the required dose of DNG needed for effective inhibition of ovulation; this paper reports findings from a secondary analysis of this study. Full inclusion and exclusion criteria have been published previously [7]. The study commenced only after the protocol was reviewed and approved by the appropriate Independent Ethics Committee or Institutional Review Board.

2.2. Study treatment

In the study, women were randomized to one of two different 28-day dosing regimens of E_2V/DNG. The first regimen (n=100) comprised 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. The second regimen (n=103) comprised E_2V 3 mg on days 1–2, E_2V 2 mg/DNG 3 mg on days 3–7, E_2V 2 mg/DNG 4 mg on days 8–24, E_2V 1 mg on days 25–26 and placebo on days 27–28. The former regimen was identified as having the lowest dose of DNG that inhibited >95% of ovulations in cycle 2. This regimen has since been approved for the indication of oral contraception. This report describes secondary outcomes in the 100 women who received this regimen in the study.

Women were enrolled for five cycles: three treatment cycles and one pre- and one posttreatment cycle. During the treatment cycles, one tablet was taken daily with no tablet-free interval between cycles. In the first treatment cycle, the first tablet was taken on the first day of menstruation.

2.3. Study variables

The primary efficacy variable of the study was the proportion of women with a Hoogland score of 5–6 (luteinized unruptured follicle or ovulation) during cycles 2 and 3. These outcomes have been reported elsewhere [7].

The current paper reports the outcomes of measurements of levels of E_2, progesterone and gonadotropins; endometrial thickness; and cervical mucus visibility, all of which were secondary efficacy variables.

Blood samples were taken for the determination of the effect of the E_2V/DNG regimen on serum levels of E_2, progesterone and gonadotropins (LH and FSH). Samples were collected as follows: every 4 days during the pretreatment cycle; day 3, day 5 and every 3 days subsequently in cycle 2; every 3 days in cycle 3; every 4 days during the posttreatment cycle; and at the final examination (day 23 of the posttreatment cycle). After drawing blood from a cubital vein, the sample rested 230–60 min and then centrifuged at 2000g. The serum was immediately frozen at −20°C. Frozen samples were sent to a central lab in batches. The timing of all measurements was ±1 day. The hormone assessments were performed centrally (Laboratory for Clinical Research, LKF GmBH, Raisdorf, Germany); hormone assays were based on the electrochemiluminescence immunoassay technology on the analyzer Elecsys (Roche Diagnostics GmbH, Mannheim, Germany) [7].

Endometrial thickness was examined by transvaginal ultrasound (TVU). In addition, the visibility of a transonic area within the uterine cervix was determined by TVU [9]. This transonic area can indicate the presence of cervical mucus, but can also be observed if blood is present in the cervix. The utility of the TVU method for evaluating cervical mucus was shown in a study by Wolman and colleagues [10]. Cervical mucus parameters were shown to correlate well with cervical canal diameter; the sensitivity, specificity and positive predictive values of cervical canal diameter for predicting quality of cervical mucus were 83.7%, 80.8% and 82.2%, respectively [10]. In the current study, TVU was performed at screening (visit 1), every fourth day during a pretreatment cycle (visits 2–8), every third day during cycles 2 and 3 (visits 9–26) and every fourth day during a posttreatment cycle (visits 27–34). No measurements were carried out during treatment cycle 1, as the investigators wished to focus on treatment cycle 3 as opposed to treatment cycle 1 in this study. This change in focus was based on observations made during another ovulation inhibition study with an identical study design [7].

2.4. Safety

The results of the safety analysis have been published previously [7].

2.5. Statistical analyses

Outcomes were assessed in the full analysis set (FAS). All women who entered the study and who took at least one tablet of study medication and for whom at least one observation after dosing was available were included in the FAS. All efficacy variables were analyzed using descriptive statistics [mean±standard deviation (SD)]. Missing data were not imputed.