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REVIEW PAPER

Risk of venous thromboembolism during the use of oral estrogen-progestogen hormone therapies in light of most recent research findings

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Abstract

Two important studies evaluating the safety profile of oral estrogen-progestogen hormonal therapies conducted in standard clinical practice with respect to the venous system were recently published.

A large prospective controlled cohort study (PRO-E2) based on the non-inferiority design has shown that the relative risk of developing venous thrombosis (VTE) in women using combined oral hormonal contraceptives (COHC) containing 17β-estradiol (1.5 mg) and nomegestrol acetate (2.5 mg) (E2/NOMAC) was not statistically different from that in users of COHC containing ethinylestradiol and levonorgestrel (EE/LNG).

The aim of the recently presented study was to compare the risk of VTE in patients treated with a product for oral continuous combined menopausal hormone therapy containing 1 mg of 17ß-estradiol and 100 mg of micronized progesterone (1 mgE2/100 mgP4) with patients taking conjugated equine estrogens and medroxyprogesterone acetate (CEE/MPA). The study was based on an analysis of records retrieved from a US health insurance database, and was therefore concerned the real-life clinical practice. The hazard ratio of VTE when comparing 1 mgE2/100 mgP4 with CEE/MPA was 0.70 (95% CI: 0.53–0.92). The difference was found to be statistically significant ($p < 0.05$).

The rewieved studies provide further evidence that the use of hormones bioidentical with endogenous steroids in oral contraception and menopausal hormone therapy creates an opportunity to combine high efficacy with a favorable safety profile.

Key words: venous thromboembolism, combined oral hormonal contraception, menopausal hormone therapy.

The results of several studies published over recent months have significantly contributed to our knowledge of the safety profile of oral estrogen-progestogen hormone therapies with respect to the venous system.

Combined hormonal contraception

With regard to the safety profile of hormonal contraception, the researchers, clinicians, and the non-medical media alike have been focusing primarily on the increased risk of venous thromboembolism (VTE) [1, 2, 3]. Until the mid-1990s, the increase in the risk of VTE during the use of combined oral hormonal contraception (COHC) was attributed solely to the prothrombotic effect of the synthetic estrogen contained in the contraceptive pill. The interest in progestogens in this context has been seen since 1995, when a study of the World Health Organization work group established to investigate the relationship between hormonal contraception and cardiovascular diseases was published [3]. The researchers found that the risk of venous thrombotic events in patients taking contraceptive pills containing ethinylestradiol (EE) and either desogestrel or gestodene (1 case per over 3,000 population) was more than twice as high as in women using contraceptive pills with levonorgestrel. The risk of VTE does not increase with the duration of COHC: the highest number of VTE events occurred during the first year of contraception use [1, 2].

This publication received an extraordinary amount of attention not only in medical circles but also

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in the mainstream media. One of the misconceptions that accompanied the media buzz around the study was related to the generalizability of its findings to all birth control pills. Moreover, the results of this study do not apply to the newer COHC products, especially those containing 17ß-estradiol – bioidentical to that produced in the female body – as the estrogen component.

The current state of knowledge on the risk of VTE associated with combined hormonal contraception can be synthesized as follows:

- any type of combined hormonal contraception may increase the risk of venous thrombosis due to the prothrombotic effect of estrogen that is potentiated in some contraceptive products by the action of progestogen,
- there are considerable differences in the prothrombotic effect of combined hormonal contraceptives depending on the type of estrogen and progestogen used [1, 2].

Particularly promising in this context are the findings of the PRO-E2 study published in the final weeks of 2021 [4]. The study compared the risk of thrombosis in patients taking combined oral hormonal contraceptives containing 17β-estradiol (1.5 mg) and nomegestrol acetate (2.5 mg) (E2/NOMAC) compared to women using COHC containing ethinylestradiol and levonorgestrel (EE/LNG). It was a large prospective controlled cohort study based on the non-inferiority design. Patients for the study were recruited in 12 countries in Australia, Europe, and South America. A total of 101,498 women (49,598 in the E2/NOMAC group and 51,900 in the EE/LNG group) were included in the analysis. The clinical follow-up period was up to 2 years (144,901 women-years (WY) of observation). PRO-E2 is one of the largest prospective studies ever conducted to investigate the adverse effects of hormonal contraception. The women enrolled in this study had not used any other combined hormonal contraception for at least two months previously, and had no pre-defined risk factors for thrombosis at the time of study recruitment. During prospective follow-up in the study, a total of 46 cases of VTE were confirmed (including deep vein thrombosis of the lower extremities and/or pulmonary embolism). The incidence of VTE among E2/NOMAC users was 2.5 per 10,000 WY (95% CI: 1.3–4.3), and it was insignificantly different from the rate found in the group of women using COHC containing levonorgestrel [3.7 per 10,000 WY (95% CI: 2.3–5.7)]. The incidence of VTE among users of other combined contraceptive pills in the study was 6.0 per 10,000 WY (95% CI: 2.0–14.1). The relative risk of developing VTE in women using E2/NOMAC was not shown to be statistically different from that in users of the EE/LNG contraceptive pills – the hazard ratio of E2/NOMAC vs. EE/LNG (adjusted for age, BMI, family history of VTE, and current duration of hormonal contraception) was 0.59 (95% CI: 0.25–1.35). When interpreting the findings of this study, it needs to be noted that in light of the findings of multiple studies, levonorgestrel-containing pills are considered to be the safest combined hormonal contraception for the venous system [2, 5].

The conclusions of this study are consistent with the results of previous research showing that E2/NOMAC has a lesser effect than EE-containing contraceptive pills on the biochemical markers of the risk of cardiovascular adverse effects associated with COHC [6, 7, 8].

In light of study findings published to date, E2/NOMAC appears to be a contraceptive option close to the concept of 'natural balance' [9], which is based on the following premises:

- the use of micronized 17ß-estradiol in COHC helps avoid excessive stimulation of estrogen receptors, which has an impact on the safety profile,
- appropriate choice of progestogen and its dose ensures an effective antigonadotropic activity with the absence of clinically relevant affinity for receptors other than progesterone ones.

Menopausal hormone therapy

For nearly 20 years, there has been a heated debate on the benefit-risk ratio of menopausal hormone therapy (MHT), which was triggered by the publication of results of the *Women's Health Initiative* study in 2003 [10]. It has now been established that the risk of adverse effects associated with combined MHT, especially involving the mammary gland and the cardiovascular system, depends on the type of progestogen and the type and dose of estrogen [11]. A number of reliable studies indicate that from the point of view of the safety profile, the most beneficial form of combined oral MHT is 17β-estradiol with micronized progesterone [5, 12, 13]. This assumption laid the foundation for the concept of body-identical hormone replacement (BIHR) therapy that was proposed in 2014 by Nick Panay [14]. In this context, great hopes are being placed on the first oral combination drug approved for MHT containing a low dose of 17β-estradiol and micronized progesterone. Both compounds used as the active substances in the drug are molecularly and chemically bioidentical to the endogenous hormones [15]. It is, therefore, the first drug to meet BIHR criteria [15, 16].

The World Congress of the International Society of Gynecological Endocrinology (ISGE) held in Florence in May this year saw the first announcement of the findings of an observational retrospective study evaluating the risk of venous thrombosis in perimenopausal women treated with oral estradiol and micronized progesterone in comparison with patients taking conjugated estrogens combined with medroxyprogesterone [17].

The primary endpoint of the study was to compare the risk of VTE in patients treated with a product for

oral continuous combined menopausal hormone therapy containing 1 mg of 17ß-estradiol and 100 mg of micronized progesterone (1 mgE2/100 mgP4) with patients taking conjugated equine estrogens and medroxyprogesterone acetate (CEE/MPA).

The study was based on an analysis of records retrieved from a US health insurance database, and was therefore concerned the real-life clinical practice. The methods of statistical analysis used in this study took into account the impact of potential confounding variables – such as age, BMI, and comorbidities – on the results. A total of 17,388 patients treated with the 1 mgE2/100 mgP4 combination and 18,673 patients treated with the CEE + MPA combination were enrolled in the study.

The hazard ratio of VTE when comparing 1 mgE2/100 mgP4 with CEE/MPA was 0.70 (95% CI: 0.53–0.92). The difference was found to be statistically significant ($p < 0.05$).

The conclusion of this study confirms, on the basis of data from real-world clinical practice, the results of the large phase 3 REPLENISH trial of the world's first MHT combination containing estradiol and progesterone [16]. REPLENISH was a prospective, randomized, double-blind, placebo-controlled, parallel group, multicenter trial with a follow-up period of 12 months. During the 12-month treatment with 1 mgE2/100 mgP4, there were no clinically significant differences in blood coagulation parameters such as antithrombin activity, protein S level, partial thromboplastin activation time, prothrombin time, fibrinogen concentration, and prothrombin index. Moreover, one-year follow-up of patients treated with 1 mgE2/100 mgP4 showed no cardiovascular adverse events that might demonstrate a causal relationship with the ongoing therapy [18]. Full-text publication in a peer-reviewed journal of the results recently presented at the ISGE World Congress will enable better assessment of relevance of the findings obtained in this important study for clinical practice.

Recent studies evaluating the safety profile of oral estrogen-progestogen hormonal therapies conducted in standard clinical practice with respect to the venous system provide further evidence that the use of hormones bioidentical with endogenous steroids in COHC and MHT creates an opportunity to combine high efficacy with a favorable safety profile.

Disclosure

MB – received honoraria as consultant/member of advisory boards/lecturer from: Bayer, Exeltis, Gedeon Richter, Polpharma, Theramex; AJ – received honoraria as consultant/member of advisory boards/lecturer from: Exeltis, Gedeon Richter, Theramex; TP – received honoraria as consultant/member of advisory boards/lecturer from: Adamed, Bayer, Exeltis, Gedeon Richter, Janssen Cilag, MSD, Polpharma, Teva, Theramex; LP – received honoraria as consultant/member of advisory boards/lecturer from: Exeltis, Gedeon Richter, Novo Nordisk, Theramex; VSP – received honoraria as consultant/member of advisory boards/lecturer from: Adamed, Angelini, Bayer, Exeltis, Gedeon Richter, Janssen Cilag, MSD, Polpharma, Teva, Theramex.

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