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REVIEW ARTICLE

Evaluation of the safety profile of prolonged-release EE/DNG oral contraceptives: a critical appraisal

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ABSTRACT

Recent publications have suggested that a novel prolonged-release formulation of ethinylestradiol (EE) 20 µg and dienogest (DNG) 2 mg offers improved bleeding profiles and minimal impact on coagulation. These conclusions, however, are based on incomplete safety assessments and potentially misleading pharmacokinetic assumptions. This critical appraisal highlights several concerns: (1) discrepancies between published and regulatory data on bleeding/spotting rates compared to established EE/DRSP combinations; (2) inappropriate reliance on clotting-time-based activated protein C resistance (APCr) assays that fail to detect contraceptive-induced hypercoagulability; and (3) a strikingly high incidence of venous thromboembolism (VTE) reported in clinical trials of prolonged-release EE/DNG, significantly exceeding rates associated with both traditional EE-based and newer body-identical estrogen-containing contraceptives. Furthermore, these VTE cases are not transparently discussed in the peer-reviewed literature, raising ethical concerns about selective reporting. The pharmacokinetic profile of this formulation does not appear to mitigate estrogenic hepatic effects in a clinically meaningful way. Robust evaluation using validated thrombin generation assays such as the endogenous thrombin potential (ETP)-based APCr test, alongside independent post-marketing studies, is essential before asserting a neutral or favorable safety profile. Until then, claims regarding improved safety remain unsubstantiated.

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Introduction

Recent investigations portray the novel prolonged-release formulation of 2 mg dienogest (DNG) and 20 µg ethinylestradiol (EE), formally, KELZYN®, as a technological advance in oral contraception, emphasizing its improved bleeding profile and presumed neutrality regarding hemostatic risk [1,2]. This conclusion is based on the results of articles by Regidor et al. and Biskupska-Bodova et al., which suggest that this formulation 'was not associated with any meaningful changes in the analyzed coagulation and fibrinolytic parameters' and that 'the prolonged-release DNG 2 mg/EE 0.02 mg offers a significant decrease in unscheduled bleeding/spotting compared with an immediate-release COC, DRSP/EE' [3,4].

While the pharmacokinetic 'innovation,' namely, the reduced C_{MAX} and delayed T_{MAX}, is clinically interesting with certain class of therapeutics whose action is directly correlated with their circulating level, i.e. calcium channel blockers used to treat hypertension and/or arrythmias, the clinical implications of these kinetic changes on estrogenic and progestin effects on hemostasis and on the endometrium are not convincingly demonstrated. Both EE and DNG exert their main effects via nuclear receptors; thus, the therapeutic impact of modifying the absorption profile is unlikely to be immediate and might not alter estrogen- and progestin-sensitive protein synthesis in a clinically meaningful way [5]. A closer examination of the Public Assessment Report (PAR) for KELZYN® (SE/H/2381/01/DC) provides additional context and raises questions about these claims [6].

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Inappropriate conclusion that the modified pharmacokinetics improves the bleeding/spotting profile of EE/DNG

According to the PAR, the proportion of unscheduled bleeding/spotting days in the EE/DNG (LPRI–424) group ($n = 716$) was lower than that in the EE/DRSP group ($n = 288$). Specifically, the highest incidence in the EE/DNG group occurred in cycle 1 (54.9%), which decreased to 24.8% by cycle 9. In contrast, unscheduled bleeding/spotting in the EE/DRSP group exceeded 50% during cycles 2–4 and remained above 40% in all subsequent cycles. These findings stand in contrast to data from a large, pooled analysis of four clinical studies evaluating the bleeding profile of 1,285 women using 20 µg EE/3 mg drospirenone (DRSP) in a 24/4 regimen. The incidence of unscheduled intracyclic bleeding during cycles 2–7 ranged from 10.2% to 14.9% (Table 1), with the majority of such bleeding episodes being classified as spotting [7]. The methodological discrepancies, especially in the definitions of scheduled versus unscheduled bleeding and the intensity classification, likely contribute to the divergent bleeding profiles reported in these studies [4,7]. The pooled analysis of Anttila et al. aligns more closely with WHO recommendations [8] and offers better comparability with other historical data, whereas the definitions used in the prolonged-release 20 µg EE/2 mg DNG formulation study may lead to an overestimation of unscheduled bleeding, particularly in early cycles. The reasons for these discrepancies are unclear and not discussed by the authors. They may cast doubt on the reliability of the data on incidence of spotting/bleeding with the new contraceptive and on the statement that the modified pharmacokinetics reduces the prevalence of unscheduled spotting/bleeding.

Inappropriate use and interpretation of APC resistance assays

More concerning is the interpretation of safety data regarding coagulation and VTE risk.

Regidor et al. relied on a clotting-time-based assay to assess activated protein C resistance (APCr) and concluded that the prolonged-release 20 µg EE/2 mg DNG formulation did not significantly affect coagulation [3]. Similarly, in their study, 20 µg EE/3 mg DRSP did not influence APC resistance, showing the inappropriateness of the assay used to reflect the impact of COC on hemostasis [3]. As Morimont et al. have rigorously detailed, such assays, typically based on the activated partial thromboplastin time (aPTT) or other clotting methods, are specific for detecting the Factor V Leiden mutation and are not sensitive to the acquired APC resistance induced by hormonal contraceptives (Figure 1) [9].

Table 1. Description and comparison of the definitions and methods used for irregular bleeding across studies.

	Anttila et al. (2011) [7]	Biskupska-Bodova et al. (2025) [4]
Definition of bleeding and spotting		
Recording method	Daily diary cards filled in by participants.	Electronic diaries are completed daily by participants.
Spotting	Vaginal bleeding requiring no sanitary protection, except panty liners.	Vaginal bleeding that does not require the use of sanitary protection.
Bleeding	Further subdivided: - *Light*: less than normal menses - *Normal*: like usual menses - *Heavy*: more than usual menses.	Bleeding requiring sanitary protection, regardless of quantity.
Scheduled bleeding	Bleeding starts during or ≤4 days before the hormone-free interval, continuing into the hormone-free interval.	Bleeding that occurs during the hormone-free interval (days 25–28 of the 24/4 regimen).
Unscheduled bleeding	Any bleeding occurring outside the scheduled window. Bleeding at the start of cycle 1 is also classified as unscheduled.	Bleeding or spotting that occurs on days 1–24 of the cycle, i.e. during the active treatment phase.
Analysis periods		
Reference period	90-day reference periods (WHO recommendation).	Per-cycle analysis (cycle-by-cycle reporting from cycle 1 to cycle 9).
Bleeding outcomes	Focused on incidence and type of unscheduled intracyclic bleeding during cycles 2–7.	Reported proportion of women with no bleeding, scheduled bleeding only, and unscheduled bleeding or spotting per cycle.
Unscheduled bleeding/spotting results		
Percentage of unscheduled bleeding/spotting	EE/DNG (21/7): - Cycles 2–7: 8.6%–13.8% EE/DRSP (24/4): - Cycles 2–7: 10.2%–14.9%	EE/DNG PR (24/4): - Cycles 2–6: 50.5% EE/DRSP (24/4): - Cycles 2–6: 72.8%

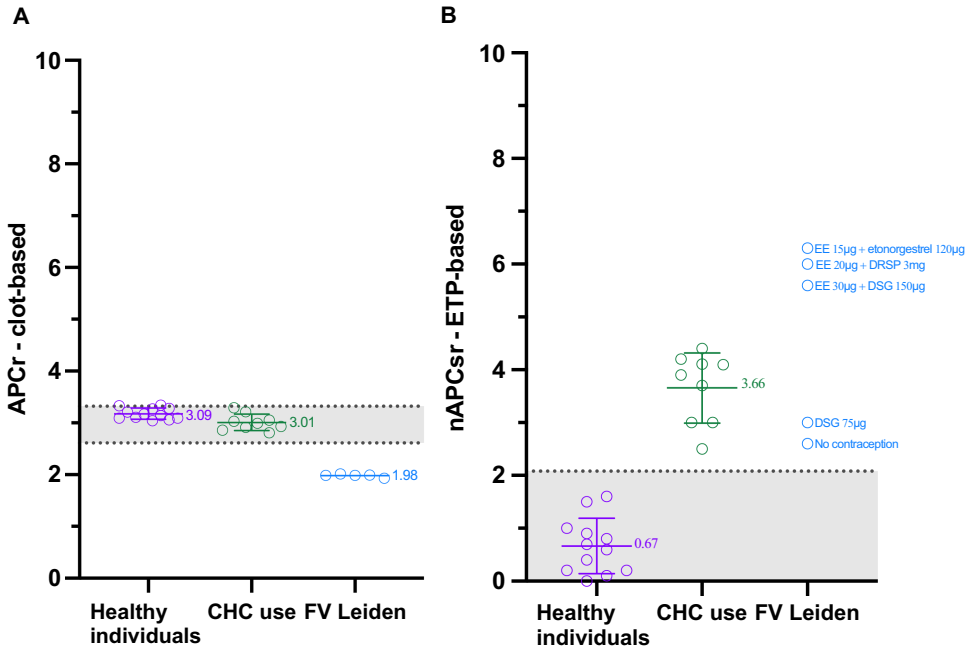

Figure 1. Comparison of the assessment of APC resistance of healthy individuals, carriers of heterozygous FV Leiden mutation, and women using combined hormonal contraceptives, using (A) the aPTT-based (with predilution) or (B) the ETP-based APC resistance assays. The gray areas on both graphs represent normal ranges. Clot-based APCr assays are not able to capture the impact of CHC on coagulation. This is mainly because these tests are designed to be specific to the FV Leiden mutation and thus are not sensitive towards decreases in protein S, which is the main driver of APCr with CHC use. *Abbreviations: APCr, activated protein C ratio; CHC, combined hormonal contraceptive; EE, ethinylestradiol; DRSP, drospirenone; DSG, desogestrel; nAPCsr, normalized activated protein C sensitivity ratio.*

In contrast, the endogenous thrombin potential (ETP)-based APC resistance assay is considered by the International Society on Thrombosis and Hemostasis as the gold standard assay to evaluate the phenotypic hypercoagulable state induced by combined hormonal contraceptives [10–12]. It is also recommended by the EMA for the evaluation of the impact of steroid contraceptives on hemostasis [13]. This test captures the global thrombin-generating capacity and better reflects the increased VTE risk associated with exogenous hormones, as well as genetic thrombophilia [9]. The absence of ETP-based testing in the safety evaluation of this prolonged-release formulation represents a significant methodological weakness. Based on their other coagulation investigations, no difference exists between prolonged-release EE/DNG and EE/DRSP making their conclusion that '*this novel COC can be considered neutral regarding potential changes in blood coagulation as there is no effect on the liver-dependent coagulation factor*' incorrect and misleading. Additionally, such assumptions would have meant that EE/DRSP is neutral for the hemostatic system as well. Several reports have demonstrated that EE/DRSP influenced highly coagulation, an observation linked to an increased thrombotic risk [14–17].

High incidence of VTE in clinical trials of the prolonged-release formulation

The clinical trials summarized in the PAR of KELZYN® (SE/H/2381/01/DC) report a total of 8 confirmed VTE events in approximately 1465 woman-years of exposure [6]. This corresponds to an incidence of 54.6 (95% CI, 23.6–98.5) per 10,000 woman-years, well above 6.1 (95% CI, 3.1–11.0), 3.3 (95% CI, 1.4–6.5) or 3.7 (95% CI, 0.09–17.4; estimation based on phase−3 studies) per 10,000 woman-years with estradiol (E2) valerate/dienogest, E2/nomegestrol acetate, and estetrol (E4)/DRSP, respectively [18–20]. Similar results using meta-analytical methods or pharmacovigilance database confirmed these observations that body-identical estrogens are associated with lower reporting of thrombotic events compared to EE-containing pills [18,21].

While the marketing authorization holder attempts to mitigate this in the PAR (SE/H/2381/01/DC) by attributing 3 of these events to individual risk factors (as listed in the Summary of Product

Characteristics—Section 4.4 (Special warnings and precautions for use)) or chance, the accumulation of 8 VTEs, including one case of pulmonary embolism, across studies cannot be dismissed as incidental. Even when these 3 cases were excluded, the residual estimated incidence was still 34.1 (95% CI, 13.4–71.7) per 10,000 woman-years. Recent developments of EE-based contraceptives such as EE 10 µg/NETA 1 mg (pill) [22], EE 13 µg/segesterone 150 µg (vaginal ring) [23], or EE 30 µg/LNG 120 µg (patch) [24], consistently demonstrate higher VTE incidences compared to body-identical estrogens (ranging between 15 and 33 per 10,000 women-years in similarly sized cohorts), further reinforcing concerns regarding the thrombotic safety of the EE/DNG prolonged-release formulation.

This elevated rate contrasts with the narrative of 'neutrality' in hemostatic effect. The claim that the slower hepatic first-pass and reduced peak plasma levels might explain the lower impact on hepatic protein synthesis is also not substantiated by clinical observations [3,6]. While this hypothesis has been suggested by Regidor et al., we would like to emphasize that (i) the effects of estrogens on hepatic protein synthesis are largely governed by the area under the curve (AUC) rather than Cmax, and (ii) EE absorption via the vaginal route, although it produces flatter profiles, still induces hepatic protein synthesis changes and is associated with increased VTE risk, as shown with contraceptive vaginal rings [25]. Therefore, the altered pharmacokinetic profile of this EE/DNG formulation does not inherently confer hemostatic neutrality.

Despite the VTE cases being recorded and publicly disclosed in the PAR (SE/H/2381/01/DC), they are notably absent from the discussion in the published articles [3,4]. This omission undermines the objectivity of the safety assessment and risks misleading clinicians. The ethical imperative to fully disclose known safety signals in peer-reviewed scientific literature is critical, particularly in reproductive health, where millions of women are affected by contraceptive recommendations [26].

Conclusion

While the development of novel release profiles in oral contraceptives may hold promise for improving user contraceptive efficacy and adherence, claims about tolerability and safety, particularly in relation to bleeding patterns and coagulation, must be held to the highest evidence standards. The current data do not support the assertion that the prolonged-release EE/DNG formulation offers a superior risk profile regarding VTE compared to other COC on the market. The high incidence of VTE cases observed during the clinical trial, the inappropriate use of APC resistance testing, and the lack of rigorous evaluation using validated thrombin generation assays, warrants caution when extrapolating the results to clinical practice. Further post-marketing epidemiological and mechanistic studies, using gold-standard assays such as the ETP-based APC resistance test, are essential before broader clinical endorsement can be justified, especially in the absence of reassuring clinical data. To date, only body-identical estrogens have been demonstrated to have a lower risk of VTE compared to EE-containing pills.

Author contributions

J.D. conceptualized the critical appraisal, performed the literature review, and drafted the manuscript. J.-M.F. and U.G. contributed to the interpretation of the clinical and pharmacological data and critically revised the manuscript for important intellectual content. N.F. and L.M. contributed to the pharmacological and methodological assessments and supported data synthesis and manuscript revision. All authors reviewed and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Disclosure statement

Prof. Jonathan Douxfils has received consultancy fees from Gedeon Richter, Estetra, and Mithra Pharmaceuticals. He is also the founder of QUALIblood SA, a company involved in the development and validation of the ETP-based activated protein C resistance assay.

Prof. Jean-Michel Foidart is the founder of Mithra Pharmaceuticals and has received consultancy fees from Mithra Pharmaceuticals and Estetra.

Prof. Ulysse Gaspard has received consultancy fees from Mithra Pharmaceuticals.

Dr. Nina Flerin is a full-time employee of Estetra, a wholly owned subsidiary of Gedeon Richter.

Dr. Laure Morimont is a full-time employee of QUALIblood.

The authors declare that these affiliations and financial relationships have had no influence on the content or conclusions of this manuscript.

Data availability statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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