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Authors

Doux fils, Jonathan
Chabbert-Buffet, Nathalie
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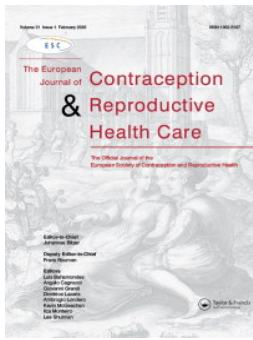
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Jonathan Doux fils , Nathalie Chabbert-Buffet , Mitchell D. Creinin , Marie Didembourg , Jean-Michel Dogné , Jean-Michel Foidart , Ulysse Gaspard , Oskari Heikinheimo , Øjvind Lidegaard , Médéa Locquet , Laure Morimont , Lucie Raskin , Kristina Gemzell Danielsson & Helena Kopp-Kallner

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LETTER TO THE EDITOR



Critical assessment of a prolonged-release EE/DNG contraceptive safety analysis

Dear Editor

The recently published rapid communication by Grandi et al. [1] on the “one-year clinical experience” with the prolonged-release ethinylestradiol (EE) 0.02 mg/dienogest (DNG) 2 mg combined oral contraceptive (COC) reports an “incidence” of venous thromboembolism (VTE) of 2.36 cases per 10,000 women-years based on spontaneous reports aggregated over 50,861 women-years of exposure. This figure is presented as the first real-life estimate of VTE risk for this formulation and implicitly compared to the VTE incidence of other COCs. In our view, this interpretation is methodologically untenable and risks misleading prescribers and regulators about the thrombotic safety of this product. We present five major methodological flaws of the paper in detail below.

First, the central numerical result of the article, i.e. an “incidence” expressed per 10,000 women-years, is derived from a numerator consisting of spontaneously reported cases and a denominator constructed from defined daily doses (DDD) transformed into “women-years.” The numerator in this calculation is inherently subject to massive under-reporting, in part related to heterogeneous reporting practices across countries. Additionally, the authors performed no case validation. When spontaneous reporting databases such as EudraVigilance or FDA Adverse Event Reporting System (FAERS) are used in pharmacovigilance, they should be analysed strictly as signal-detection systems, in accordance with European Medicine Agency (EMA) Good Pharmacovigilance Practice (GVP) Module IX and contemporary reporting standards such as REporting of A Disproportionality Analysis for DrUg Safety Signal Detection Using Individual Case Safety Reports in Pharmacovigilance (READUS-PV). These frameworks emphasise that analyses should rely on individual case safety reports using validated disproportionality methods, coupled with transparent case definitions, duplicate handling, and clinical review, and they explicitly caution against interpreting spontaneous reports as incidence or comparative risk, or using them to imply “safety” claims [2]. Also, the denominator, DDD, is not linked to specific persons, but is an overall measure of the use. Thereby any adjustments for important confounders such as age, thrombotic predispositions, BMI and other VTE risk factors are not possible. Especially, the lack of age adjustment is a crucial limitation, because both the risk of venous thromboembolism and the use of hormonal contraception is closely linked to this variable.

Secondly, the database and methods used to derive the numerator are insufficiently described to allow independent appraisal. The authors state that they collected VTE reports from multiple regions during the first year of marketing in more than 17 countries, but do not identify the pharmacovigilance systems involved, the time windows for each country, the MedDRA definitions or Standardised MedDRA Queries used for VTE, the handling of duplicates, or the criteria for case validation. Combining heterogeneous national pharmacovigilance systems with very different reporting cultures, regulatory triggers and background levels of stimulated reporting into a single crude rate assumes homogeneity that is unlikely to exist.

Thirdly, the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) and the REporting of studies Conducted using Observational Routinely-collected Data (RECORD-PE) call on authors, reviewers and editors to avoid causal language, risk estimation and safety endorsements when working only with spontaneous reporting data [2]. The Grandi et al. Rapid Communication on prolonged-release EE/DNG ignores these guidelines and does the opposite: it uses spontaneous reports without disproportionality analysis, constructs a DDD-based denominator to derive an “incidence,” and then suggests a comparatively low VTE risk in the absence of any proper comparator [1].

Fourth, the article ignores the substantial thrombotic signal that emerged during the clinical development of prolonged-release EE/DNG [3]. As summarised in a recent critical appraisal, the phase III programme and regulatory assessment by the Swedish Medical Products Agency documented a strikingly high incidence of VTE with this formulation, exceeding the rates typically observed with both conventional EE-containing COCs and newer preparations containing body-identical oestrogens [3]. These data were sufficiently concerning for the national competent authority to issue explicit warnings in the product assessment report by classifying VTE as “uncommon” (incidence $\geq 1/1\ 000$ and $< 1/100$) where it is “rare” (incidence $\geq 1/10\ 000$ and $< 1/1\ 000$) in the Summary of Product Characteristics of other COCs. Yet, in the rapid communication, these regulatory findings are neither presented nor discussed [4].

Fifth, the article is part of a broader series from the same group that repeatedly minimises the haemostatic impact and VTE risk of EE-based COCs. In previous publications, the authors concluded that prolonged-release EE/DNG had “no relevant impact” on haemostasis based on clotting-time-based activated protein C resistance (APCr) assays and limited coagulation panels [3]. These conclusions are at odds with current understanding of estrogen-induced hypercoagulability and the recognised limitations of aPTT-based APCr tests [5]. Phenotypic APCr in combined hormonal contraception users is factor V Leiden-independent and mediated by complex changes in thrombin generation, protein C pathway and procoagulant factors [5]. To date, only the ETP-based APCr assays capture this phenotype and have been standardised and validated as global biomarkers of VTE risk in contraceptive users [5]. The International Society on Thrombosis and Haemostasis- Scientific and Standardisation Committee (ISTH SSC) and subsequent reviews on phenotypic APCr explicitly emphasise that clotting-time-based assays are inadequate to evaluate contraceptive-induced APC resistance and should not be used to claim absence of haemostatic impact [5]. In this context, the claim that prolonged-release EE/DNG and even EE/DRSP have “no impact on haemostasis” is not only unsupported by appropriate assays, but also contradicts a substantial body of literature demonstrating EE-dependent shifts in thrombin generation and APCr across multiple combined hormonal contraceptives.

Taken together, these points outline why the VTE estimates for EE/DNG published by Grandi et al. are scientifically invalid. The true thrombotic risk associated with prolonged-release EE/DNG, based on all available evidence, is unlikely to be lower, and may in fact be higher, than that of established EE/DNG and EE/DRSP preparations. All journals publishing pharmacovigilance analyses should maintain the highest methodological guidelines and standards and require, as a minimum, full transparency on data sources, methods and regulatory context.

Conflicts of interest

J.D. (Jonathan Douxflis) reports personal fees from Daiichi-Sankyo, Diagnostica Stago, Gedeon Richter, GyneBio Pharma, Mayne Pharma, Mithra Pharmaceuticals, Norgine, Roche, Roche Diagnostics, Technoclone, Werfen, and YHLO, all outside the submitted work. He is also one of the inventors of the nAPCsr kit.

N.C.-B. (Nathalie Chabbert-Buffet) has served on advisory boards for Besins, Exeltis, and Gedeon Richter.

M.D.C. (Mitchell D. Creinin) has received speaking honoraria from Gedeon Richter, Libbs, and Mayne; has served on advisory boards for Estetra SRL; holds stock options with Femasys; and has consulted for Mayne, Medicines360, and Merck Sharp & Dohme. The Department of Obstetrics and Gynaecology, University of California, Davis, receives contraceptive research funding for Dr. Creinin from Femasys, Merck, Sebela, and Myovant (Sumitomo Pharma).

M.D. (Marie Didembourg) declares no competing interests relevant to this work.

J.-M.D. (Jean-Michel Dogné) declares no competing interests relevant to this work.

N.F. (Nina Flerin) is a full-time employee of Estetra, a wholly owned subsidiary of Gedeon Richter.

J.-M.F. (Jean-Michel Foidart) has received grants from Gedeon Richter.

U.G. (Ulysse Gaspard) has received consultancy fees from Mithra Pharmaceuticals.

O.H. (Oskari Heikinheimo) has received consulting fees from Orion Pharma and Nordic Pharma; payments or honoraria for lectures from Bayer AG and Gedeon Richter; payments for expert testimony from Medaffcon Oy (Espoo, Finland); and support for attending meetings from Gedeon Richter. He has participated in Data Safety Monitoring Boards and/or advisory boards organised by Bayer AG and Gedeon Richter. He is chairman of the Finnish national Current Care Guidelines on Induced Abortion.

Ø.L. (Øjvind Lidegaard) declares that the Juliane Marie Centre of Rigshospitalet received a grant from Exeltis to conduct a European Medicines Agency-requested postauthorization safety study on a new progestogen-only pill with drospirenone. Dr Lidegaard is the primary investigator on this study. The grant was paid to his institution and he will not receive personal payment for his investigator work.

M.L. (Médéa Locquet) declares no competing interests relevant to this work.

L.M. (Laure Morimont) is one of the inventor of the nAPCs.

L.R. (Lucie Raskin) declares no competing interests relevant to this work.

K.G.-D. (Kristina Gemzell-Danielsson) has received payments or honoraria for lectures from Bayer AG, Organon, Gedeon Richter, Natural Cycles, Exelgyn, Exeltis, Cirql, RemovAid, and ObsEva, and holds leadership or fiduciary roles in FIAPAC, FIGO, FSRH-RCOG (UK), and SFOG.

H.K.K. (Helena Kopp Kallner) has received honoraria for lectures from AbbVie, Actavis, Bayer, Consilient Health, Exeltis, Ferring, Gedeon Richter, Medice, Merck, Mithra, Natural Cycles, Nordic Pharma, Organon, Takeda, and Teva. She has provided expert opinion/consultancy to Bayer, Evolan, Gedeon Richter, Exeltis, Merck, Teva, TV4, Natural Cycles, Pharmiva, Dynamic Code (engagement ended), Ellen, Estercare, Gedeon, Gesynta, Essity, Preglife, and Herbox. She has been an investigator in clinical trials sponsored by Bayer, MSD, Mithra, Ethicon, Azanta/Norgine, Gedeon Richter, Gedeon, Organon, Bionorica, Agnomed, Pharmiva, and Takeda. She has also taught in courses sponsored by Organon, Bayer, and Gedeon Richter.

Data availability statement

Not applicable to this document.

Author contributions

CRediT: **Marie Didembourg**: Validation, Writing – review & editing; **Jean-Michel Dogné**: Validation, Writing – review & editing; **Médéa Locquet**: Validation, Writing – review & editing; **Laure Morimont**: Validation, Writing – review & editing; **Lucie Raskin**: Validation, Writing – review & editing; **Jonathan Douxfils**: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing; **Nathalie Chabbert-Buffet**: Validation, Writing – review & editing; **Mitchell D. Creinin**: Validation, Writing – review & editing; **Jean-Michel Foidart**: Validation, Writing – review & editing; **Ulysse Gaspard**: Validation, Writing – review & editing; **Oskari Heikinheimo**: Validation, Writing – review & editing; **Øyvind Lidegaard**: Validation, Writing – review & editing; **Kristina Gemzell Danielsson**: Validation, Writing – review & editing.

ORCID

Helena Kopp-Kallner  <http://orcid.org/0000-0001-7184-9165>

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Jonathan Douxfils
Clinical Pharmacology and Toxicology Research Unit,
Namur Research Institute for Life Sciences (NARILIS), Faculty of Medicine, University of Namur, Namur, Belgium
Department of Biological Hematology, CHU Clermont-Ferrand, Hôpital Estaing, Clermont-Ferrand, France
 jonathan.douxfils@unamur.be

Nathalie Chabbert-Buffet
Department of Obstetrics, Gynecology and Reproductive Medicine,
Tenon Hospital AP-HP Sorbonne University, Paris, France

Mitchell D. Creinin
Department of Obstetrics and Gynecology, University of California, Davis, Sacramento, USA

Marie Didembourg, Jean-Michel Dogné
*Clinical Pharmacology and Toxicology Research Unit,
Namur Research Institute for Life Sciences (NARILIS), Faculty of Medicine, University of Namur, Namur, Belgium*

Jean-Michel Foidart, Ulysse Gaspard
Department of Obstetrics and Gynecology, University of Liège, Liège, Belgium

Oskari Heikinheimo
*Department of Obstetrics and Gynaecology,
University of Helsinki and Helsinki University Hospital, Helsinki, Finland*

Øjvind Lidegaard
*Department of Gynaecology, Fertility, & Obstetrics,
Copenhagen University, Copenhagen, Denmark*

Médéa Locquet, Laure Morimont, Lucie Raskin
*Clinical Pharmacology and Toxicology Research Unit, Namur Research Institute for Life Sciences (NARILIS), Faculty of
Medicine, University of Namur, Namur, Belgium*

Kristina Gemzell Danielsson
*Department of Women's and Children's Health, Karolinska Institutet and Karolinska University Hospital Solna, Stock-
holm, Sweden*

Helena Kopp Kallner 
*Department of Obstetrics and Gynaecology, Danderyd University Hospital, Stockholm, Sweden
Department of Clinical Sciences at Danderyds Hospital, Karolinska Institutet, Stockholm, Sweden*

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