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ORIGINAL RESEARCH

Venous Thromboembolism with Combined Oral Contraceptives Based on Estrogen and Progestin Content: A disproportionality analysis of the United States Food and Drug Administration Adverse Event Reporting System database.

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CONDENSATION PAGE

Tweetable statement

In the FDA Adverse Event Reporting System database, venous thromboembolism was reported more often with synthetic estrogen than with body-identical estrogen-containing oral contraceptives.

Short Title

Venous thromboembolism with body-identical estrogen-based combined oral contraceptives in FAERS.

AJOG at a Glance

A. Why was this study conducted?

- Body-identical estrogen-based combined oral contraceptives (17β-estradiol, estetrol) have shown reduced venous thromboembolism risk compared to ethinyl estradiol-based pills across biological, clinical, and real-world data.
- This study used disproportionality analysis of the FDA Adverse Event Reporting System database to assess venous thromboembolism reporting trends by estrogen and progestin content.

B. What are the key findings?

- Combined oral contraceptives with estetrol or 17β-estradiol had lower venous thromboembolism reporting rates than ethinyl estradiol-based combined oral contraceptives, with proportions similar to progestin-only pills.

C. What does this study add to what is already known?

- Findings align with recent EudraVigilance data, supporting a consistent safety profile across regulatory systems.
- These results suggest a need to reconsider current prescribing practices in favor of body-identical estrogen-based options.

ABSTRACT

Objectives

To compare the proportionality reporting rate (PRR) of venous thromboembolic adverse events in the Food and Drug Administration Adverse Reporting System database between two body-identical estrogen combined oral contraceptives available in the United States, 17β-estradiol valerate (E2V)/dienogest and estetrol/drospirenone, and combined oral contraceptives containing ethinyl estradiol (EE).

Study Design

We extracted individual case safety reports and adverse events from the Food and Drug Administration Adverse Reporting System database from its inception to October 2024. We performed a PRR analysis of venous thromboembolic events associated with various combined oral contraceptives as compared to reference standards of EE-levonorgestrel combined oral contraceptives and the entire therapeutic class. Secondarily, we assessed the PRR with drospirenone-only pills and norethindrone-only pills.

Results

Compared to EE/levonorgestrel, we found lower PRRs with estetrol/drospirenone (0.54, 95% CI 0.30-0.99) and E2V/dienogest (0.79(5), 95% CI 0.65-0.97), which were similar to the PRRs for drospirenone-only pills (0.64, 95% CI 0.55-0.74) and norethindrone-only pills (0.69, 95% CI 0.60-0.79). EE/drospirenone had the highest PRR at 5.18 (95% CI 4.95-5.42). Using the entire therapeutic class as reference, we similarly found lower PRRs with estetrol/drospirenone (0.17, 95% CI 0.09-0.31) and E2V/dienogest (0.25, 95% CI 0.21-0.30), both of which were similar to the PRR observed for drospirenone-only pills (0.20, 95% CI

0.17-0.23) and norethindrone-only pills (0.21, 95% CI 0.19-0.24); the highest PRR, for EE-drospirenone, was 4.52 (95% CI 4.41-4.63).

Conclusion

Combined oral contraceptives containing body-identical estrogens, estetrol, and 17β-estradiol, have lower proportions of venous thromboembolism reports than EE-based pills and are similar to progestin-only pills. These findings suggest a potentially safer thrombotic profile of body-identical estrogen-based combined oral contraceptives.

KEYWORDS

Combined oral contraceptive, disproportionality reporting ratio, estradiol, estetrol, ethinyl estradiol, venous thromboembolism

Introduction

Combined hormonal contraceptive (CHC) use is a well-recognized risk factor for venous thromboembolism (VTE). Most CHC users worldwide select oral formulations,[1,2] for which the VTE incidence is estimated as 5 to 12 cases per 10,000 woman-years, depending on the COC used.[2] In the United States (U.S.), over 9,000 COC-associated VTE cases occur each year.[2,3] Although this risk is not negligible, regulatory authorities recognize that the overall favorable benefit-to-risk balance for CHCs is favorable, mainly because the VTE risk is significantly higher during and immediately after delivery.[4,5]

Ethinyl estradiol (EE) has been the primary estrogen used in CHCs since the 1960s.[2] In some countries, the combination of EE with levonorgestrel is the preferred COC based on VTE risk, with an approximate risk of 2.3 compared to non-CHC users (including progestin-only contraceptives).[1,6] Newer COCs containing body-identical estrogens first became available in the U.S. in 2010, with 17β-estradiol valerate (E2V)/dienogest, followed in 2021 by estetrol/drospirenone. Biological studies have consistently shown that body-identical estrogens present a reduced effect on coagulation proteins compared to EE.[7-12] In addition, a recent meta-analysis demonstrated that COCs containing E2 (i.e., E2V/dienogest or E2/nomegestrol acetate) are associated with a 49% lower risk of VTE compared to EE/levonorgestrel.[13]

As part of post-marketing surveillance, the U.S. Food and Drug Administration (FDA) and other regulatory authorities worldwide maintain passive-reporting adverse drug reaction databases. The EudraVigilance database from the European Medicines Agency was recently utilized to conduct a disproportionality analysis, indicating a superior thrombotic safety profile of body-identical estrogens.[14] Since the results were limited to the European database, we performed a similar analysis using the FDA Adverse Event Reporting System

(FAERS) database to assess the proportionality reporting rates (PRR) of VTE events for various COCs, with a particular emphasis on the comparison between COCs containing body-identical estrogens (estetrol/drospirenone and E2V/dienogest) and those containing EE.

Materials and Methods

We accessed the FAERS database to extract individual case safety reports (ICSRs) and all adverse events (AEs) associated with body-identical estrogen products, including estetrol/drospirenone and E2V/dienogest, as well as EE-based combined oral contraceptives (COCs), all of which are FDA-approved. The data collection period extended from the beginning of the database until October 2024, with a data lock on September 30, 2024. We searched each contraception association for product and generic names. Research was conducted by reaction group for VTE events as listed in the Supplementary Appendix, according to the MedDRA dictionary. We also extracted ICSRs and all AEs of drospirenone 4 mg and norethindrone 0.35 mg for secondary comparison of COC outcomes to progestin-only oral pills (POPs). The full research protocol and data extraction procedures are available on the Open Science Framework (OSF) (https://osf.io/z5pcy/?view_only=798d67e4aa5a41e4846c86d23ca60aa3).[13]

For each product, we calculated reporting rates (RR) by computing the total number of thrombotic AEs as defined in **Supplementary Appendix 1** and dividing by the total number of ICSRs. We performed PRR and ROR analyses computed from the same 2×2 contingency tables. Because the spontaneous-report data do not allow adjustment, stratification, or redefinition of the reference set, refined ROR approaches to reduce denominator distortion [15] were not undertaken. For clarity, PRR results are presented in **Figure 1**, and unadjusted RORs are reported in the Supplementary Appendix. We computed the PRR and ROR of each

specific COC versus (i) EE/LNG or (ii) the therapeutic class (i.e., all COCs). Based on Evans et al,[16] we considered a PRR to be disproportionate when the PRR exceeded 2. We considered the ROR to indicate a signal of disproportionality when the lower bound of 95% CI did not cross one.[17] More details on disproportionality analysis and the FAERS database structure are provided in the **Supplementary Appendix 2.** Furthermore, we used a Multi-item Gamma-Poisson-Shrinker (MGPS) algorithm, a Bayesian method that compares observed and expected counts of specific drug-event combinations.[17] All results are available in the OSF folder.

We repeated these primary analyses by grouping EE/levonorgestrel and EE/norgestrel together, as levonorgestrel and norgestrel are essentially identical products. Norgestrel contains the inactive dextro- and the active levo-enantiomers of norgestrel, while levonorgestrel contains only the active enantiomers.

We conducted two sensitivity analyses. First, we evaluated the robustness of our results in the presence of product-specific excess AEs (i.e., thrombotic AEs) because the signal could be weakened by the presence of numerous AEs unrelated to VTE events. For this analysis, we used the same exploratory sensitivity method previously applied.[14] We simulated scenarios in which we reduced the total number of ICSRs by 5%, 10%, 15%, 20%, 50%, 60%, and 80%. We recalculated PRRs and their 95% CIs for each reduction level. Second, we conducted an analysis using the total number of AEs rather than the total number of ICSRs. Primary analyses were conducted at the case level using ICSRs, where each ICSR corresponds to a single patient. To evaluate robustness to within-case multiplicity of events, a sensitivity analysis was conducted at the event level using counts of AEs. In this analysis, each AE was counted separately; for example, an ICSR listing three AEs contributed

three event counts. All summary measures were re-estimated using AE counts to evaluate whether the conclusions depended on the choice of case-versus event-level denominator.

However, subgroup analyses were not conducted due to the limited individual-level information (e.g., obesity, smoking status, thrombophilia) in the ICSRs.

This disproportionality reporting ratio (DPRR) analysis was reported according to the READUS-PV (the REporting of A Disproportionality analysis for drUg Safety signal detection using individual case safety reports in PharmacoVigilance) statement. We performed all statistical analyses using Medcalc.org (MedCalc Software Ltd. Relative Risk Calculator, https://www.medcalc.org/calc/relative_risk.php, Version 22.023) and GraphPad Prism 10 (www.graphpad.com).

Results

Reporting rate for combined oral contraceptives and progestin-only pills

The detailed analysis of the total number of thrombotic AEs and ICSRs extracted from the FAERS database for all COCs as well as for drospirenone- and norethindrone-only pills are reported in **Table 1**. Estetrol/drospirenone and E2V/dienogest presented the lowest RRs (0.064 and 0.094, respectively). These rates were relatively similar to the RRs of drospirenone (0.076) and norethindrone (0.082) and lower than the RRs of EE/LNG (0.119). The highest RR was observed for the EE/drospirenone combination (0.614).

Disproportionality reporting rate for combined oral contraceptives

When comparing to EE/levonorgestrel or the entire COC therapeutic class, both estetrol/drospirenone and E2V/dienogest demonstrated significantly lower PRRs and RORs, while EE/drospirenone showed the highest disproportionality estimates (**Figure 1 and Table 2**). The PRR indicated disproportionality (ratios >2) as compared to EE/levonorgestrel for

EE/desogestrel and EE/drospirenone, and only for EE/drospirenone compared to the average in the therapeutic class. The ROR indicated the same disproportionalities as the PRR for both comparisons. When grouping EE/levonorgestrel and EE/norgestrel together, the results do not change (**Supplementary Appendices 5 and 6**).

Sensitivity analysis

In the first sensitivity analysis, aiming to reduce potential signal dilution by overreporting of non-VTE events, estetrol/drospirenone and E2V/dienogest no longer showed significantly lower PRRs compared to EE/levonorgestrel once a 5% reduction in ICSRs was applied (**Supplementary Appendix 7**). The PRRs became disproportionate for EE/NETA when an artificial 50% decrease in AEs is applied (PRR: 2.34, 95%CI 2.20-2.48), 60% for EE/norgestimate (PRR: 2.27, 95%CI 2.11-2.44), and EE/norgestrel (PRR: 2.70, 95%CI 2.44-2.99) while an 80% dilution of the signal was needed for E2V/dienogest (PRR: 3.97, 95%CI 3.41-4.62). No statistically significant disproportionality was observed with estetrol/drospirenone (PRR: 2.72, 95%CI 1.63-4.54). When compared to the therapeutic class, for each reduction applied except for the 80% reduction, results remained statistically lower for estetrol/drospirenone and E2V/dienogest. No statistically significant disproportionality was observed when compared to the therapeutic class, except for EE/drospirenone (**Supplementary Appendix 8**).

In the second sensitivity analysis, we used the total number of AEs as described in **Table 1** rather than the total number of ICSRs (**Supplementary Appendix 9**). Among COC users, a mean number of 3.41 AEs per patient is reported (range from 1.82 with estetrol/drospirenone to >4 with EE/desogestrel). For drospirenone and norethindrone users, the mean AEs per patient were 2.54 and 2.99, respectively. The PRR for

estetrol/drospirenone was not significantly lower than EE/levonorgestrel (0.71, 95% 0.38-1.31). Estetrol/drospirenone and E2V/dienogest had lower PRRs than those observed for EE-based combinations. EE/drospirenone showed the highest PRRs compared to EE/levonorgestrel (2.97, 95% 2.83-3.12) and the therapeutic class (2.88, 95% 2.81-2.96). ROR analysis confirmed these results.

Discussion

Principal findings

In this disproportionality analysis of the FAERS database, we found that COCs containing body-identical estrogens, estetrol combined with drospirenone and E2V combined with dienogest, were associated with significantly lower PRRs for VTE compared to EE-based COCs. These lower estimates remained within the same range as POPs such as drospirenone- and norethindrone- alone. Overall, reports in the FAERS database related to estetrol/drospirenone were 46% less likely to be related to VTE compared to EE/levonorgestrel and 83% less likely compared to all other COCs. Similarly, reports related to E2V/dienogest were 20% less likely to be related to VTE compared to EE/levonorgestrel and 75% less likely compared to all other COCs. Of note, reports related to EE/drospirenone were 420% more likely to be related to VTE as compared to EE/levonorgestrel and 352% more likely as compared to all other COCs. Sensitivity analyses confirmed the robustness of the primary findings, although we observed a minor loss of significance when artificially reducing the reporting base, particularly in low-prevalence products such as estetrol/drospirenone.

Results in the context of what is known

Our results align with prior evidence from biological investigations, observational studies, and other pharmacovigilance datasets.[8,13,14,18,19] Mechanistically, both E2 and

226 estetrol exert milder effects on the coagulation cascade than EE,[7] particularly by inducing
227 lower values of the normalized activated protein C sensitivity ratio (nAPCsr), a validated
228 marker of thrombotic potential recommended by the International Society of Thrombosis
229 and Haemostasis (ISTH).[20,21] These findings were substantiated in a recent meta-analysis,
230 which reported a 33% reduction in VTE odds with E2-based COCs compared to EE-based
231 formulations (OR 0.67, 95% CI 0.51–0.87), and a 49% reduction when directly compared to
232 EE/levonorgestrel after multivariate adjustment (HR 0.51, 95% CI 0.29–0.90).[13]

233 Two previously published disproportionality studies using the FAERS database have
234 also explored COC-associated thromboembolic risk and similarly reported increased VTE
235 signals for EE-containing products.[22,23] However, these studies used the entire FAERS
236 database (i.e., all drugs across all therapeutic classes) as the comparator group. Using a
237 therapeutic-class-based reference, as we do in this report, improves the signal-to-noise ratio
238 and enhances the specificity of the safety signal.[24] Additionally, their lack of adjustment to
239 COC comparator may lead to confounding by indication and class-specific usage patterns,
240 which are partially mitigated in our methodologically stricter design. Our analysis, in line with
241 READUS-PV guidelines, provides a more reliable context for evaluating within-class safety
242 signals among COCs.

243 Although our results also mirror those from a recent disproportionality analysis of the
244 EudraVigilance database,[14] two key differences between the FAERS and EudraVigilance
245 datasets have to be highlighted and may explain the reduced statistical significance observed
246 in some sensitivity scenarios. First, the reporting rate of thrombotic events for
247 EE/levonorgestrel was markedly lower in FAERS (0.12) (**Table 1**) compared to EudraVigilance
248 (0.29),[14] which reduces the contrast when comparing it to other formulations and limits the

likelihood of detecting statistically significant differences. Second, the absolute number of reported events, both thrombotic and overall, for estetrol/drospirenone (10 thrombotic events over 284 events) and E2V/dienogest (97 thrombotic events over 3455 events) was lower in FAERS (**Table 1**) than in EudraVigilance (34 thrombotic events over 507 events for estetrol/drospirenone and 428 thrombotic events over 3330 events for E2V/dienogest),[14] thus reducing the statistical power to detect robust signals. These factors jointly contribute to the attenuation of signal detection in FAERS, especially in sensitivity analyses relying on adjusted or reduced sample denominators.

Clinical implications

These findings contribute to the growing body of evidence suggesting that body-identical estrogens may offer a safer thrombotic profile than EE-based contraceptives. Importantly, our results from the FAERS pharmacovigilance database are consistent with those from controlled observational studies reporting adjusted incidence rates,[25,26] as well as a recent meta-analysis confirming a significant reduction in VTE risk with E2-based combinations.[13] Furthermore, biological investigations have provided mechanistic explanations for these observations,[8,18,19,27] notably through reduced impacts on coagulation pathways, which strongly support a causal relationship.[21] Taken together, this multi-level evidence strengthens the validity of our findings.*Research implications*

Prospective comparative effectiveness studies, ideally with head-to-head designs, are needed to quantify the risk differential between body-identical estrogens and EE-containing COCs more precisely. It also remains unclear whether estetrol/drospirenone confers the same thrombotic risk profile as drospirenone alone, warranting further investigation,

271 although this trend has been consistently observed in two independent pharmacovigilance
272 databases.

273 *Strengths and Limitations*

274 The strengths of our study include its transparent and reproducible methodology. The
275 study protocol was preregistered and is publicly available on OSF. All analyses were
276 conducted using publicly accessible databases, employing conservative analytical methods
277 and relying directly on the original data sources. In addition, the use of a comparator strategy
278 using both a clinical gold standard (EE/levonorgestrel) and the entire COC therapeutic class
279 improves signal-to-noise discrimination and strengthens the validity of comparative
280 inferences. Moreover, the use of multiple disproportionality methods and sensitivity analyses
281 enhances the robustness of the findings.

282 However, our analysis has limitations inherent to spontaneous reporting systems,
283 including underreporting, duplicate entries, indication bias, and the inability to calculate true
284 incidence. The lack of adjustments for individual-level risk factors (e.g., obesity, smoking,
285 thrombophilia), along with the limited availability of estrogen and progestin dosages, is
286 another constraint. In light of these limitations, data must be interpreted carefully.
287 Nevertheless, it should be noted that body-identical estrogens are available at a single
288 estrogen dose (e.g., estradiol or estetrol). Additionally, body-identical formulations may be
289 prescribed to patients with risk factors different from those associated with EE-based COCs.
290 For example, their price may limit access to populations with higher socioeconomic status or
291 education, who are also known to be at lower risk of VTE.[28] However, post-authorization
292 safety studies indicate that, after adjustment for confounding risk factors, a consistently

lower hazard ratio (HR) is observed. This supports the interpretation that body-identical estrogens may be preferentially prescribed to a higher-risk population.[25,26,29]

Additionally, our study includes recently introduced contraceptive products, such as estetrol/drospirenone, that entered the market recently, resulting in fewer ICSRs and, consequently, limited statistical power. Furthermore, differences in mean number of adverse events per ICSR (e.g., 1.82 for estetrol/drospirenone vs. 2.39 for EE/levonorgestrel) may mathematically distort PRRs when analyses are based on events rather than individuals. Lastly, potential confounding from media attention or product novelty (e.g., overreporting for EE/drospirenone) cannot be excluded, though internal comparisons with drospirenone-alone mitigate this concern.

Conclusions

Combined oral contraceptives containing body-identical estrogens, particularly estetrol/drospirenone and E2V/dienogest, are associated with a lower signal for VTE events compared to EE-based combinations in the FAERS database. These findings, consistent with biological, epidemiological, and previous pharmacovigilance evidence, may suggest an improved thrombotic safety profile with body-identical estrogens.

Consent for publication

All authors approved the final version of the manuscript

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None

Conflict of interest statements

MDC has received speaking honoraria from Mayne, has stock options with Femasys, and has consulted for Danco, Estetra SRL, Gedeon Richter, Mayne, Medicines360, and Merck Sharpe Dohme. The Department of Obstetrics and Gynecology, University of California, Davis, receives contraceptive research funding for Dr. Creinin from Femasys, Medicines360, Merck, Sebela, and Myovant (Sumitomo Pharma).

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Authors' contributions

JDO and CBE conceptualized the study. Data collection and curation was conducted by LRA, MDI and MLO. The formal analysis was carried out by LRA and MDI. LRA, CBE and JDO contributed to the original draft of the manuscript, whereas all authors (LRA, MDI, MLO, JMD, MCR, MDC, CBE and JDO) participated in the review and editing process. CBE and JDO provided supervision throughout the project, with JDO also overseeing project administration. Visualization was conducted by LRA, and validation was performed by MDI, MLO, CBE, and JDO. CBE was responsible for providing resources and software for the study. Funding acquisition was not applicable. All authors read and approved the final manuscript.

Data availability statement

Material related to this analysis is freely available on Open Science Framework (OSF): https://osf.io/z5pcy/?view_only=798d67e4aa5a41e4846c86d23ca60aa3.

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Not applicable

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Figure legends:

Figure 1

Title: Proportionality reporting rate and reporting odds ratio formulas.

Footer: The PRR compares the proportion of reports mentioning a specific adverse event (i.e. thrombotic AEs) for a drug (A / (A + B)) with that for a comparator (C / (C + D)), where A is the total number of thrombotic AEs and B the total number of ICSRs without thrombotic AEs for the drug under evaluation; C is the total number of thrombotic AEs and D the total number of ICSRs without thrombotic AEs for the comparator. Therefore, (A / [A + B]) and (C / [C + D]) are ratios of a number of adverse events (i.e. thrombotic AEs) over the number of patients who reported adverse events (total number of ICSRs).

Abbreviations: AEs: adverse events; ICSR: individual case safety report; PRR: proportionality reporting rate; ROR: reporting odds ratio

Figure 2.

Title: Proportionality reporting ratios and reporting odds ratio and their 95% confidence intervals, based on the number of individual case safety reports, for each estrogen-progestin combination. A: PRR, versus EE/LNG. B: PRR, versus the therapeutic class. C: ROR, versus EE/LNG. D: ROR, versus the therapeutic class. Red lines represent the thresholds for disproportionality for PRR and ROR analyses.

Footer: Abbreviations: CI, confidence interval; DNG, Dienogest; DRSP, Drospirenone; DSG, Desogestrel; E2V, 17β-estradiol valerate; E4, Estetrol; EE, Ethinyl estradiol; ICSR, Individual Case Safety Report; LNG, Levonorgestrel; NOR, Norgestrel; NGM, Norgestimate; NETA,

Norethindrone acetate; POP, Progestin-Only Pill; PRR, proportionality reporting rate; ROR, Reporting Odds Ratio; RR, Reporting Rate.

Table 1: Number of extracted thrombotic events and individual case safety reports from the FAERS database for all combined oral contraceptives and drospirenone alone

Contraceptive		Number of thrombotic events reported*	Number of ICSRs	RR	Number of AEs	Mean Number of PT per ICSR	RR
Synthetic estrogen	EE/DRSP	26892	43810	0.61	182220	4.16	0.15
	EE/DSG	996	3581	0.28	15634	4.37	0.06
	EE/NOR	305	2381	0.13	5372	2.26	0.06
	EE/NGM	860	7993	0.11	20578	2.57	0.04
	EE/NETA	1928	13915	0.14	35644	2.56	0.05
	EE/LNG	1693	14278	0.12	34076	2.39	0.05
Body - identical estrogen	E2V/DNG	97	1029	0.09	3455	3.36	0.03
	E4/DRSP	10	156	0.06	284	1.82	0.035
All COCs		32781	87143	0.38	297263	3.41	0.11
POP	DRSP†	168	2216	0.08	5624	2.54	0.03
	NET†	207	2523	0.08	7556	2.99	0.03

Abbreviations: AE, adverse event; CI, confidence interval; DNG, Dienogest; DRSP, Drospirenone; DSG, Desogestrel; E2V, 17β-estradiol valerate; E4, Estetrol; EE, Ethinyl estradiol; FAERS, FDA Adverse Event Reporting System; ICSR, Individual Case Safety Report; LNG, Levonorgestrel; NOR, Norgestrel; NGM, Norgestimate; NET, Norethindrone; NETA, Norethindrone acetate; POP, Progestin-Only Pill; PRR, proportionality reporting rate; ROR, Reporting Odds Ratio; RR, Reporting Rate.

* Thrombotic refers to all events listed in Supplementary Table 3.

† Drospirenone and norethindrone are not included in the class total; they are not COCs.

Table 2: Summary of proportionality reporting rate and reporting odds ratio estimates for all combined oral contraceptives relative to therapeutic class and relative to the EE/LNG gold standard, based on the number of individual case safety reports.

Contraceptive		PRR [95% CI] vs. EE/LNG	p-value	PRR [95% CI] vs. therapeutic area	p-value
Synthetic estrogen	**EE/DRSP**	5.18 [4.95-5.42]	**< 0.0001**	4.52 [4.41-4.63]	**< 0.0001**
	EE/DSG	2.35 [2.19-2.51]	**< 0.0001**	0.73 [0.69-0.77]	**< 0.0001**
	EE/NOR	1.08 [0.96-1.21]	**0.18**	0.33 [0.30-0.37]	**< 0.0001**
	EE/NGM	0.91 [0.84-0.98]	**0.01**	0.27 [0.25-0.28]	**< 0.0001**
	EE/NETA	1.17 [1.10-1.24]	**< 0.0001**	0.33 [0.32-0.34]	**< 0.0001**
	EE/LNG	1	**NA**	0.28 [0.27-0.29]	**< 0.0001**
Body - identical estrogen	**E2V/DNG**	0.79(5) [0.65-0.97]	**0.02**	0.25 [0.21-0.30]	**< 0.0001**
	E4/DRSP	0.54 [0.30-0.99]	**0.045**	0.17 [0.09-0.31]	**< 0.0001**
POP	**DRSP***	0.64 [0.55-0.74]	**< 0.0001**	0.20 [0.17-0.23]	**< 0.0001**
	NET*	0.69 [0.60-0.79]	**< 0.0001**	0.21 [0.19-0.24]	**< 0.0001**

Abbreviations: CI, confidence interval; COC, combined oral contraceptive; DNG, Dienogest; DRSP, Drospirenone; DSG, Desogestrel; E2V, 17β-estradiol valerate; E4, Estetrol; EE, Ethinyl estradiol; LNG, Levonorgestrel; NA, Not Applicable; NOR, Norgestrel; NGM, Norgestimate; NET, Norethindrone; NETA, Norethindrone acetate; POP, Progestin-Only Pill; PRR, proportionality reporting rate.

* Drospirenone and norethindrone are not included in the total of the class; they are not COCs.

Table 3: Summary of proportionality reporting rate and reporting odds ratio estimates for all combined oral contraceptives relative to therapeutic class and relative to the EE/LNG gold standard, based on the number of adverse events.

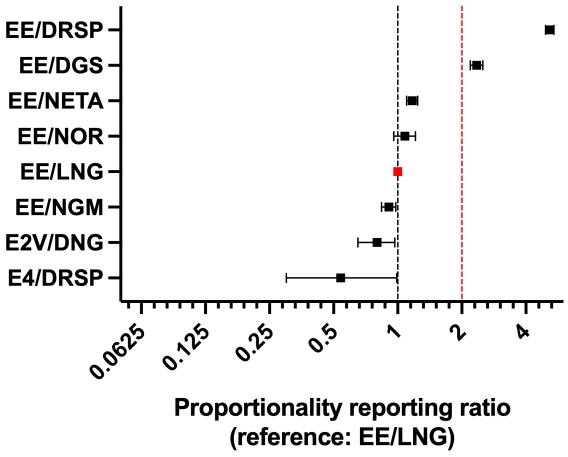
Contraceptive		PRR [95% CI] vs. EE/LNG	p-value	PRR [95% CI] vs. therapeutic area	p-value
Synthetic estrogen	**EE/DRSP**	2.97 [2.83-3.12]	**< 0.0001**	2.88 [2.81-2.96]	**< 0.0001**
	EE/DSG	1.28 [1.19-1.38]	**< 0.0001**	0.56 [0.53-0.60]	**< 0.0001**
	EE/NOR	1.14 [1.02-1.29]	**0.03**	0.51 [0.46-0.57]	**< 0.0001**
	EE/NGM	0.84 [0.78-0.91]	**< 0.0001**	0.36 [0.34-0.39]	**< 0.0001**
	EE/NETA	1.09 [1.02-1.16]	**0.01**	0.46 [0.44-0.48]	**< 0.0001**
	EE/LNG	1	**NA**	0.42 [0.40-0.44]	**< 0.0001**
Body-identical estrogen	**E2V/DNG**	0.57 [0.46-0.69]	**< 0.0001**	0.25 [0.21-0.31]	**< 0.0001**
	E4/DRSP	0.71 [0.38-1.31]	**0.27**	0.32 [0.17-0.59]	**0.0002**
POP	**DRSP***	0.60 [0.51-0.70]	**< 0.0001**	0.27 [0.23-0.31]	**< 0.0001**
	NET*	0.55 [0.48-0.64]	**< 0.0001**	0.24 [0.21-0.28]	**< 0.0001**

Abbreviations: AE, adverse event; CI, confidence interval; COC, combined oral contraceptive; DNG, Dienogest; DRSP, Drospirenone; DSG, Desogestrel; E2V, 17β-estradiol valerate; E4, Estetrol; EE, Ethinylestradiol; LNG, Levonorgestrel; NOR, Norgestrel; NGM, Norgestimate; NET, Norethindrone; NETA, Norethindrone acetate; POP, Progestin-Only Pill; PRR, proportionality reporting rate; ROR, reporting odds ratio.

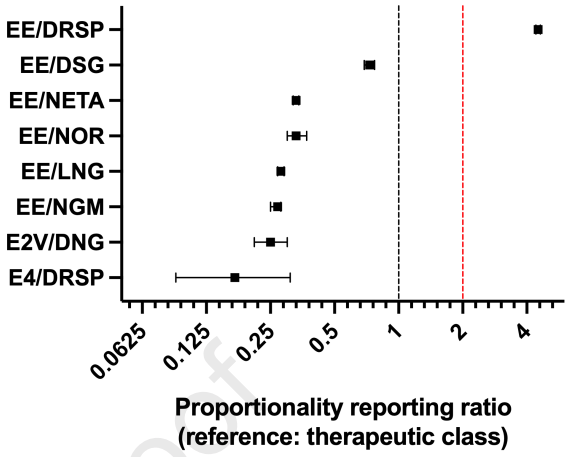
* Drospirenone and norethindrone are not included in the total of the class; they are not COCs.

$$PRR = \frac{\frac{A}{A+B}}{\frac{C}{C+D}} \qquad ROR = \frac{A*D}{B*C}$$

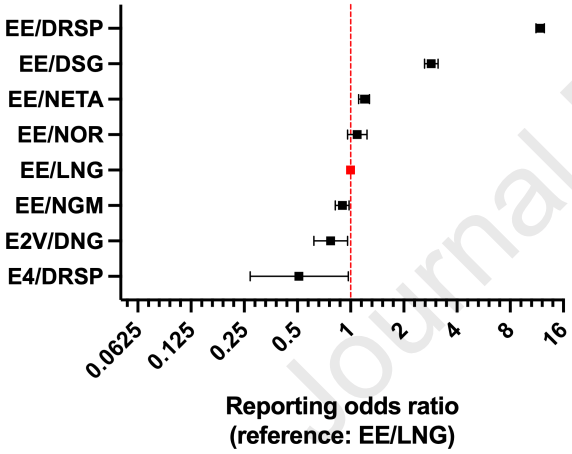
A. PRR - EE/LNG as reference



B. PRR - Therapeutic class as reference



C. ROR - EE/LNG as reference



D. ROR - Therapeutic class as reference