Title

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Correspondence

Errors in the use of the FAERS database to assess the safety of Yasmin

To the editor:

We found a recent article, "Safety assessment of Yasmin: Real-world adverse event analysis using the FAERS database," [1] to lack clarity in the calculations and filled with multiple errors. Reports such as this should use the READUS-PV guidelines for reporting their outcomes to ensure transparency, completeness, accuracy of reporting, and proper interpretation [2]; this paper does not. The FAERS database, as a passive reporting system, cannot be used to make definite conclusions and has limited value unless comparing reports of the entire product class, i.e. all combined oral contraceptives, during a single time period. To understand whether the statistical methods reflect relevant findings, the authors needed to report the numbers of adverse events (AEs) for ethinyl estradiol (EE)/drospirenone, numbers of AEs for a reference product and therapeutic class, and then perform proportional reporting ratio calculations comparing EE/drospirenone to the reference.

Among the errors, EE units are mcg, not mg. More importantly, the authors do not understand the impact of various hormones on coagulation and misquote several references, especially as it relates to clinical estrogen use and gall bladder disease.

While EE does increase venous thromboembolism (VTE) risk, the mechanism is poorly understood. The difference in VTE risk specific to oral contraceptives containing the same dose of EE is the consequence of differences in the progestin's hepatic modulation of the procoagulant effect of EE [3,4]. In the liver, androgenic progestins, like levonorgestrel, partly offset the procoagulant activity of EE [5]. EE/drospirenone causes more undesirable coagulation system impact compared to other combinations, such as EE/levonorgestrel [4], because drospirenone is a liver neutral progestin and does not counterbalance the procoagulant effect of EE. Thus, with EE/drospirenone, we see the full impact of EE on coagulation whereas levonorgestrel likely blunts the EE effect somewhat. Drospirenone alone, like other progestin-only pills, does not significantly impact coagulation factors and is believed to have little to no effect on VTE risk [6].

A recent systematic literature review and *meta*-analysis incorporating data from five observational studies involving over 560,000 women, showed a significant 33% reduction in VTE risk among E2-based combined oral contraceptive users compared to those using EE-based products [7]. The substitution of natural estrogens for the potent EE results in lower impact on coagulation markers and VTE risk. The association of natural estrogens with non-androgenic progestins does not carry the risk of VTE observed with EE.

Also, the authors state that "*Previous studies have investigated the effect of oral contraceptives on bile composition and gallbladder motility and suggested that estrogen can increase biliary cholesterol saturation, potentially leading to cholesterolosis. This effect may be exacerbated by DRSP, thereby affecting gallbladder function.*" The reference used for the first sentence, #33, makes no such statement to support this claim [8]. Articles relating cholesterol, EE-containing contraceptives and gall bladder disease are old and relate primarily to findings with high-dose EE (>50 mcg) products. The evidence that any low-dose EE containing oral contraceptive induces excess gall bladder disease risk is cursory at best. The article referenced for the second sentence (#34), concludes that the risk between drospirenone and gallbladder diseases was very low such that no harm could be presumed from prescribing drospirenone for contraception [9].

Unfortunately, the methodological flaws and misinterpretations undermine the findings of this study. Proper use of the FAERS database requires comprehensive comparisons and adherence to guidelines like READUS-PV for appropriate reporting and interpretation of disproportionality analyses. Future studies must employ rigorous methods and correct data interpretation to provide reliable and unbiaised safety assessments for contraceptives.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: MDC has received speaking honoraria from Gedeon Richter, Mayne, and Organon, has stock options with Femasys, and has consulted for Curai, Estetra, Medicines360, and Organon. The Department of Obstetrics and Gynecology, University of California, Davis, receives contraceptive research funding for Dr. Creinin from Chemo Research SL, Femasys, Medicines360, Merck, Sebela, and Sumitomo Pharma. JD is the scientific director and founder of Qualiblood, a contract research organization that received funding from Mithra. He also reports personal fees from Daiichi Sankyo, Diagnostica Stago, Gedeon Richter, Portola, Roche and Roche Diagnostics. CB: no declarations. JMF was a board member for Mithra.

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