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ORIGINAL RESEARCH

# Drospirenone-containing oral contraceptives and venous thromboembolism: an analysis of the FAERS database

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**Introduction:** Substantial evidence suggests that drospirenone-containing oral contraceptives may cause a higher risk of venous thrombotic events than earlier-generation oral contraceptives.
**Methods:** To gain insight into recent real-world implications, we conducted an analysis using the US Food and Drug Administration's Adverse Event Reporting System.
**Results:** Venous thrombotic events continue to be reported at a much higher rate with drospirenone-containing oral contraceptives than the general background. The disproportionality has been rising since 2010. The same behavior is not seen with levonorgestrel-containing oral contraceptives.
**Conclusion:** Our results are consistent with decreased physician and patient awareness of risks associated with drospirenone-containing oral contraceptives.
**Keywords:** drug safety, Yaz, venous thrombotic events, FDA adverse event reporting system, disproportionality

## Introduction

Oral contraceptives are among the most widely used drugs[1] and questions about oral contraceptive safety have occupied regulators, physicians, and patients for decades. Venous thrombotic risks associated with oral contraceptives have attracted particular scrutiny. A substantial body of evidence linked the first generation of oral contraceptive pills (OCPs) to significant risk of venous thromboembolism (VTE). The estrogen-like compounds in these OCPs appeared to be the cause. Subsequently, drug developers decreased the VTE risk of OCPs by lowering the delivered estrogen content by adding progestins such as levonorgestrel.[2] More recently, OCPs with the progestin drospirenone (Yaz/Yasmin) have enjoyed considerable commercial success, in part by emphasizing potential benefits such as reduced acne.[3,4]

Evidence began to emerge in the 2000s, however, that drospirenone-containing OCPs may cause higher risk of VTE than earlier generation OCPs. Recent systematic reviews show elevated risk,[5,6] but others emphasize the modest absolute risk: "Regardless of whether the thrombotic risk of drospirenone OCs compared to levonorgestrel OCs is increased by 1.5-fold or threefold, the absolute risk is still low."[7]

The US Food and Drug Administration's Adverse Event Reporting System (FAERS) database contains voluntarily submitted adverse event reports. The data can be downloaded from the FDA's website (http://bit.ly/2naXeJU). To shed light on real-world experience with drospirenone OCPs and using standard analytical techniques, we considered reporting of VTE associated with drospirenone OCPs as compared with the rest of the drugs in FAERS and also considered reporting of VTE associated with

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levonorgestrel OCPs as compared with the rest of the drugs in the database.

## Methods

For each year since the introduction of drospirenone-containing OCPs, we compared the cumulative reporting of VTE events in the FAERS database associated with these OCPs with the general background using a standard measure of disproportionality. We conducted a similar analysis for levonorgestrel-containing OCPs. Because this study involved analysis of publicly available deidentified data, no Institutional Board Approval was required.

### Identification of VTE events

Our analysis uses the Standardized MedDRA Query (SMQ) "Embolic and Thrombotic Events, Venous." Table 1 provides the included MedDRA preferred terms. SMQs are groupings of MedDRA preferred terms that relate to a defined medical condition or area of interest. The included terms may relate to signs, symptoms, diagnoses, syndromes, physical findings, laboratory, and other physiologic test data, etc, related to the medical condition or area of interest. SMQs were developed to facilitate retrieval of MedDRA-coded data as a first step in investigating drug safety issues in pharmacovigilance and clinical development. Below, we refer to the "Embolic and Thrombotic Events, Venous" SMQ endpoint as "Venous Thrombotic (SMQ)."

### Inclusion criteria for oral contraceptives

The medical literature concerning epidemiological studies of oral contraceptives frequently groups oral contraceptives according to progestin (eg, Dinger et al[8] or Jick et al[9]). In our analysis, we considered two progrestins: drospirenone and levonorgestrel. We included products that were listed on the investigational new drug application for each of these progestins and that have oral contraception as an indication. Table 2 lists the specific products that we included.

**Table 1** MedDRA terms included in the SMQ Embolic and Thrombotic Events, Venous

| Venous thrombotic (SMQ) preferred terms | |
|---|---|
| **Axillary vein thrombosis** | **Pulmonary thrombosis** |
| Budd–Chiari syndrome | Pulmonary vein occlusion |
| Catheterization venous | Pulmonary veno-occlusive disease |
| Cavernous sinus thrombosis | Pulmonary venous thrombosis |
| Central venous catheterization | Renal vein embolism |
| Cerebral venous thrombosis | Renal vein occlusion |
| Compression stockings application | Renal vein thrombosis |
| Deep vein thrombosis | Retinal vein occlusion |
| Deep vein thrombosis postoperative | Retinal vein thrombosis |
| Embolism venous | SI QIII TIII pattern |
| Hepatic vein occlusion | Splenic vein occlusion |
| Hepatic vein thrombosis | Splenic vein thrombosis |
| Homans' sign positive | Subclavian vein thrombosis |
| Iliac vein occlusion | Superior sagittal sinus thrombosis |
| Inferior vena cava syndrome | Superior vena cava syndrome |
| Inferior vena caval occlusion | Thrombophlebitis |
| Intracranial venous sinus thrombosis | Thrombophlebitis migrans |
| Intravenous catheter management | Thrombophlebitis neonatal |
| Jugular vein thrombosis | Thrombosed varicose vein |
| May–Thurner syndrome | Thrombosis corpora cavernosa |
| Mesenteric vein thrombosis | Transverse sinus thrombosis |
| Obstetrical pulmonary embolism | Vascular graft |
| Paget–Schroetter syndrome | Vena cava embolism |
| Pelvic venous thrombosis | Vena cava filter insertion |
| Penile vein thrombosis | Vena cava thrombosis |
| Phlebectomy | Venogram abnormal |
| Phleboplasty | Venoocclusive disease |
| Portal vein occlusion | Venoocclusive liver disease |
| Portal vein thrombosis | Venous occlusion |
| Postprocedural pulmonary embolism | Venous operation |
| Postthrombotic syndrome | Venous recanalisation |
| Postoperative thrombosis | Venous stent insertion |
| Postpartum venous thrombosis | Venous thrombosis |
| Pulmonary embolism | Venous thrombosis in pregnancy |
| Pulmonary infarction | Venous thrombosis limb |
| Pulmonary microemboli | Venous thrombosis neonatal |

**Abbreviation:** SMQ, Standardized MedDRA Query.

### Disproportionality metric

We used the lower bound of a 90% interval for the "information component (IC)" statistic.[10] This statistic is commonly referred to as IC05. Because it is the lower end of the interval, IC05 is always closer to one than the IC and is thus more conservative than IC. The IC05 calculations stratify by age, sex, and year of report.

In practice, disproportionality metrics are often used with "signal thresholds" that dictate whether or not a given drug–outcome pair generates a signal. For example, Szarfman et al[11] proposed using a threshold of 2 for the "EB05" measure, quantitatively very similar to the IC05.[11] We indicate this threshold in Figure 1.

The IC and IC05 are used by the World Health Organization for safety assessment in its program for International Drug Monitoring.[10,12]

## Results

A signal of disproportionate reporting for drospirenone-containing OCPs appeared in 2002, well before any epidemio-

logical studies raised any concerns, and persists to this day. It is unclear why the IC05 declined in the 2005–2010 period (albeit remaining well above the standard signaling threshold of 2), but it has increased steadily since then and is currently above 11. The IC05 for drospirenone-containing OCPs is approximately five times higher than that for levonorgestrel-containing OCPs.

Figure 1 shows the IC05 values for each quarter from the first quarter of 2000 through the first quarter of 2016.

**Table 2** Specific drugs included

| Progestin | Products |
|---|---|
| Drospirenone | Drospirenone and Ethinyl Estradiol |
| | Yasmin |
| | Yaz |
| | Ocella |
| Levonorgestrel | Alesse |
| | Aviane |
| | Enpresse |
| | Lessina |
| | Levlite |
| | Levora |
| | Loseasonique |
| | Low-ogestrel |
| | Lybrel |
| | Nordette |
| | Portia |
| | Seasonale |
| | Seasonique |
| | Triphasil |
| | Trivora |

## Discussion

Spontaneous report databases remain a mainstay of modern pharmacoepidemiology. Lester et al[13] provide a recent demonstration of the importance of spontaneous report analyses in characterizing drug safety issues. The article considered all drug label changes in 2010 and reported that "Spontaneous reports were the most common evidence source from which drug safety issues were identified that resulted in safety-related label changes in 2010 when analyzed both by unique safety issue and drug (52% and 55% of all evidence sources, respectively)." Moore et al[14] conducted a similar exercise, in their case looking at 2009 label changes involving major regulatory safety actions. The authors state that spontaneous reports "formed the basis of 77 of 135 new regulatory actions (57%) and 19 of 25 new boxed warnings (76%)." Hennessy and Strom[15] state: "Spontaneous reporting systems remain to this day a crucial means of uncovering important postapproval drug safety information."

Spontaneous report data have some inherent, well-documented limitations relying as they do on voluntary reporting. Underreporting is a particular concern that has been well documented and, furthermore, the data provide limited temporal information to inform analyses.[16] Some authors refer to the possibility of "stimulated" or publicity-triggered reporting to FAERS. A recent comprehensive review of FDA safety alerts suggests modest evidence for

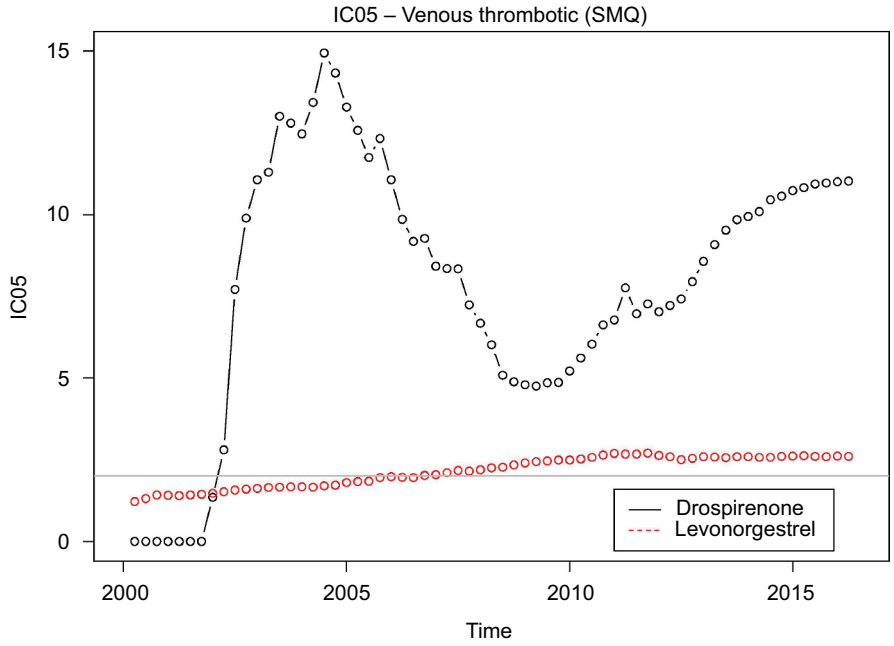


**Figure 1** IC05 values for drospirenone-containing OCPs and levonorgestrel-containing OCPs.
**Abbreviations:** OCP, oral contraceptive pills; SMQ, Standardized MedDRA Query.

significant reporting changes associated with the issuance of alerts.[17] Some earlier studies drew similar conclusions.[18,19] Disproportionality analyses provide limited opportunity for adjustment for potential confounding and this possibility cannot be ruled out.

## Conclusion

Our analysis suggests that drospirenone-containing OCPs may result in many more VTEs than levonorgestrel-containing OCPs and that the gap is widening in recent years.

## Disclosure

Dr Madigan testified for plaintiffs in litigation related to Yaz in 2011. The authors report no other conflicts of interest in this work.

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