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Research article

Comparing the risk of deep vein thrombosis of two combined oral contraceptives: Norethindrone/ethinyl estradiol and drospirenone/ethinyl estradiol

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ABSTRACT

Background: Deep vein thrombosis (DVT) has been reported as an adverse event for patients receiving combined oral contraceptives. Norethindrone/ethinyl estradiol (NET/EE) and drospirenone/ethinyl estradiol (DRSP/EE) are two commonly prescribed combined hormonal oral contraceptive agents used in the United States, differing in their progestin component.

Objective: The purpose of this study was to determine the association between the progestin component of a combined oral contraceptive and the risk of DVT in patients taking oral contraceptives for birth control using data derived from the FDA Adverse Event Reporting System (FAERS).

Methods: The risk of DVT was compared between patients that had taken NET/EE with those that had taken the DRSP/EE COC formulation for birth control. In addition, age was assessed as a possible confounder and the outcome severity for those diagnosed with DVT were compared between the two groups. Finally, association rule mining was utilized to identify possible drug-drug interactions that result in elevated DVT risk.

Results: DVT was the fourth most commonly adverse event reported for patients taking DRSP/EE accounting for 8558 cases and the seventeenth most commonly reported adverse event for NET/EE accounting for 298 cases. Age was found to be a significant confounder for users of DRSP/EE with regards to DVT risk across all age groups assessed: $20<\text{Age} \leq 30$ (ROR = 1.33, 95% CI 1.23–1.45), $30<\text{Age} \leq 40$ (ROR = 2.16, 95% CI 1.98–2.35), and Age>40 (ROR = 3.69, 95% CI 3.37–4.04) However, there was only a statistically significant elevated risk in patients over 40 years of age taking NET/EE (ROR = 1.98, 95% CI 1.36–2.88). Patients that had taken DRSP/EE and the corticosteroid prednisone simultaneously had an approximately 3-fold increase in DVT risk (ROR = 2.77, 95% CI 2.43–3.15) relative to individuals that had only taken DRSP/EE.

Conclusion: Based on this analysis, there is a higher risk of developing DVT when taking DRSP/EE than when taking NET/EE as hormonal contraception. In addition, a possibly significant drug-drug interaction between different COC formulations and prednisone were identified. This

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interaction may result in elevated DVT risk due to a synergistic impairment of fibrinolysis and a decrease in plasmin production.

1. Introduction

Combined oral contraceptives (COCs) are a class of therapeutics containing two distinct synthetic hormones, estrogen and progestin, and are a commonly prescribed means for birth control by inhibiting ovulation and thinning the lining of the uterus. While progestins primarily promote the resulting contraceptive effects including atrophy of the endometrial tissue and decreased tubal motility, the addition of estrogen stimulates progestin functionality and allows for effective contraception at lower doses [1].The first generation of oral contraceptives, marketed as Enovid, was approved by the Food and Drug Administration (FDA) in 1960 and was composed of the synthetic estradiol mestranol as well as the second-generation progestin norethisterone [2]. However, severe side effects including significant menstrual cramps and bleeding (dysmenorrhea), cardiovascular complications, and cervicitis were frequently reported among patients taking Enovid [1,3]. Over the years, various modifications to the initial COC formula have resulted in reduced adverse events and stronger regulation of the menstrual cycle including reduction of ethinyl estradiol (EE) concentration, inclusion of 17β estradiol, and use of different progestins including norethindrone, drospirenone, and norgestimate [4].

Most oral contraceptives are 28-day cyclic formulations in nature where 21 pills containing active ingredients are first prescribed followed by a 7-day period in which hormone-free pills are used [1,4]. Some of the most common modern formulations for COCs used in the United States include ethinyl estradiol as the estrogen component and either norethindrone (NET/EE) or drospirenone (DRSP/EE) as the progestin constituent [1]. In these formulations, norethindrone promotes suppression of ovulation through the thickening of the cervical mucus, of which results in the inhibition of sperm penetration, slowed movement of the ovum through the fallopian tubes, and changes in endometrial thickness [4]. In contrast, formulas containing drospirenone have the additional effect of having antimineralocorticoid properties, of which counteract the increase in sodium retention propagated by the estrogen component and facilitates elevated water excretion from the kidneys [4].

Previous studies have implicated the use of oral contraceptives in the increased risk of developing deep vein thrombosis (DVT), a condition characterized by the growth of blood clots (termed a thrombus) in at least one deep vein and that frequently form in the legs [5]. Clot formation may be either asymptomatic or result in significant swelling in the extremities and may migrate to the lungs and block arterial blood flow to part of the lungs in what is referred to as a pulmonary embolism [4,6]. One meta-analysis of 25 publications found that the use of COCs was associated with a 2.5-fold increase in relative risk (RR = 3.5, 95% CI 2.9–4.3) when compared to women not using COCs [5]. Another systematic review of 15 publications including case control studies, mortality studies, and cohort studies found that users of hormonal contraceptives containing third generation progestins such as desogestrel (OR = 4.9, 95% CI 2.5–9.4) or gestodene (OR = 6.2, 95% CI 5.6–7.0) were 3–9 times more likely than nonusers to develop DVT [6]. In addition, individuals using oral contraception containing third generation progestins were approximately twice as likely to develop DVT than those who had been taking COCs containing second-generation progestins [6]. Thus, there is a previous established precedent in the literature to implicate various COC formulations in the development of DVT in women taking oral contraceptives for birth control.

Since their initial production in the 1960s, the number of women of childbearing age that are prescribed oral contraception has significantly increased. In 2020, estimates showed that approximately 88.2% of women aged 15–44 in the United States use at least one form of contraception [7]. Due to their increasing popularity, there are several different types and brands of birth control pills, with new ones coming out regularly. As with any drug, these new oral contraceptives have undergone the required clinical studies to be approved for use by the FDA. However, there is limited research on the drugs post-market including the comparison of the efficacy of contraceptive drugs. This limits the guidelines when prescribing COCs and ultimately, provides limited recommendations to distinguish between appropriate formulations for patients.

Although several studies have suggested an association between the use of COCs and the subsequent development of DVT, many studies conducted are either performed on a small-scale, are older and thus do not assess differential risk among users of COCs containing third generation progestins, or only compare differential risk across generations of progestins without taking into consideration individual progestins used. In this study, data derived from the FDA Adverse Event Reporting System (FAERS) database; a large-scale repository of real-world data collected from patients globally, were collected and analyzed [8–11]. The FAERS database provides invaluable data concerning reliable information regarding possible drug adverse events and stores post-marketing data from reports submitted to the FDA from patients, medical professionals, and drug manufacturers [8]. As of September 2022, the FAERS database has received a total of approximately 25 million reports with over 1 million new reports recorded each year. Thus, this study seeks to further establish whether or not a significant association exists between the usage of COCs, specifically NET/EE and DRSP/EE, for birth control and subsequent development of DVT in patients.

2. Material and methods

2.1. FAERS spontaneous reports

The publicly accessible FAERS dashboard was utilized in order to search and download FDA FAERS records. These records from the FAERS dashboard contain the following 7 key information categories: 1.) Drug information; 2.) Adverse drug events (ADEs); 3.) Patient outcome for the reported adverse event (outcome severity); 4.) Patient demographic information (includes such predictors as patient

sex, age, and body weight); 5.) Source of the reported adverse event; 6.) Reporting dates and 7.) The indications for use. FAERS records dated up to August 2023 were ultimately included in this study.

Adverse drug events that were reported for a drug of interest were extracted from the FAERS dashboard by inputting both the generic name of the drug (for instance drospirenone or DRSP/EE) and known brand names (such as Loryna). The "suspect product names" or "suspect product active ingredients" columns of a record containing either the generic or brand names for the drugs of interest will be outputted from the FAERS dashboard.

2.2. Removal of duplicate FAERS reports

Most of the FAERS records saved in the FAERS dashboard are directly reported to the FDA by a patient, a pharmaceutical company, or a health professional. However, certain FAERS reports are derived indirectly from publications rather than originating directly from submissions by consumers or practitioners. These records that were indirectly taken from publications were excluded in this study for three reasons. First, these reports are generally reported to the FDA by multiple companies and sources, resulting in 2–10 duplicate reports for the same patient and adverse events. Inclusion of these duplicated records would subsequently generate false positives in further calculations. Second, the reports from different companies may be inconsistent due to different sources interpreting the findings from the publications or reports differently. Finally, these records only comprise approximately 2∼3% of the total cases in FAERS; therefore, excluding these records would have little effect on the final conclusions of this study. Data analysis was performed using R statistical software version 4.3.2.

Table 1
Top 20 adverse events related to NET/EE (n = 13597) and DRSP/EE (n = 43220).

NET/EE	Total case: 13597	
	Adverse Drug Events	Frequency
1	unintended pregnancy	1513
2	drug ineffective	1012
3	pulmonary embolism	679
4	amenorrhea	631
5	menometrorrhagia	607
6	headache	582
7	intermenstrual bleeding	561
8	nausea	556
9	anxiety	455
10	pain	416
11	off label use	407
12	pregnancy on oral contraceptive	382
13	breast cancer	372
14	cerebrovascular accident	364
15	product dose omission issue	360
16	alopecia	330
17	**deep vein thrombosis**	298
18	depression	292
19	vomiting	279
20	heavy menstrual bleeding	275
DRSP/EE	**Total case: 43220**	
	Adverse Drug Events	**Frequency**
1	pain	12982
2	injury	10885
3	pulmonary embolism	9608
4	**deep vein thrombosis**	8558
5	anxiety	6870
6	emotional distress	6475
7	cholecystitis chronic	5773
8	cholelithiasis	4223
9	gallbladder disorder	4082
10	general physical health deterioration	3333
11	abdominal pain	2789
12	nausea	2746
13	dyspnoea	2380
14	anhedonia	2279
15	thrombosis	2118
16	chest pain	1950
17	vomiting	1940
18	abdominal pain upper	1900
19	pain in extremity	1830
20	cholecystectomy	1804

2.3. Disproportionality analysis

A disproportionality analysis was conducted in order to compare the risk of a DVT outcome between patients that used combined NET/EE oral contraceptives and those that were prescribed DRSP/EE COC formulations for birth control. The reporting odds ratio (ROR) and accompanying 95% confidence interval (CI) for this comparison were then calculated. A lower bound value greater than 1.0 for the 95% confidence interval was indicative of a statistically significant higher likelihood of reporting DVT in the experimental group (DRSP/EE) than in the control group (NET/EE). RORs were calculated using the Medcalc odds ratio online calculator (https://www.medcalc.org/calc/odds_ratio.php).

2.4. Association rule mining (ARM)

Finally, association rule mining was used to assess whether DVT were associated with other adverse events that are commonly reported by users of either the NET/EE or DRSP/EE COC formulations. The association rules were analyzed using the arules package in R. The following formulas were used to calculate the support, confidence, and lift values.

$$Support(\{X\} \rightarrow \{Y\}) = \frac{Number\ of\ reports\ containing\ both\ X\ and\ Y}{Total\ number\ of\ reports}$$

$$Lift(\{X\} \rightarrow \{Y\}) = \frac{Support\ (X \rightarrow Y)}{Support(X) * Support(Y)}$$

$$Confidence(\{X\} \rightarrow \{Y\}) = \frac{Number\ of\ reports\ containing\ both\ X\ and\ Y}{Number\ of\ reports\ containing\ X}$$

3. Results

1. Top 20 adverse drug events associated with NET/EE and DRSP/EE

A total of 13597 and 43220 case reports were obtained for patients prescribed NET/EE or DRSP/EE for birth control respectively in FAERS after excluding the records sourced from publications. The top 20 most frequently reported adverse events by patients taking either NET/EE or DRSP/EE for birth control are presented in Table 1. Deep vein thrombosis (DVT) was the 17th most reported ADE among patients prescribed a COC containing NET/EE (n = 298) and the 4th most frequently reported ADE by patients prescribed DRSP/EE (n = 8558). Additional reported adverse events by patients prescribed NET/EE oral contraceptive formulations comprising the top 5 include unintended pregnancy (n = 1513), drug ineffective (n = 1012), pulmonary embolism (n = 679), amenorrhea, (n = 631), and menometrorrhagia (n = 607). Other reported adverse events by patients prescribed DRSP/EE comprising the top 5 include pain (n = 12982), injury (n = 10885), pulmonary embolism (n = 9608), and anxiety (n = 6870). The high frequency of unintended pregnancies reported by those taking NET/EE for birth control suggests that COCs containing DRSP/EE are more effective at halting ovulation and preventing pregnancy.

2. Comparison of DVT risks between NET/EE and DRSP/EE

DVT was first identified as a commonly reported adverse event for patients prescribed either NET/EE (298 out of 13597) or DRSP/EE (8558 out of 43220) for birth control. Next, the likelihood of reporting DVT as an adverse event was compared between patients taking NET/EE and those that were prescribed DRSP/EE for birth control. As shown in Table 2, patients taking DRSP/EE oral contraceptives were approximately 11 times more likely (ROR = 11.01, 95% CI 9.80–12.39) to report DVT as an adverse drug event to the FAERS database when compared to patients taking NET/EE for birth control.

3. Outcome comparison of patients diagnosed with DVT

In order to assess the severity of the reported DVT cases, patient outcome was compared between individuals diagnosed with DVT after taking NET/EE for birth control and those patients that subsequently were diagnosed with DVT after being prescribed DRSP/EE oral contraceptives. Patient outcome indicates patient condition relating to the reported ADE and may be classified as non-severe, requiring hospitalization, life-threatening, or resulting in patient death. As shown in Table 3, of the 298 reported cases of DVT by

Table 2
Comparison of DVT risk between NET/EE and DRSP/EE.

Group	DVT	No DVT	ROR (95% CI) and p-value
NET/EE	298	13299	
DRSP/EE	8558	34662	11.01 (9.80–12.39), p = < 0.0001

Total case: NET/EE (n = 13597) and DRSP/EE (n = 43220).

patients taking NET/EE, 188 patients were hospitalized (63.09%), 9 died from complications (3.02%), and 55 cases were considered life-threatening (18.46%). Furthermore, 1294 patients were hospitalized (9.73%) and 241 were considered to be in life-threatening condition (1.81%) among individuals that had taken NET/EE for birth control yet had not developed DVT. No significant difference in the relative mortality frequency was observed between patients diagnosed with DVT (3.02%) and those that were not diagnosed with DVT (2.55%) among patients prescribed NET/EE oral contraceptives.

A total of 43,220 spontaneous case reports indicating DRSP/EE oral contraceptive usage were obtained from the FAERS database. Among the subset of 8558 reports that indicated DRSP/EE use as well as DVT as an adverse event, 6043 were hospitalized (70.61%), 129 died due to complications (1.51%), and 507 cases were classified as life-threatening (5.92%). In contrast, of the remaining 34662 case reports that did not indicate DVT as an ADE after being prescribed DRSP/EE for birth control, 14586 cases were hospitalized (43.08%) and 1366 cases were classified as life-threatening (3.94%). Comparable to the data observed for patients that had taken NET/EE for birth control, no significant difference in the relative mortality frequency was observed between patients diagnosed with DVT (1.51%) and those that were not diagnosed with DVT (1.67%) among patients prescribed DRSP/EE oral contraceptives for birth control. These findings suggest that patients that had taken DSRP/EE and subsequently developed DVT were more likely to be hospitalized than patients that had developed DVT after taking NET/EE for birth control.

4. Age difference in DVT risk

Age was next assessed as a possible confounding variable for the association between the COC formulation and the likelihood of subsequent development of DVT. Patients were partitioned into the following 4 distinct age groups: age $\leq$ 20, 20<age $\leq$ 30, 30<age $\leq$ 40, and age>40. As indicated in Table 4, no statistically significant difference in DVT likelihood was observed in patients prescribed NET/EE for birth control for individuals in the 20<age $\leq$ 30 age demographic (ROR = 0.73, 95% CI 0.49–1.10) and 30<age $\leq$ 40 age demographic (ROR = 1.01, 95% CI 0.66–1.53) relative to the age $\leq$ 20 group (control). However, individuals in the >40 age group had a 98% increased likelihood of DVT (ROR = 1.98, 95% CI 1.36–2.88) after taking NET/EE for birth control relative to individuals in the age $\leq$ 20 demographic.

In contrast to the trend observed in individuals prescribed the NET/EE formulation for birth control, the likelihood of subsequent DVT development after taking DRSP/EE increases with respect to age (Table 4). Relative to the youngest age demographic, individuals in the 20<age $\leq$ 30 demographic were 33% more likely (ROR = 1.33, 95% CI 1.23–1.45) to develop DVT after being prescribed DRSP/EE for birth control. A 116% increase in the likelihood (ROR = 2.16, 95% CI 1.98–2.35) was observed when comparing individuals comprising the 30<age<40 group with the control group. Finally, relative to the youngest age demographic, individuals older than 40 years of age that had taken DRSP/EE for birth control had a 269% increase (ROR = 3.69, 95% CI 3.37–4.04) in DVT likelihood relative to individuals aged 20 or younger.

5. Association rule for DVT and drug pairs.

Finally, association rule mining was used in order to identify drug pairs that were associated with an increased the risk of DVT in patients that had taken DRSP/EE for birth control along with one other therapeutic (Table 5). A lift value greater than 1 indicates that the given drug and DVT occurred more than expected among all cases of DRSP/EE. The glucocorticoid steroid, prednisone, shows highest lift value (lift = 2.01) which indicated that the drug pair (DRSP/EE and prednisone) was associated with an increased DVT risk. Other top drugs included acetaminophen (lift = 1.81), Percocet (lift = 1.81), Synthroid (lift = 1.77), naproxen (lift = 1.76), Vicodin (lift = 1.72), ibuprofen (lift = 1.65), and Tylenol (lift = 1.62). The likelihood of DVT was then assessed among patients that had reported taking prednisone with either NET/EE or DRSP/EE. As indicated in Table 6, patients that had taken NET/EE and prednisone simultaneously had an approximately 6-fold increase (ROR = 6.26, 95% CI 2.17–17.82) in DVT risk than individuals that had taken NET/EE without prednisone. Patients that had taken DRSP/EE and prednisone simultaneously had a near 3-fold increase (ROR = 2.77, 95% CI 2.43–3.15) in DVT risk than individuals that had taken DRSP/EE without prednisone.

Table 3
Clinical outcomes for individuals prescribed NET/EE.

NET/EE		
	With DVT	Without DVT
Hospitalized	188 (63.09%)	1294 (9.73%)
Death	9 (3.02%)	339 (2.55%)
Life-Threatening	55 (18.46%)	241 (1.81%)
Total Cases	298	13299
DRSP/EE		
	With DVT	**Without DVT**
Hospitalized	6043 (70.61%)	14586 (43.08%)
Death	129 (1.51%)	579 (1.67%)
Life-Threatening	507 (5.92%)	1366 (3.94%)
Total Cases	8558	34662

Table 4
Age effects for patients prescribed NET/EE and DRSP/EE.

NET/EE			
Group	DVT	No DVT	ROR (95% CI) and p-value
Age ≤ 20	40	1225	
20<Age ≤ 30	62	2595	0.73 (0.49–1.10), p = 0.13
30<Age ≤ 40	51	1553	1.01 (0.66–1.53), p = 0.98
Age>40	101	1562	1.98 (1.36–2.88), p = 0.0003
DRSP/EE			
Group	**DVT**	**No DVT**	**ROR (95% CI) and p-value**
Age ≤ 20	877	4998	
20<Age ≤ 30	2410	10296	1.33 (1.23–1.45), p < 0.0001
30<Age ≤ 40	2446	6464	2.16 (1.98–2.35), p < 0.0001
Age>40	2014	3110	3.69 (3.37–4.04), p < 0.0001

Table 5
Association rules between drugs and DVT risk ({drug = 1} -> {DVT = 1}) for DRSP/EE cases.

Drug Name	Support	confidence	coverage	lift	count
Prednisone or Deltasone or Rayos	0.009	0.399	0.023	2.013	397
acetaminophen\hydrocodone bitartrate	0.011	0.359	0.031	1.812	484
Percocet	0.010	0.358	0.027	1.806	414
Synthroid	0.009	0.350	0.026	1.765	389
naproxen	0.008	0.349	0.024	1.760	367
Vicodin	0.011	0.341	0.033	1.723	493
Ibuprofen or advil or Motrin	0.033	0.327	0.100	1.650	1416
Tylenol	0.011	0.321	0.034	1.622	466
albuterol	0.012	0.301	0.041	1.518	537
Lexapro	0.007	0.293	0.025	1.478	321

Table 6
Drug-drug interaction between prednisone and NET/EE.

NET/EE			
Group	DVT	No DVT	ROR (95% CI) and p-value
NET/EE without Prednisone	294	13270	
Prednisone without NET/EE	788	98891	0.36 (0.31–0.41), p < 0.0001
NET/EE + Prednisone[a]	4	29	6.26 (2.17–17.82), p = 0.0007
DRSP/EE			
DRSP/EE without Prednisone	8161	34063	
Prednisone without DRSP/EE	395	98321	0.017 (0.015–0.018), p < 0.0001
DRSP/EE + Prednisone[a]	397	599	2.77 (2.43–3.15), p < 0.0001

Total case with DVT: NET/EE (n = 298) and DRSP/EE (n = 8558).
[a] Searching terms including "Prednisone", "Prednisone Acetate", "Prednisone Intensol", "Deltasone", and "Rayos".

4. Discussion

DVT occurs when a blood clot forms in one of the deep veins, usually the legs, and may result in pulmonary embolism if the blood clot migrates to an arterial vessel in the lungs, ultimately inhibiting proper blood flow [6].

Wound development is rapidly followed by the formation of a platelet network over the site of vessel damage containing collagen, platelets, tissue factor VIIIA, and VWF/factor VIII complex [12,13]. The formation of the platelet layer is then subsequently followed by the initiation of the clotting cascade, either through the intrinsic or extrinsic pathway [14]. Although both pathways converge at the point in which factor X is converted to activated factor XA, the intrinsic pathway is initiated by the release of exposed collage by damaged endothelial tissue and the extrinsic pathway cascade begins with the release of tissue factor VIIIA [13,14]. Newly activated factor XA then associates with the cofactor factor V and mediates the conversion of inactive prothrombin to thrombin (factor IIA) [14]. Next, factor IIA initiates the conversion of fibrinogen into fibrin as well as generates a positive feedback loop in which various clotting factors including factor XI, factor VII, and factor V are upregulated [13]. Finally, fibrin subunits join to form fibrin stands that subsequently interact with factor XIII, creating a fibrin mesh that stabilizes the platelet plug at the site of injury [14]. The process of blood clotting is presented in Fig. 1.

In order to prevent the formation of aberrant blood clots and slowly degrade existing fibrin meshes as a wound heals, blood clots undergo a process referred to as fibrinolysis [15]. In this process, inactive plasminogen is deposited onto the surface of fibrin strands

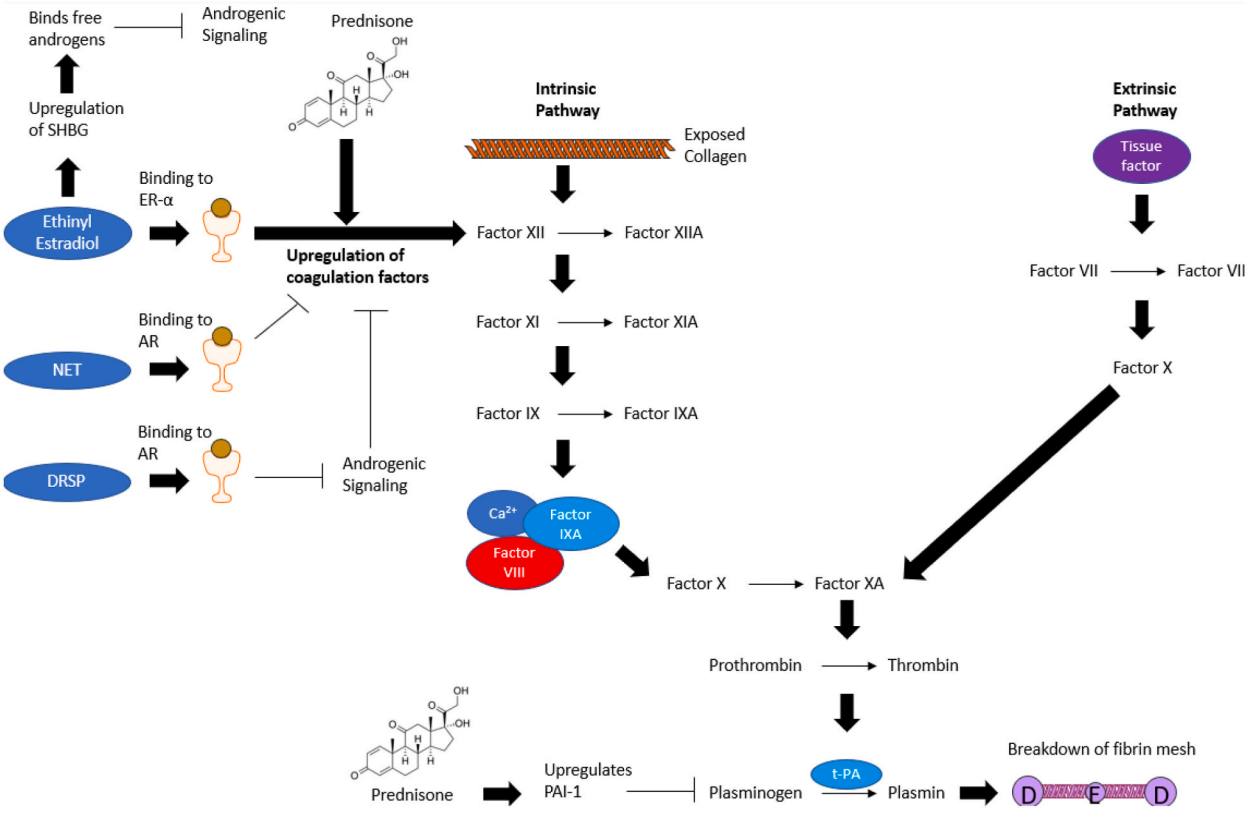

Fig. 1. Overview of the interactions between EE and progestin component as well as drug interaction with prednisone.

and converted to the active fibrinolysin plasmin by either tissue plasminogen activator (t-PA) or urokinase plasminogen activator (u-PA) that subsequently break down the fibrin mesh [13,15]. This process ensures that fibrin clots do not remain once the epithelial damage is healed (Fig. 1).

Hemostasis is a tightly regulated physiological process that is largely mediated by the interplay between the three major classes of sex hormones: estrogens, progestogens, and androgens [16]. Binding of estrogens to their cognate receptor triggers downstream release of coagulant factors as well as the upregulation of the cognate progestogen receptor (PGRs), the latter of which binds to progestogen and initiates a signaling cascade that ultimately downregulates the expression of estrogen receptors (ESRs) [15,16]. This feedback loop is essential in modulating cellular responses to estrogen and promoting effective clotting mechanisms. In contrast, binding of androgens to their cognate receptors stimulates the release of anticoagulant factors such as plasminogen activator inhibitor type I (PAI-1) as well as fibrinolytic factors such as t-PA [15,17]. The carefully constructed relationship between these three sex hormones helps to ensure proper blood clotting and dissolution of blood clots once wounds are healed.

Ethinyl estradiol (EE) is a potent agonist of the ESR, particularly estrogen receptor α (ESR-α), and has been shown to upregulate the expression of coagulation factors by the liver while simultaneously suppressing the release of anticoagulant factors including protein C and antithrombin [16,18]. In addition, EE has strong antiandrogenic properties that function through the stimulation of sex-hormone binding globulin (SHBG) synthesis by the liver and through the suppression of luteinizing hormone (LH) secretion from the pituitary gland [16,19]. SHBG is a protein that circulates through the bloodstream and binds free-floating testosterone, reducing androgen-mediated signaling that results in the production of anticoagulant factors and plasmin required for fibrinolysis of fibrin meshes, while decreased LH secretion decreases the amount of testosterone produced [20]. The combined effects of these two anti-androgenic mechanisms limits the ability to break down clots as well as the ability to prevent the formation of irregular thrombi, resulting in increased DVT risk. Thus, the baseline elevated risk in DVT observed in all users of COCs is due to the activity of the ethinyl estradiol component.

Two distinct properties of DRSP/EE may explain the observed differential risk of DVT in patients that had taken DRSP/EE and those that were prescribed the NET/EE formulation for birth control. First, the progestin component of the DRSP/EE formulation, drospirenone, has significant anti mineralocorticoid activity while norethindrone does not, a property that lowers salt and water retention as well as decreases blood pressure [21,22]. One study found a 74% increase in risk (HR = 1.74, 95% CI 1.20–2.51) of DVT in older patients with orthostatic hypotension while another study found that patients with a systolic blood pressure (SBP) < 70 mmHg had a 4.4-fold increase in the likelihood (adjusted OR = 4.4, 95% CI 2.7–7.2) of dying from a pulmonary embolism after 30 days [23]. Decreased blood flow forces heart muscles to function more vigorously, increasing the chance of aberrant clot formation. Second,

drospirenone has significant antiandrogenic activity while norethindrone has moderate androgenic activities [24,25]. Because of this property, the procoagulatory effects of EE are balanced to some degree by the androgenic function of norethisterone in the NET/EE COC formulation due its stimulation of anticoagulant secretion by the liver and its ability to promote dissolution of clots [24]. Conversely, drospirenone functions as a competitive inhibitor of the androgen receptor, downregulating androgen signaling and elevating the procoagulatory state promoted by ethinyl estradiol [24]. It is this lack of a counterbalance to ethinyl estradiol's significant estrogenic activity and the resulting increase in coagulant factor secretion that may be responsible for the elevated risk of DVT in women taking DRSP/EE relative to the risk observed in those that had taken a COC formulation containing androgenic progestins including norethisterone or levonorgestrel [26,27]. Fig. 1 summarizes the proposed mechanisms in which DRSP/EE may confer elevated risks in patients when compared with those that had taken NET/EE for birth control.

Age was identified as a possible confounding factor for the association between the use of COCs containing drospirenone and the risk of subsequent development of DVT. Conversely, no statistically significant modulation of DVT risk was observed for patients that had used norethindrone-containing oral contraceptives with the exception of individuals in the >40 age demographic. Multiple studies have previously implicated alterations in hemostasis as the primary mechanism in which DVT risk increases with age [28]. As age increases, hemostasis equilibrium shifts in the direction of pro-coagulation due to the increase in plasma concentrations of many coagulation factors including von Willebrand factor (VWF), factor VII, factor VIII, factor IX, factor XII, and fibrinogen while the concentration of anticoagulation factors remains relatively constant [29,30]. This naturally occurring increase in plasma clotting factors, coupled with the pro-clotting properties of some formulations of COCs, synergistically function together to elevate the risk of DVT development.

Association rule mining was used to find possible drug-drug interactions with NET/EE and DRSP/EE by identifying therapeutics that were more associated with DVT than expected. Among the identified drugs, the glucocorticoid steroid prednisone was ultimately identified as the drug with the strongest association with DVT. In addition, individuals that had taken NET/EE and prednisone simultaneously had an approximately 6-fold increase in DVT risk (ROR = 6.26, 95% CI 2.17–17.82) while patients that were prescribed both DRSP/EE and prednisone had a nearly 3-fold increase in DVT risk (ROR = 2.77, 95% CI 2.43–3.15) when compared to those that had only taken DRSP/EE. Previous studies have demonstrated a significant association between the use of corticosteroids such as prednisone and the risk of either DVT or pulmonary embolism outcome. One study conducted on data from the American College of Surgeons National Surgical Quality Improvement Program database found that patients taking a prolonged corticosteroid regiment after neurosurgical procedures were and 55% more likely (OR = 1.55, 95% CI 1.28–1.87) to develop DVT than the controls [31]. Another meta-analysis that assessed 36 different manuscripts in the literature found consistent increases in the coagulation factors VII, VIII, and VI in patients administered such corticosteroids as dexamethasone, prednisone, and hydrocortisone [32]. In addition, treatment with prednisone was shown to result in increased levels of PAI-1 as well as decreased levels of fibrinogen [33–35]. Thus, the significant increase in DVT risk may be a result of a synergistic relationship between the progestin component of the COC formulation and prednisone with regards to disruption of the fibrinolytic pathway and promotion of a hypercoagulative state (Fig. 1).

Despite these findings, the present study conducted has some limitations. First, due to the nature of retrospective studies, the findings from this study can only suggest a strong association between the formulation of COC used and DVT risk, it cannot ultimately determine a definitive causative link. This also extends to the possible drug-drug pairs identified from association rule mining as it is not possible to determine whether the additional drug beyond the COC that was prescribed preceded or followed DVT development (cannot prove causality). For instance, the painkiller Percocet may have been administered to a patient before development of DVT for another reason such as recent surgery, thus making an interaction temporally possible, or was provided to reduce patient discomfort from DVT recovery. In addition, the proposed drug-drug interaction need further biological validation with *in vivo* studies for verification. Finally, the sample size for patients that had taken both NET/EE and prednisone was rather small (only 4 cases), resulting in the calculation of a possibly inflated odds ratio for the association between combined drug use and DVT risk. Consequently, more data needs to be collected in order to determine whether the combined DVT risk in those prescribed NET/EE and prednisone simultaneously is truly significant from the DVT risk in those prescribed DRSP/EE and prednisone.

To our knowledge, this is the first comparative analysis assessing differential DVT risk between first generation and fourth generation COC formulations using FAERS-derived pharmacovigilance data. In addition, this manuscript provides further credence to the use of association rule mining to identify possible drug-drug interactions using pharmacovigilance data. Findings from this study contribute to the growing body of literature demonstrating a link between COC use and elevated DVT risk and may be beneficial in guiding informed decision for patients and practitioners based on pre-existing conditions and possible drug-drug interactions. Future studies will seek to validate the proposed mechanisms in this study as well as identify other potential drug-drug interactions with COCs.

5. Conclusion

NET/EE and DRSP/EE are common formulations of oral contraceptives used for birth control in the United States. DVT is a notable reported ADE by patients using COCs. Patients that had taken DRSP/EE had a 11-fold greater increase in DVT risk than individuals who had taken NET/EE for birth control. Age was identified as a confounding variable in the association between DVT risk and COC formulation for users of DRSP/EE but was only a significant confounder for individuals aged 40 and up that had taken NET/EE for birth control. The observed elevated risk in DVT in patients that had taken one of the aforementioned COCs and the corticosteroid prednisone simultaneously may be a consequence of a synergistic suppression of the fibrinolysis pathway and impaired clearing of blood clots.

CRediT authorship contribution statement

Jennifer Stalas: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Robert Morris:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Kun Bu:** Methodology, Formal analysis. **Kevin von Bargen:** Data curation, Conceptualization. **Rebekah Largmann:** Data curation, Conceptualization. **Kathryn Sanford:** Data curation, Conceptualization. **Jacob Vandeventer:** Data curation, Conceptualization. **Weiru Han:** Methodology. **Feng Cheng:** Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] M.V. Dragoman, The combined oral contraceptive pill – recent developments, risks and benefits, Best Pract. Res. Clin. Obstet. Gynaecol. 28 (2014) 825–834, https://doi.org/10.1016/j.bpobgyn.2014.06.003.
[2] S. Christin-Maitre, History of oral contraceptive drugs and their use worldwide, Best Pract. Res. Clin. Endocrinol. Metabol. 27 (2013) 3–12, https://doi.org/10.1016/j.beem.2012.11.004.
[3] R.P. Sturtevant, Long-term experience with Enovid among clinic patients: results after 2 and one-half to 6 years of individual patient use, J. Reprod. Med. 5 (1970) 90–95.
[4] D.B. Cooper, P. Patel, H. Mahdy, Oral Contraceptive Pills, StatPearls, 2022.
[5] M. de Bastos, B.H. Stegeman, F.R. Rosendaal, A. Van Hylckama Vlieg, F.M. Helmerhorst, T. Stijnen, O.M. Dekkers, Combined oral contraceptives: venous thrombosis, Cochrane Database Syst. Rev. (2014) CD010813, https://doi.org/10.1002/14651858.CD010813.pub2.
[6] L. Keenan, T. Kerr, M. Duane, K. Van Gundy, Systematic review of hormonal contraception and risk of venous thrombosis, Linacre Q. 85 (2018) 470–477, https://doi.org/10.1177/0024363918816683.
[7] L.E. Britton, A. Alspaugh, M.Z. Greene, M.R. McLemore, CE: an evidence-based update on contraception, Am. J. Nurs. 120 (2020) 22–33, https://doi.org/10.1097/01.NAJ.0000654304.29632.a7.
[8] A. Kumar, The newly available FAERS public dashboard: implications for health care professionals, Hosp. Pharm. 54 (2019) 75–77, https://doi.org/10.1177/0018578718795271.
[9] R. Morris, H. Luboff, R.P. Jose, K. Eckhoff, K. Bu, M. Pham, D. Rohlsen-Neal, F. Cheng, Bradycardia due to donepezil in adults: systematic analysis of FDA adverse event reporting System, J Alzheimers Dis 81 (2021) 297–307, https://doi.org/10.3233/JAD-201551.
[10] R. Morris, G. Umeukeje, K. Bu, F. Cheng, The association between use of rivastigmine and pneumonia: systematic analysis of FDA adverse event reporting System, J Alzheimers Dis 83 (2021) 1061–1071, https://doi.org/10.3233/JAD-210662.
[11] K. Bu, D. Patel, R. Morris, W. Han, G. Umeukeje, T. Zhu, F. Cheng, Dysphagia risk in patients prescribed rivastigmine: a systematic analysis of FDA adverse event reporting System, J Alzheimers Dis 89 (2022) 721–731, https://doi.org/10.3233/JAD-220583.
[12] P.V. Jenkins, O. Rawley, O.P. Smith, J.S. O'Donnell, Elevated factor VIII levels and risk of venous thrombosis, Br. J. Haematol. 157 (2012) 653–663, https://doi.org/10.1111/j.1365-2141.2012.09134.x.
[13] J.A. Maybin, H.O. Critchley, Menstrual physiology: implications for endometrial pathology and beyond, Hum. Reprod. Update 21 (2015) 748–761, https://doi.org/10.1093/humupd/dmv038.
[14] R. Chaudhry, S.M. Usama, H.M. Babiker, Physiology, Coagulation Pathways, StatPearls, 2022.
[15] J.C. Chapin, K.A. Hajjar, Fibrinolysis and the control of blood coagulation, Blood Rev. 29 (2015) 17–24, https://doi.org/10.1016/j.blre.2014.09.003.
[16] R.M. Marquardt, T.H. Kim, J.H. Shin, J.W. Jeong, Progesterone and estrogen signaling in the endometrium: what goes wrong in endometriosis? Int. J. Mol. Sci. 20 (2019) https://doi.org/10.3390/ijms20153822.
[17] D.A. Chistiakov, V.A. Myasoedova, A.A. Melnichenko, A.V. Grechko, A.N. Orekhov, Role of androgens in cardiovascular pathology, Vasc. Health Risk Manag. 14 (2018) 283–290, https://doi.org/10.2147/VHRM.S173259.
[18] A.C. Cleuren, I.K. Van der Linden, Y.P. De Visser, G.T. Wagenaar, P.H. Reitsma, B.J. Van Vlijmen, 17alpha-Ethinylestradiol rapidly alters transcript levels of murine coagulation genes via estrogen receptor alpha, J. Thromb. Haemostasis 8 (2010) 1838–1846, https://doi.org/10.1111/j.1538-7836.2010.03930.x.
[19] S. Caruso, S. Cianci, M. Cariola, V. Fava, S. Di Pasqua, A. Cianci, Improvement of low sexual desire due to antiandrogenic combined oral contraceptives after switching to an oral contraceptive containing 17beta-estradiol, J Womens Health (Larchmt) 26 (2017) 728–734, https://doi.org/10.1089/jwh.2016.5801.
[20] Y. Zimmerman, M.J. Eijkemans, H.J. Coelingh Bennink, M.A. Blankenstein, B.C. Fauser, The effect of combined oral contraception on testosterone levels in healthy women: a systematic review and meta-analysis, Hum. Reprod. Update 20 (2014) 76–105, https://doi.org/10.1093/humupd/dmt038.
[21] W. Oelkers, Drospirenone, a progestogen with antimineralocorticoid properties: a short review, Mol. Cell. Endocrinol. 217 (2004) 255–261, https://doi.org/10.1016/j.mce.2003.10.030.
[22] P.A. Regidor, A.E. Schindler, Antiandrogenic and antimineralocorticoid health benefits of COC containing newer progestogens: dienogest and drospirenone, Oncotarget 8 (2017) 83334–83342, https://doi.org/10.18632/oncotarget.19833.
[23] A. Quezada, D. Jimenez, B. Bikdeli, L. Moores, M. Porres-Aguilar, M. Aramberri, J. Lima, A. Ballaz, R.D. Yusen, M. Monreal, R. investigators, Systolic blood pressure and mortality in acute symptomatic pulmonary embolism, Int. J. Cardiol. 302 (2020) 157–163, https://doi.org/10.1016/j.ijcard.2019.11.102.
[24] G. Morgante, V. Cappelli, L. Troia, V. De Leo, Evaluation of different antiandrogenic progestins on clinical and biochemical variables in polycystic ovary syndrome, Eur. J. Contracept. Reprod. Health Care 25 (2020) 176–181, https://doi.org/10.1080/13625187.2020.1736546.
[25] W. Elger, S. Beier, K. Pollow, R. Garfield, S.Q. Shi, A. Hillisch, Conception and pharmacodynamic profile of drospirenone, Steroids 68 (2003) 891–905, https://doi.org/10.1016/j.steroids.2003.08.008.
[26] L. Han, J.T. Jensen, Does the progestogen used in combined hormonal contraception affect venous thrombosis risk? Obstet. Gynecol. Clin. N. Am. 42 (2015) 683–698, https://doi.org/10.1016/j.ogc.2015.07.007.
[27] M. Farris, C. Bastianelli, E. Rosato, I. Brosens, G. Benagiano, Pharmacodynamics of combined estrogen-progestin oral contraceptives: 2. effects on hemostasis, Expet Rev. Clin. Pharmacol. 10 (2017) 1129–1144, https://doi.org/10.1080/17512433.2017.1356718.
[28] S.N. Tchaikovski, J. Rosing, Mechanisms of estrogen-induced venous thromboembolism, Thromb. Res. 126 (2010) 5–11, https://doi.org/10.1016/j.thromres.2010.01.045.

[29] D. Mari, G. Ogliari, D. Castaldi, G. Vitale, E.M. Bollini, D. Lio, Hemostasis and ageing, Immun. Ageing 5 (2008) 12, https://doi.org/10.1186/1742-4933-5-12.
[30] E.J. Favaloro, M. Franchini, G. Lippi, Aging hemostasis: changes to laboratory markers of hemostasis as we age - a narrative review, Semin. Thromb. Hemost. 40 (2014) 621–633, https://doi.org/10.1055/s-0034-1384631.
[31] B.A. Lieber, J. Han, G. Appelboom, B.E. Taylor, B. Han, N. Agarwal, E.S. Connolly Jr., Association of steroid use with deep venous thrombosis and pulmonary embolism in neurosurgical patients: a national database analysis, World Neurosurg 89 (2016) 126–132, https://doi.org/10.1016/j.wneu.2016.01.033.
[32] B. van Zaane, E. Nur, A. Squizzato, V.E. Gerdes, H.R. Buller, O.M. Dekkers, D.P. Brandjes, Systematic review on the effect of glucocorticoid use on procoagulant, anti-coagulant and fibrinolytic factors, J. Thromb. Haemostasis 8 (2010) 2483–2493, https://doi.org/10.1111/j.1538-7836.2010.04034.x.
[33] E. Nordborg, R. Andersson, L. Tengborn, S. Eden, B.A. Bengtsson, von Willebrand factor antigen and plasminogen activator inhibitor in giant cell arteritis, Ann. Rheum. Dis. 50 (1991) 316–320, https://doi.org/10.1136/ard.50.5.316.
[34] P. De Feo, F.F. Horber, M.W. Haymond, Meal stimulation of albumin synthesis: a significant contributor to whole body protein synthesis in humans, Am. J. Physiol. 263 (1992) E794–E799, https://doi.org/10.1152/ajpendo.1992.263.4.E794.
[35] S. Schreiber, M. Buyse, The CRP initial response to treatment as prognostic factor in patients with polymyalgia rheumatica, Clin. Rheumatol. 14 (1995) 315–318, https://doi.org/10.1007/BF02208345.