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Systematic review

Drospirenone-containing oral contraceptive pills and the risk of venous and arterial thrombosis: a systematic review

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Background Previous studies have provided conflicting results regarding the effect of drospirenone-containing oral contraceptive pills (OCPs) on the risk of venous and arterial thrombosis.

Objectives To conduct a systematic review to assess the risk of venous thromboembolism (VTE), myocardial infarction (MI), and stroke in individuals taking drospirenone-containing OCPs.

Search strategy We systematically searched CINAHL, the Cochrane Library, Dissertation & Abstracts, EMBASE, HealthStar, Medline, and the Science Citation Index from inception to November 2012.

Selection criteria We included all case reports, observational studies, and experimental studies assessing the risk of venous and arterial thrombosis of drospirenone-containing OCPs.

Data collection and analysis Data were collected independently by two reviewers.

Main results A total of 22 studies [six case reports, three case series (including 26 cases), and 13 comparative studies] were included in our systematic review. The 32 identified cases suggest a possible link between drospirenone-containing OCPs and venous and arterial thrombosis. Incidence rates of VTE among drospirenone-containing OCP users ranged from 23.0 to 136.7 per 100 000 woman-years, whereas those among levonorgestrel-containing OCP users ranged from 6.64 to 92.1 per 100 000 woman-years. The rate ratio for VTE among drospirenone-containing OCP users ranged from 4.0 to 6.3 compared with non-users of OCPs, and from 1.0 to 3.3 compared with levonorgestrel-containing OCP users. The arterial effects of drospirenone-containing OCPs were inconclusive.

Author's conclusions Our systematic review suggests that drospirenone-containing OCP use is associated with a higher risk for VTE than both no OCP use and levonorgestrel -containing OCP use.

Keywords Arterial thrombosis, deep vein thrombosis, drospirenone, myocardial infarction, oral contraceptive pills, pulmonary embolism, venous thrombosis.

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Introduction

Oral contraceptive pills (OCPs) are associated with an increased risk of thrombotic events.[1–3] Fourth-generation OCPs were introduced to the North American market in 2000.[4] This new generation is characterised by the addition of the progestin drospirenone, which was believed to be associated with a lower risk of thrombosis.[5] Drospirenone-containing OCPs are currently the only available oral contraceptive with three indications: contraception; the treatment of premenstrual dysphoric disorder; and the treatment of moderate acne.[6] However, recent observational studies have provided conflicting results regarding the effects of drospirenone-containing OCPs on the risk of venous thrombosis.[7–10] In addition, the effect of drospirenone-containing OCPs on the risk of arterial thrombosis

remains controversial.[10,11] We therefore conducted a systematic review to synthesise the available data regarding drospirenone-containing OCPs and the risk of venous and arterial thrombotic events, including deep vein thrombosis (DVT), pulmonary embolism (PE), myocardial infarction (MI), and stroke.

Methods

Data sources

We systematically searched the CINAHL (from 1981 to November 2012), Cochrane Library (from 1898 to November 2012), Dissertation & Abstracts (from 1861 to November 2012), EMBASE (from 1947 to November 2012), HealthStar (from 1966 to November 2012), Medline (from 1946 to November 2012), and the Science Citation Index (from 1900 to November 2012) databases to identify all reports of thrombotic events in women taking OCPs (Appendix S1). In this systematic review, OCPs pertain to hormonal oral contraceptive pills containing a combination of estrogen and progestin. Keywords used were levonorgestrel, desogestrel, gestodene, norgestimate, and drospirenone. In addition, we searched www.clinicaltrialresults.org for potentially relevant randomised controlled trials (RCTs). We limited our search to studies conducted in the female adult population, and reported in English or French. The references of included studies were handsearched to identify any additional potentially relevant publications.

Inclusion criteria

Studies were included if they: (1) were case reports, case series, or comparative studies of women taking drospirenone-containing OCPs; (2) reported at least one of the venous and arterial thrombotic outcomes of interest [DVT, PE, MI, and cerebrovascular events, such as stroke or transient ischemic attack (TIA)]; and (3) were published in English or French. All studies failing to meet these criteria were excluded.

Data extraction

Two reviewers independently extracted the data from the studies included. Disagreements were resolved by consensus or, when necessary, by a third reviewer. Study characteristics such as study design, study period, population, and country of origin were extracted. For each outcome of interest, we extracted incidence rates (IRs) by exposure status and comparative effect measures, including hazards ratios (HRs), odds ratios (ORs), and rate ratios (RRs). Outcome data were extracted with corresponding 95% confidence intervals (95% CIs).

We performed this systematic review according to the MOOSE (Meta-analysis of Observational Studies in Epidemiology) statement, as all included studies were observational.[12] The results of our systematic search are detailed in a flow chart that follows the guidelines outlined by the PRISMA statement (Figure 1).[13]

Results

Literature search

Our search identified 9148 potentially relevant articles (Figure 1). Of these, 9123 were excluded because they were irrelevant to the subject of study (n = 9013), were editorials or commentaries (n = 62), or were other review articles (n = 48). A total of 25 full-text articles were retrieved for further review. Three additional studies were excluded: one presented the rationale and design for a prospective study, and the two others were subgroup analyses of a study already included. A total of 22 studies [six case reports, three case series (including 26 cases), and 13 comparative studies] were included in our systematic review. No interventional studies met our inclusion criteria.

Case reports and case series

The six case reports and three case series contained a total of 32 cases of thrombotic events that occurred in drospirenone-containing OCPs users (Table 1). All reports occurred in women residing in Europe, and were published between 2003 and 2012. A total of 31 women were taking a combination of 30 μg of ethinyl estradiol and 30 mg of drospirenone; one woman was taking a combination of 20 μg of ethinyl estradiol and 30 mg of drospirenone. The median age of women was 33.5 years (range: 17–50 years), and the median duration of drospirenone-containing OCP use before the thrombotic event was 150.5 days (range: 15–2557 days). Twenty of the 32 women described in the case reports and case series included had at least one known risk factor for thrombotic disease, including an age of >35 years, diabetes mellitus, family history of thrombotic disease, hyperlipidemia, hypertension, immobilisation, obesity, pregnancy/delivery, smoking, and surgical intervention. Six women also reported a genetic predisposition for thrombotic disease: factorV Leiden mutation; prothrombin G20210A mutation; or positive IgG anticardiolipin antibodies. A total of 27 women experienced VTEs, including two reports of venous thrombosis,[14,15] nine DVTs,[14–18] two pulmonary thromboses,[14,15] 12 PEs (one fatal),[15,17] and two women with both DVT and PE.[15] Risk factors were unspecified in 12 of the 27 women with confirmed venous thrombosis. Arterial thrombotic events were reported in four women, three of which had an MI,[5,19,20] and one of which had a TIA.[21] All four women had at least one of three risk factors: smoking, family history of MI, and recent surgery.

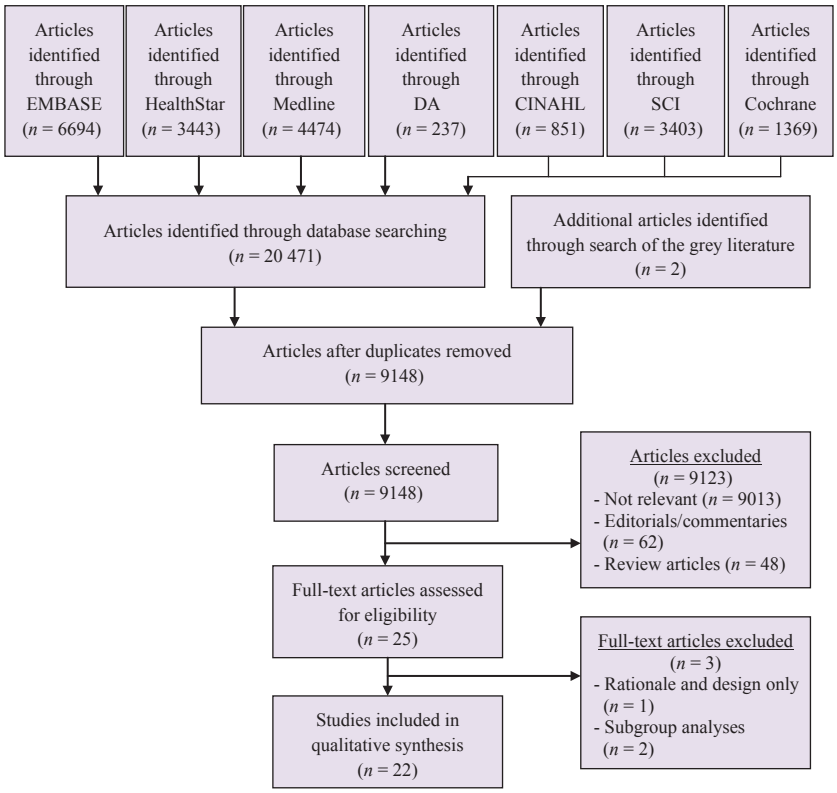

Figure 1. PRISMA flow diagram of the systematic literature search. DA, Dissertation & Abstracts; SCI, Science Citation Index.

Comparative studies and VTE

A total of 13 comparative studies evaluating the risk of thrombotic events related to the use of drospirenone-containing OCPs were identified (Table 2). Nine of the 13 identified studies were cohort studies, and the remaining four were case–control studies. No RCTs were identified. The total patient populations in the individual studies ranged from 867 to 1 626 158 women. Studies were reported [either published or included in Food and Drug Administration (FDA) briefing material] between 2007 and 2012, and included data from databases of developed countries, notably the National Registry of Medicinal Products Statistics, National Registry of Patients, Statistics of Denmark, the European Active Surveillance Study (EURAS), German outpatient offices, Ingenix Research Data Mart, the Multiple Environmental and Genetic Assessment study (MEGA), the UK General Practice Research Database (GPRD), the US PharMetrics database, Kaiser Permanente Northern California, Kaiser Permanente Southern California, US State Medicaid databases, and the Israeli Clalit Clinical database. The duration of follow-up ranged from 12 to 180 months, and occurred from 1995 to 2011. There was heterogeneity in inclusion criteria and user definitions, with six studies including prevalent users and seven involving new users or initiators (Appendix S2).

The primary endpoint was VTE for 12 of the comparative studies included (Table 3), and arterial thrombosis for one of the studies included (Table 4). Eight studies compared the risk of VTE between drospirenone-containing and levonorgestrel-containing OCP users. The incidence rates for VTE ranged from 23.0 to 136.7 per 100 000 women-years for drospirenone-containing OCP users, and from 6.64 to 92.1 per 100 000 woman-years for levonorgestrel-containing OCP users. Drospirenone-containing OCP users had an increased risk of VTE compared with users of levonorgestrel-containing OCPs, with relative risks ranging from 1.0 to 3.3. In the eight studies comparing the risk of VTE between levonorgestrel- and drospirenone-containing OCPs, five reported a greater risk for VTE among users of drospirenone-containing OCPs,[7,8,11,22,23] whereas the three other studies were inconclusive.[9,24,25] Two studies examined these associations in both 'all users' and a subgroup of 'new users' of drospirenone-containing OCPs.[11,23] In both studies, the 'new user' analysis produced results that were consistent with those of the 'all user' analysis with respect to VTE (Table 3).

Two studies investigated the risk of VTE in drospirenone-containing OCP users compared with that in users of other oral contraceptives.[26,27] One study involved 18 cases of VTE among drospirenone users and 39 among users of

Table 1. Case reports and case series of thrombotic events among users of drospirenone-containing oral contraceptive pills

Study*	Year	Country	Age (years)	Past OCP	Duration (days)†	Risk factors for thrombotic events	Event
van Grootheest[14]	2003	Netherlands	17	NR	183	None specified	Fatal PE
			28	DSG/EE	122	None specified	DVT
			45	NR	61	None specified	DVT
			50	NR	91	None specified	DVT
			35	NR	17	Patient had given birth 4 months earlier	PT
Vaya[21]	2003	Spain	21	NR	15	Smoking 15 cigarettes/day	TIA
Pearce[17]	2005	UK	21	None	155	Smoking, homozygous for factor V Leiden	DVT
			22	CPA/EE	161	Smoking	DVT
			29	CPA/EE	42	Smoking, DVT in a sibling, heterozygous for factor V Leiden	DVT
			44	NR	320	Prothrombin mutation	DVT
			46	NR	95	Smoking	DVT
			27	LNG/EE	149	Smoking	PE
			30	DSG/EE	361	Heterozygous for prothrombin gene mutation and moderate positive IgG anticardiolipin antibodies	PE
			31	None	117	Smoking	PE
			34	NR	71	Smoking, varicose veins	PE
			36	NR	224	None specified	PE
			37	LNG/EE	74	None specified	PE
			41	NR	263	Obesity (BMI = 30 kg/m^2)	PE
			43	LNG/EE	382	None specified	PE
Cabou[19]	2006	France	33	LNG/EE	15	Smoking, 15 days before MI, she had undergone a left ovarian cyst excision and left salpingectomy for an ectopic pregnancy	MI
Orti[5]	2007	Spain	39	NR	731	Smoking, father died at 40 years old of MI	MI
Oo[16]	2009	USA	28	NR	731	None specified	DVT
Lopez[15]	2009	Spain	43	NR	45	Obesity (BMI = 46 kg/m^2)	PE
			37	NR	365	Smoking, hypertension, hyperlipidemia, diabetes, obesity (BMI = 38.22 kg/m^2)	PT
			28	NR	21	Was immobilised for several weeks, obesity (BMI = 35.15 kg/m^2)	PE
			35	CPA/EE	122	Heterozygous carrier of prothrombin G20210A mutation	DVT, PE
			23	CPA/EE	91	None specified	PE
			33	NR	365	None specified	DVT
			29	NR	365	None specified	VT
			21	NR	152	Heterozygous carrier of prothrombin G20210A mutation	DVT, PE

Table 1. (Continued)

Study*	Year	Country	Age (years)	Past OCP	Duration (days)†	Risk factors for thrombotic events	Event
Zehir[20]	2011	Turkey	36	NR	2557	Smoking 10 cigarettes/day	MI
Marti Gil[18]	2012	Spain	36	Norgestimate/EE, gestodene/EE	304‡	None specified	DVT

BMI, body mass index; CPA, cyproterone acetate; DSG, desogestrel; DVT, deep vein thrombosis; EE, ethinyl estradiol; LNG, levonorgestrel; MI, myocardial infarction; NR, not reported; OCP, oral contraceptive pill; PE, pulmonary embolism; PT, pulmonary thrombosis; TIA, transient ischemic attack.

*All women except the case reported by Marti Gil 2012 had been taking OCPs with 30 μg of ethinyl estradiol and 30 mg of drospirenone; the case reported by Marti Gil had been taking an OCP with 20 μg of ethinyl estradiol and 30 mg of drospirenone.

†Duration of drospirenone-containing OCP use before thrombotic event.

‡Approximated duration in days based on usage from November 2010–August 2011.

other oral contraceptives. The comparison between these different formulations of oral contraceptives was inconclusive because of the sparse data (RR 0.9, 95% CI 0.5–1.6). The other study involved 17 cases of VTE among drospirenone users and four among norgestimate and desogestrel users. The authors reported an incidence rate ratio of 6.4.[27]

Three of the included studies compared the risk of VTE in drospirenone-containing OCP users with non-users of OCPs.[22,25,28] The incidence rate for VTE ranged from 78.3 to 93 per 100 000 woman-years among drospirenone-containing OCP users, and from 37 to 54.7 per 100 000 woman-years among non-users of OCPs. After adjusting for potential confounding factors (Appendix S3), drospirenone-containing OCP users had a substantially higher risk of VTE (relative risk ranging from 4.0 to 6.3) compared with non-users.

Comparative studies and arterial thrombosis

Our literature search identified four studies that compared the risk of arterial thrombosis between drospirenone-containing and other OCP users (Table 4). Incidence rates for arterial thrombosis ranged from 6.3 to 58 per 100 000 woman-years among drospirenone-containing OCP users, and from 13.2 to 123 per 100 000 woman-years among levonorgestrel-containing OCP users. In the Long-term Active Surveillance Study (LASS),[10] drospirenone-containing OCP users had a substantial reduction in the risk of arterial thrombosis compared with levonorgestrel-containing OCP users (HR 0.4, 95% CI 0.2–0.9), whereas the results of Gronich,[23] and the FDA analysis of all users,[11] were inconclusive, with relative risks ranging from 0.81 to 0.87, and the limits of their 95% CIs including both clinically important harms and benefits. In contrast, when the FDA analysis was restricted to new users,[11] the HR increased to 1.64 (95% CI 0.79–3.40), although the broad 95% CIs arising from sparse data prevent strong conclusions from being drawn from this analysis.

The comparison of the arterial thrombotic effects of drospirenone-containing OCPs with those of other OCPs also produced heterogeneous results (Table 4). The LASS found that drospirenone-containing OCP users had a substantial reduction in arterial thrombosis (HR 0.4, 95% CI 0.2–0.8),[10] whereas the FDA's analysis of all users resulted in an HR of 0.99 (95% CI 0.58–1.69). Restriction to new users in the FDA study resulted in an increased risk of arterial thrombosis among drospirenone-containing OCPs users, compared with users of other OCPs (HR 2.01, 95% CI 1.06–3.81).

The 2012 Lidegaard study compared arterial thrombotic risk in drospirenone-containing OCP users with that in non-users.[29] In this study, drospirenone-containing OCPs were associated with an increased risk of stroke (RR 1.64, 95% CI 1.24–2.18) and MI (RR 1.65, 95% CI 1.03–2.63).

Discussion

Main findings

Our study was designed to summarise the available evidence regarding the venous and arterial thrombotic risk of drospirenone-containing OCPs. The evidence to date suggests that drospirenone-containing OCPs may increase the risk of VTE compared with levonorgestrel-containing OCPs and non-use of OCPs. The effects of drospirenone-containing OCPs on the risk of arterial thrombosis remain unclear, with the studies included in this review providing conflicting results: some suggested a protective effect[23]; and others suggested a doubling of risk.[11]

Twenty out of the 32 cases identified in case reports and case series had at least one concomitant risk factor for thrombotic events, highlighting the need to screen for thrombotic risk factors before initiating OCPs. Furthermore, although the duration of OCP use varied among cases, the majority of thrombotic events occurred during the first year of OCP use (28 out of 32 cases). Comparative studies involving women starting OCP therapy also had greater inci-

Table 2. Study characteristics of comparative studies examining the thrombotic effects of drospirenone-containing oral contraceptive pills

Study*	Study design	*n*	Data origin	Study period	Study population
Dinger 2007[24]	Prospective cohort	42 875	EURAS study	2000–2005	Initiators of OCP treatment (first-ever users or switchers to a new product)
Seeger 2007[26]	Prospective, claims-based, cohort	67 287	Ingenix Research Data Mart	2001–2004	Aged 10–59 years starting DRSP or other OCs
Lidegaard 2009[25]	National cohort	NS	Four Danish registries	1995–2005	Aged 15–49 years with no history of cardiovascular or malignant disease
Vlieg 2009[28]	Population-based, case–control	1556	MEGA study	1999–2004	Aged <50 years who were not pregnant, not within 4 weeks postpartum, not using a hormone-excreting IUD or depot contraceptive
Dinger 2010[9]	Community-based, case–control	366	German outpatient offices	2002–2008	Aged 15–49 years, with a clinical diagnosis of VTE
Parkin 2011[7]	Nested case–control	276	UK General Practice Research Database	2002–2009	Aged 15–44 years without major risk factors for VTE who started a new episode of use of an OCP
Jick 2011[8]	Nested case–control and cohort	867	US PharMetrics database	2002–2008	Aged 15–44 years and current users of OCPs
Lidegaard 2011[22]	National cohort	1 436 130	Four Danish registries	2001–2009	Aged 15–49 years with no previous venous, arterial thrombotic events, or cancers
FDA 2011[11]	Population-based cohort	835 826	KPNC, KPSC, and two State Medicaids	2001–2007	Aged 10–55 years and current users of OCPs
Gronich 2011[23]	Population-based cohort	329 995	Israeli Clalit clinical database	2002–2009	Aged 12–50 years with no previous diagnoses of thrombotic events
LASS 2011[10]	Prospective cohort	47 799†	EURAS study + 5–year extended follow-up	2000–2011	Initiators of OCP treatment (first-ever users or switchers to a new product)
Leppee 2012[27]	Cohort	1 050 000	HALMED	2008–2010	Aged 15–49 years
Lidegaard 2012[29]	National historical cohort	1 626 158	Four Danish registries	1995–2009	Aged 15–49 years, not pregnant, with no history of cardiovascular disease, cancer, venous or arterial thrombotic event, coagulopathy, bilateral oophorectomy, unilateral oophorectomy two times, hysterectomy, or sterilisation procedure

DRSP, drospirenone; EURAS, European Active Surveillance; FDA, Food and Drug Administration; HALMED, Agency for Medicinal Products and Medical Devices of Croatia; IUD, intrauterine device; KPNC, Kaiser Permanente Northern California; KPSC, Kaiser Permanente Southern California; LASS, Long-term Active Surveillance Study; MEGA, Multiple Environmental and Genetic Assessment; *n*, total population, including the drospirenone and comparison groups; NS, not specified; OCs, other oral contraceptives; OCP, oral contraceptive pill; VTE, venous thromboembolism.
*Studies are listed according to their year of publication, from the earliest to the most recent.
†Includes women not receiving drospirenone- or levonorgestrel-containing OCPs.

dence rates for VTE,[24,26] compared with studies involving prevalent OCP users.[7,8] This trend is consistent with conclusions drawn from previous studies investigating thrombotic risk with the use of second- and third-generation OCPs.[25]

Interpretation in light of previous studies

The elevated VTE risk that occurs following the initiation of OCP use has important implications for the design and analysis of observational studies of this association. With the greatest risk occurring following the start of therapy among first-time users, the failure to properly account for history of OCP use may result in spurious findings.[30,31] In addition, the inclusion of prevalent or current users may result in an important underestimation of treatment effects, as those who experienced events early after the start of therapy (but before the study period) are excluded for hav-

Table 3. Rates of VTE in comparative studies examining the thrombotic effects of drospirenone-containing oral contraceptive pills

Study	DRSP *n**	Comparator *n*	DRSP users		Comparator		Effect measure	Point estimate	95% CI
			IR†	95% CI	IR†	95% CI			
Drospirenone- versus levonorgestrel-containing OCPs									
Dinger 2007[24]	16 534	26 341	91	59–33	80	52–117	HR	3.3	0.9–10
Dinger 2010[9]	NR‡	NR	NR	NR	NR	NR	OR	1.0	0.5–1.8
Parkin 2011[7]	NR§	NR	23.0	13.4–36.9	9.1	6.6, 12.2	OR	3.3	1.4–7.6
Jick 2011[8]	NR‖	NR	30.8	25.6–36.8	9.6	9.6, 15.9	OR	2.4	1.7–3.4
Lidegaard 2011[22]	NR	NR	93	NR	75	NR	RR	2.12¶	1.68–2.66
FDA 2011 (all users)[11]	142 166	198 839	102.2**	NR	6.64**	NR	RR	1.45	1.15–1.83
FDA 2011 (new users)[11]	NR	NR	136.7**	NR	92.1**	NR	RR	1.57	1.13–2.18
Gronich 2011 (all users)[23]	73 629	21 546††	86‡‡	NR	69‡‡	NR	RR	1.65	1.02–2.65
Gronich 2011 (new users)[23]	NR	NR	NR	NR	NR	NR	RR	1.67	0.98–2.86
LASS 2011[10]	NR	NR	107	81–139	92	69, 120	HR	1.1	0.8–1.7
Drospirenone-containing OCPs versus other OCP users									
Seeger 2007[26]	22 429	44 858	130	80–200	NR	NR	RR	0.9	0.5–1.6
Leppee 2012[27]	NR	NR	NR§§	NR	NR‖‖	NR	Incidence RR	6.4	NR
Drospirenone-containing OCPs versus non-users of OCPs									
Lidegaard 2009[25]	NR	NR	78.3	NR	54.7	NR	RR	4.0	3.3–4.9
Vlieg 2009[28]	NR¶¶	NR	NR	NR	NR	NR	OR	6.3	2.9–13.7
Lidegaard 2011[22]	NR	NR	93	NR	37	NR	RR	4.47	3.91–5.11***

CI, confidence interval; Comparator *n*, sample size of the comparison group, those unexposed to drospirenone-containing OCPs; DRSP, drospirenone; DRSP *n*, sample size of the group of patients on drospirenone-containing OCPs; FDA, Food and Drug Administration; HR, hazard ratio; IR, incidence rate; LASS, Long-term Active Surveillance Study; NR, not reported. OCP, oral contraceptive pill; OR, odds ratio; RR, rate ratio; VTE, venous thromboembolism.

*Patients were given OCPs containing dropirenone and ethinyl estradiol (EE) in combination.

†Incidence rate per 100 000 women-years.

‡Report on 25 VTE cases exposed to drospirenone, 84 controls exposed to drospirenone, 60 VTE cases unexposed to drospirenone, 197 controls unexposed to drospirenone.

§Report on 17 VTE cases exposed to drospirenone, 26 controls exposed to drospirenone, 44 VTE cases unexposed to drospirenone, 189 controls unexposed to drospirenone.

‖Report on 121 VTE cases exposed to drospirenone, 313 controls exposed to drospirenone, 65 VTE cases unexposed to drospirenone, 368 controls unexposed to drospirenone.

¶Rate ratio (RR) presented is that for confirmed VTEs; among non-confirmed VTEs, the RR is 1.78 (95% CI 1.21–2.60).

**Age- and site-adjusted incidence rate.

††Comparator group includes women taking levonorgestrel/EE and norgestrel/EE.

‡‡Crude incidence rate.

§§Incidence rate: 43.8 per 100 000 women.

‖‖Incidence rate: 6.8 per 100 000 women.

¶¶Report on 19 VTE cases exposed to drospirenone, 14 controls exposed to drospirenone, 421 VTE cases unexposed to drospirenone, 1102 controls unexposed to drospirenone.

***RR presented is for 30–40 μg EE; for 20 μg EE, the RR is 4.84 (95% CI 3.19–5.11).

Table 4. Rates of arterial thrombosis in comparative studies examining the thrombotic effects of drospirenone-containing oral contraceptive pills

Study	DRSP *n**	Comparator *n*	DRSP users		Comparator		Effect measure	Point estimate	95% CI
			IR†	95% CI	IR†	95% CI			
Drospirenone versus levonorgestrel-containing OCP users									
FDA 2011 (all users)[11]	142 166	198 839	10.8	NR	16.4	NR	HR	0.81	0.45–1.44
FDA 2011 (new users)[11]	109 070	137 311	25.5	NR	22.8	NR	HR	1.64	0.79–3.40
Gronich 2011[23]	73 629	21 546‡	58§	NR	123§	NR	RR	0.87	0.56–1.33
LASS 2011[10]	NR	NR	13	5, 28	38	24, 58	HR	0.4	0.2–0.9
Drospirenone-containing OCP versus other OCP users									
FDA 2011 (all users)[11]	142 166	586 278	10.8	NR	14.4	NR	HR	0.99	0.58–1.69
FDA 2011 (new users)[11]	109 070	383 151	25.5	NR	17.6	NR	HR	2.01	1.06–3.81
LASS 2011[10]	NR	NR	13	5, 28	32	22, 45	HR	0.4	0.2–0.8
Drospirenone-containing OCP versus non-users of OCPs									
Lidegaard 2012 (stroke)[29]‖	NR	NR	18.1	NR	24.2	NR	Relative Risk	1.64	1.24–2.18
Lidegaard 2012 (MI)[29]¶	NR	NR	6.3	NR	13.2	NR	Relative Risk	1.65	1.03–2.63

CI, confidence interval; Comparator *n*, sample size of the comparison group, those unexposed to drospirenone-containing OCPs; DRSP, drospirenone; DRSP *n*, sample size of the group of patients on drospirenone-containing OCPs; FDA, Food and Drug Administration; HR, hazard ratio; IR, incidence rate; LASS, Long-term Active Surveillance Study; MI, myocardial infarction; NR, not reported. OCP, oral contraceptive pill; RR, rate ratio.

*Patients were given OCPs containing dropirenone and ethinyl estradiol (EE) in combination.

†Incidence rate per 100 000 women-years.

‡Comparator group includes women taking levonorgestrel/EE and norgestrel/EE.

§Crude incidence rate.

‖Data reported are for OCPs containing 30–40 μg of EE; for 20 μg of EE, the IR_{DRSP} is 8.7 and the relative risk is 0.88 (95% CI 0.22–3.53).

¶Data reported are for OCPs containing 30–40 μg of EE; for 20 μg of EE, the IR_{DRSP} is 0 and the relative risk is 0 (95% CI 0.00–12.99).

ing a history of thrombosis.[32] User definitions used in the studies included varied (Appendix S3), which may explain some of the observed heterogeneity of results. For example, the restriction to new users of drospirenone-containing OCPs in the FDA-funded study resulted in substantially higher risks of arterial thrombosis. Moreover, the estrogen dose, although known to be associated with a higher risk of both venous and arterial thrombosis,[25,29] was unspecified in several of the studies included. These potential methodological limitations of the studies included need to be considered when weighing the strength of the evidence supporting the association between drospirenone-containing OCPs and thrombotic risk.

Importantly, although drospirenone-containing OCPs appear to increase the risk of VTE, and have unclear effects on the risk of arterial thrombosis, the absolute risk of thrombosis when using these agents remains low. Among drospirenone-containing OCP users, the incidence rate ranged from 23.0 to 136.7 per 100 000 woman-years for VTE, and from 6.3 to 58 per 100 000 woman-years for arterial thrombosis. Hence, there is probably insufficient evidence to recommend discontinuing the use of drospirenone-containing OCPs, particularly among long-term users. However, women with VTE are also at risk for developing arterial thrombotic events,[33] and women should be provided with our current understanding of the risks and benefits associated with the use of these agents to allow for informed decision-making.

In 2011, the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK, the US FDA, and Health Canada conducted reviews concluding that drospirenone-containing OCPs may be associated with a 1.5–3 times higher risk of VTE, and warning labels have been revised to adequately reflect this risk.[11,34–36] These results are supported by the findings of our systematic review. It should be noted that the statements released by these regulatory agencies dealt only with venous effects, and that the arterial effects of drospirenone-containing OCPs remain under-investigated.

Strengths and limitations

Our systematic review was the first to evaluate the safety of drospirenone-containing OCPs with respect to both venous and arterial thrombotic outcomes. The inclusion of detailed case reports allows for a clinically relevant examination of thrombotic risk factors among exposed cases, and the inclusion of comparative studies allows for rigorous statistical adjustment for potential confounding factors and uses a comparison group to account for the underlying thrombotic risk in this population. The effect of OCPs,

including that of drospirenone-containing OCPs, on the risk of venous thrombosis was recently examined in two systematic reviews and meta-analyses.[37,38] However, the literature searches for these two previous reviews were conducted in April–May 2010, and nine studies have since been completed. Furthermore, given the heterogeneity across studies, the meta-analysis of these data is questionable.

Our study has several potential limitations. First, because of the heterogeneity of comparators, user definitions, and effect measures reported, we were unable to pool data across studies to derive a single overall summary estimate. Secondly, our systematic search did not identify any interventional studies examining this issue. Given the observational nature of the included studies, there is the possibility of confounding by indication.[39] In addition, based on the anti-mineralocorticoid and anti-androgenic properties of drospirenone, OCPs containing this progestin may have been preferentially prescribed to women with conditions associated with a higher risk of VTE and arterial thrombosis.[40] Furthermore, despite the use of rigorous statistical adjustment (Appendix S2), the possibility of residual confounding remains. All of the studies included contain various degrees of switching between OCPs, and the inadequate adjustment for prior use is likely to result in an overestimation of the risk of thrombosis. In addition, the present systematic review was limited to studies published in English or French, and may thus be affected by language bias. There is widespread awareness of the association between VTE, which is often asymptomatic, and OCP use.[40] Thus, the studies included may be affected by detection bias.[41]

Conclusion

Although studies examining the thrombotic effects of drospirenone-containing OCPs have methodological limitations, our systematic review suggests that users of these oral contraceptives may be at greater risk for VTE than either non-users of OCPs or users of levonorgestrel-containing OCPs. Despite the observed increased VTE risk, the absolute risk of thrombosis remains low. Doctors should therefore consider the indication for use and the risk–benefit profile of the individual woman prior to prescribing these OCPs. With the available studies providing conflicting results, the effect of drospirenone-containing OCPs on arterial thrombosis remains unclear. Further studies on the arterial thrombotic effects of these OCPs are warranted.

Disclosure of interests

The authors declare that they have no competing interests to disclose.

Contribution to authorship

CQW conducted the literature search, extracted data, and drafted the article. All authors contributed to the study design, interpretation of data, and critically reviewed the article for important intellectual content.

Details of ethics approval

This study involved published data, and so did not require ethics approval.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Bibliographic search strategy.

Appendix S2. User definitions used in the included comparative studies examining the thrombotic effects of oral contraceptive pills.

Appendix S3. Description of statistical adjustment and matching variables used in comparative studies examining the thrombotic effects of drospirenone-containing oral contraceptive pills. ■

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Commentary on 'Drospirenone-containing oral contraceptive pills and the risk of venous and arterial thrombosis: a systematic review'

Combined oral contraceptive pills (OCP) containing drospirenone are among the most popular pills worldwide. Although cardiovascular events such as deep vein thrombosis (DVT), myocardial infarction, and stroke are rare among OCP users, they are potentially life-threatening, and so robust data on the risk associated with use of OCPs containing different progestogens is important. However, when interpreting the data in systematic reviews such as that of Wu et al. (*BJOG* 2013;120:801–811), we need to remain cognisant of key epidemiological concepts. Firstly, outcomes such as DVT are rare and so huge numbers of subjects must be studied. There are therefore no RCTs, and so suboptimal methodologies have to be used instead, such as case–control studies or the examination of large databases or registries. Newer OCPs containing progestogens such as drospirenone are often marketed as being 'safer', and so may be selectively prescribed to women with risk factors. Many of the retrospective studies included in this review have previously been the subject of extensive critique because they lack data on important confounding variables such as body mass index, smoking, or family history of DVT (Jensen and Trussell *Contraception* 2012;86:327–329). It has also been argued that the prospective comparative studies should rank higher in terms of 'validity' than retrospective ones, and these have not shown a higher risk of DVT with drospirenone containing OCPs. Wu et al. also stress that the risk of DVT is greatest when a woman starts taking an OCP for the first time, or restarts it, and so bias can be introduced in studies comparing 'new users' of OCPs with drospirenone and established users of OCPs containing older progestogens (such as levonorgestrel). So, given these potential biases, flaws, and epidemiological criticisms, what can clinicians advise women about the use of OCPs containing drospirenone and cardiovascular risks such as DVT? Well, we can advise women that the risk of DVT is low, and even if the use of an OCP doubles or trebles this risk, it is still a rare event. We should also advise them that the risk of a DVT with the use of any OCP is much less than during pregnancy or postpartum, and so they should not discontinue an OCP because of their fear of DVT. We can put risk into context by using the absolute risk and advising them that the incidence of DVT is estimated to be 9–10 per 10 000 women-years for an OCP user (compared with 5–10 per 10 000 for non-users), but approximately 29 per 10 000 during pregnancy and 300–400 per 10 000 postpartum (combined hormonal contraception, guideline 2012, Faculty of Sexual and Reproductive Healthcare, www.fsrh.org.uk). As the effectiveness of the OCP depends on compliance, which depends on user satisfaction, it is important that women remain on an OCP with which they are satisfied (even if that OCP contains drospirenone). However, the extent (if any) to which the type of progestogen may affect the risk of DVT (or other rarer cardiovascular outcomes) in OCP users remains, unfortunately, difficult to assess.

Disclosure of interests

The author has received funding from several pharmaceutical companies (Exelgyn, HRA Pharma, and Pfizer), but not from the manufacturer of OCPs containing drospirenone. The author does not routinely prescribe OCPs containing drospirenone for contraception, as they are not approved by the Scottish Medicines Consortium on a cost-effectiveness basis. ■

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