Risk of venous thromboembolism with drospirenone-containing oral contraceptives

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Purpose. The risk of venous thromboembolism (VTE) with drospirenone-containing oral contraceptives (OCs) is reviewed.

Summary. Increasing attention and media have raised awareness and concern about whether drospirenone-containing OCs increase the risk of VTE. Two studies found that when compared with nonuse of OCs, use of drospirenone-containing OCs was associated with a fourfold to over sixfold increased risk of having a thrombotic event. One of these studies found an increased risk associated with short-term use of drospirenone-containing OCs; however, this study was limited by the small number of participants taking drospirenone despite the large number of study participants. The cohort study that found a higher rate of VTE among drospirenone users was only able to indicate an association between drospirenone use and VTE, not a cause-and-effect relationship. Three studies concluded that drospirenone-containing OCs did not appear to cause an increased risk of VTE. The hemostatic studies found no difference in the various variables assessed between drospirenone- and desogestrel-containing OCs or between cyclic and continuous administration of drospirenone-containing OCs. These results should be interpreted cautiously, as each study had limitations, such as not controlling for confounders (e.g., recent surgery, immobility, obesity), not providing *p* values to assess homogeneity between treatment groups, and not providing total numbers of participants or specific types of OCs. Patients who receive drospirenone-containing OCs should be educated regarding the signs and symptoms of VTE, along with an appropriate action plan.

Conclusion. The majority of available data does not support the conclusion that drospirenone-containing OCs pose an increased risk of VTE compared with other OCs.

Index terms: Clinical studies; Contraceptives, oral; Desogestrel; Dosage schedule; Drospirenone; Methodology; Patient information; Toxicity; Venous thromboembolism

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The risk of venous thromboembolism (VTE) associated with combined oral contraceptives (OCs) is well recognized. In fact, the World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception found that the risk of VTE among patients using OCs is approximately threefold to fourfold higher than that of patients not taking OCs.[1] Since the introduction of OCs into the American market in the 1960s, high doses of both estrogen (50 µg ethinyl estradiol) and progestin (150 µg mestranol) have been linked to VTE.[2] The safety profile of OCs improved due to dose reductions in the estrogen component and the development of new progestins with favorable safety and clinical profiles; these changes do not compromise contraceptive effectiveness.[2-4] Specifically, newer progestins have been developed to be more receptor selective to more closely resemble physiological progesterone, allowing for increased tolerability by minimizing unwanted adverse effects, such as acne, hirsutism, and bloating.[5]

In the mid-1990s, attention shifted to the risk of VTE associated with progestins. Reports of VTE began to emerge with the newer, third-generation progestins gestodene and desogestrel. Some data suggested that these progestins were associated with a higher risk of VTE compared with levonorgestrel.[6,7] A meta-analysis of cohort and case–control studies found an overall adjusted odds ratio (OR) for VTE of 1.7 (95% confidence interval [CI], 1.4–2.0) for third- versus second-generation progestins.[8] Specifically, coagulation and fibrinolytic pathways seem to be particularly affected by third-generation combined OCs.[6]

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Drospirenone and VTE risk

Unlike other progestins, drospirenone, a third-generation progestin, is a spironolactone analogue. It has antimineralocorticoid and antiandrogenic properties, with a high affinity for the progesterone and mineralocorticoid receptors and a low affinity for androgen receptors.[9] A 3-mg dose of drospirenone has been found to have similar effects to those seen with 25 mg of spironolactone. Drospirenone blunts the ability of estrogen to stimulate aldosterone release from the renin–angiotensin–aldosterone system. This reduces water and sodium retention and thus minimizes breast tenderness, edema, weight gain, and elevations in blood pressure.[10-12] Its antiandrogenic properties minimize adverse dermatological effects, such as hirsutism, acne, and seborrhea.[13] The drospirenone component of OCs may cause hyperkalemia in some women and should be avoided in patients with renal or adrenal insufficiency or hepatic dysfunction. Monitoring of serum potassium levels is recommended during the first cycle of treatment in patients taking medications that could raise serum potassium levels (e.g., angiotensin-converting-enzyme inhibitors, potassium-sparing diuretics, nonsteroidal antiinflammatory drugs).[14,15]

We conducted a literature search using MEDLINE to identify studies that assessed the risk of VTE in women taking drospirenone-containing OCs. Various combinations of the following terms were used in the search strategy: *oral contraceptives, hormonal oral contraceptives, combined oral contraceptives, drospirenone, venous thromboembolism, venous thrombosis,* and *thromboembolism.* This article reviews the clinical and hemostatic studies investigating the risk of VTE associated with drospirenone-containing OCs.

Clinical outcomes studies

Seeger et al. Seeger et al.[16] conducted a prospective, cohort study to determine the risk of VTE in women using ethinyl estradiol–drospirenone OCs compared with women using other types of OCs. The study population was selected from a research database provided by health plans affiliated with UnitedHealthCare (Atlanta, GA) and other large employer groups and limited to females age 10–59 years for whom an ethinyl estradiol–drospirenone OC was dispensed, who had not taken this type of OC before, and who were members of their health plan for at least 6 months (n = 22,429). The comparator group—females age 10–59 years using other types of OCs who were members of their health plan for at least 6 months—was selected based on a propensity score (i.e., prediction model) and contained twice as many patients as the group using ethinyl estradiol–drospirenone OCs (n = 44,858). The investigators explored insurance claims for information on diagnoses, procedures, and medications associated with VTE. Clinicians, who were blinded to information about OC use, evaluated the data to determine if each patient had a thromboembolic event. The average follow-up time was 7.8 months (14,081 woman-years) and 7.5 months (27,575 woman-years) in the study and comparator groups, respectively. Based on absolute incidence rates, 769 women would need to take an ethinyl estradiol–drospirenone OC for 1 year in order for one thromboembolic event to be observed, and 714 women would need to take another OC for 1 year in order for one thromboembolic event to be observed. Based on the investigators' calculations for the number needed to harm (NNH), OCs would have to be prescribed to 9,286 women for one more thromboembolic event to occur with ethinyl estradiol–drospirenone versus a comparator OC.

Based on as-matched results, defined by the investigators as comparable to intent-to-treat, 18 cases of VTE occurred in the ethinyl estradiol–drospirenone group compared with 39 in the comparator group. The ethinyl estradiol–drospirenone group had a VTE incidence of 1.3 per 1000 woman-years (95% CI, 0.8–2.0) versus 1.4 per 1000 woman-years (95% CI, 1.0–1.9) in the comparator group. The rate ratio for VTE between the two groups was 0.9 (95% CI, 0.5–1.6). Because all of the CIs contained the value 1, there may have been a decreased risk, no difference in risk, or an increased risk of a VTE in the ethinyl estradiol–drospirenone group compared with the comparator group. The as-treated results, based on OC exposure time, revealed that in current users of an OC, 14 cases of VTE occurred in the ethinyl estradiol–drospirenone group compared with 30 in the comparator group. The rate ratio was 1.0 (95% CI, 0.5–1.9). The investigators concluded that the risk of VTE did not significantly differ between groups. Since the propensity score data did not allow investigators to assess other confounders (e.g., smoking, body mass index [BMI]), a validation study was conducted to search for possible confounders and found no differences between the groups that could have affected the results. However, these latter results were not published. Furthermore, the investigators stated that their results could likely be extrapolated to older women (e.g., women using drospirenone-containing hormone replacement therapy [HRT]) or women with extended treatment intervals.

One of the limitations of this report was that it lacked p values,

which would have signified whether there were actual differences between the groups in baseline characteristics or medical conditions or whether the results were due to chance alone. Furthermore, the participants for this study were identified using medical health claims, so individuals without insurance were not represented. Also, the investigators did not define how many patients were taking each of the other OCs in the comparator group, nor were the comparator OCs identified. Although medical records were consulted, these records might not have been complete or might not have contained all relevant information on possible risk factors for VTE. For example, the investigators did not state whether they were able to collect information on genetic predisposition, recent surgery, immobility, or malignancy.[17] Although the investigators searched medical records for a random sample of participants in order to determine possible confounders that could affect the results, they did not gather this information for all the participants nor did they list the findings for those patients who were in the random sample. Although the investigators indicated the absolute incidence rates and the NNH, they did not explain how they determined those values. Also, the NNH was reported for all patients, regardless of the OC used, instead of for patients using only the drospirenone-containing OCs. The absolute incidence rates indicated a time period of one year, though the average study follow-up was less than one year. Furthermore, due to the study design, only an association between ethinyl estradiol–drospirenone and the risk of thromboembolism can be established, not a cause-and-effect relationship. Extrapolation of the results to older patients using drospirenone-containing HRT and patients using OCs for extended intervals cannot be presumed from this analysis, as these patients were not included in the study.

Dinger et al. (2007). Dinger and colleagues[2] conducted a prospective, noninferiority, controlled cohort study to compare the risks of using drospirenone-containing OCs with those of levonorgestrel-containing and other types of OCs. The participants came from seven European countries and consisted of women who were prescribed an OC for the first time or were switching to another OC and were willing to participate in the study. The primary cardiovascular outcome was VTE in women using drospirenone-containing OCs versus levonorgestrel-containing OCs. A sample size of 50,000 women with a minimum of 100,000 woman-years of OC use was required to provide 90% power and exclude a twofold risk of VTE. Data from 58,674 participants with a total of 142,475 woman-years were evaluated. Drospirenone-containing OC users accounted for 28,621 woman-years. Baseline characteristics of each participant were collected via a questionnaire. Every six months, the women provided follow-up information about adverse events via self-administered questionnaires. Each patient's physician was contacted to verify serious adverse events. The number of patients lost to follow-up was very minimal. Overall, 118 thromboembolic events occurred, with a total of 7 cases of pulmonary embolism (PE) in the group receiving drospirenone-containing OCs. VTE was reported in 26 patients receiving drospirenone-containing OCs and 25 patients taking levonorgestrel-containing OCs. The results indicated a VTE incidence of 9.1 per 10,000 woman-years in patients using drospirenone-containing OCs (95% CI, 5.9–13.3) versus 8.0 per 10,000 woman-years in patients using levonorgestrel-containing OCs (95% CI, 5.2–11.7). The crude hazard ratio comparing drospirenone-containing OCs with levonorgestrel-containing OCs was 1.1 (95% CI, 0.7–2.0). After adjusting for certain confounders (e.g., age, BMI), the resultant adjusted hazard ratio for drospirenone-containing OCs compared with levonorgestrel-containing OCs was 1.0 (95% CI, 0.6–1.8). The results indicated that the twofold risk was excluded, and the noninferiority of drospirenone-containing OCs for risk of VTE was established.

This report had several limitations, including a lack of *p* values. Although the mean age, weight, and BMI, as well as certain risk characteristics and preexisting conditions, were reported for the study groups, no *p* values were provided to determine whether there was homogeneity between the groups. In fact, more patients in the drospirenone-containing OC group were obese, thus increasing their baseline risk for VTE. Also, the investigators did not explicitly indicate whether they considered or compared genetic predisposition, recent surgery, or extended immobility between the groups.[17] The investigators stated that recall bias was not a factor in the length of OC use and type of OC used, as the data were collected from the national prescription registry; however, recall bias may have occurred, since the women provided information about their medical history and history of OC use. Further, while the investigators compared drospirenone-containing OCs with levonorgestrel-containing OCs and other OCs, they did not identify the other OCs used or how many patients were taking them. Based on the crude hazard ratio, the investigators could not have established noninferiority, since the CI contained the value 2.0. Once the hazard ratio was adjusted for confounders, the twofold risk of VTE with the use of drospirenone-containing OCs versus levonorgestrel-containing OCs was excluded. The involvement of employees of the study funder, Schering AG, which supplies drospirenone-containing OC products, is unknown. An independent advisory council concluded that there were no

major differences between the groups regarding the rate of general and organ-system-specific serious adverse events, outcome-specific and general mortality, and general and organ-system-specific cancer. An increased risk was not observed for any of the outcomes (e.g., VTE, arrhythmia) evaluated in this study in women using a drospirenone-containing OC. The investigators concluded that cardiovascular risks were comparable between drospirenone-containing OCs and other types of OCs. In addition, the study was only powered to establish the noninferiority of drospirenone-containing OCs compared with levonorgestrel-containing OCs for the risk of VTE, even though multiple regimens were compared.

Lidegaard et al. Another cohort study, conducted by Lidegaard et al.,[18] evaluated the risk of VTE among nonpregnant women age 15–49 years with no history of cancer or cardiovascular disease who used various formulations of hormonal contraception. A total of 10.4 million woman-years were observed, 3,253,131 of which were attributed to current OC users. Drospirenone-containing OC users accounted for 131,541 woman-years. The primary outcome was a first-time thrombotic event, including but not limited to deep venous thrombosis (DVT) and PE. This study found that a first-time VTE occurred in 4,213 women, 2,045 of whom were current OC users. Among those using a drospirenone-containing OC, 103 developed VTE. When comparing the risk of developing a VTE between women using drospirenone-containing OCs and women classified as nonusers of OCs (i.e., those who had never used an OC and those who were former users), the adjusted rate ratio was 4.00 (95% CI, 3.26–4.91). When comparing the risk of VTE in women who used a drospirenone-containing OC versus a levonorgestrel-containing OC, the adjusted rate ratio was 1.64 (95% CI, 1.27–2.10). The reported rate ratio was adjusted for age, calendar year, education level, and amount of time the OC was used. These results suggest a higher rate of first-time VTE among those who used an OC containing drospirenone.

This study had several limitations. Similar to the previous studies discussed, *p* values were not reported, and the investigators did not control for all confounders (e.g., recent surgery, smoking, genetic predisposition, BMI, sedentary lifestyle, long-distance travel, restricted mobility). Patient demographics were not reported, and baseline characteristics were not analyzed for homogeneity between the groups. Although the total number of woman-years was reported, the total number of women in the study and the number of women taking each type of hormonal contraceptive were not provided. Furthermore, the study design only allowed the investigators to determine whether an association existed between the use of hormonal contraception and the risk of VTE; a cause-and-effect relationship could not be established from this study, especially when considering the confounders that were not addressed. The investigators concluded that further studies focusing on drospirenone and its effect on arterial outcomes must be conducted before any clinical recommendations can be made.[18]

Van Hylckama Vlieg et al. A population-based, case–control study conducted by Van Hylckama Vlieg et al.[4] evaluated OC use among patients treated in an anticoagulation clinic with a first-time DVT or PE. Study participants included nonpregnant, premenopausal women age 18–49 years who were at least four weeks postpartum at the time VTE occurred and not taking nonoral formulations of contraception. Smoking status and BMI of participants were also evaluated. Patients were recruited from six anticoagulation clinics based on diagnosis of VTE and were classified as drospirenone-containing OC users (n = 1524) or nonusers of drospirenone-containing OCs (control group, n = 1760). An increase in the risk of VTE was associated with the current use of OCs (OR, 5.0; 95% CI, 4.2–5.8). When the results were adjusted for age and inclusion period, the OR was 6.3 (95% CI, 2.9–13.7) for patients who used a drospirenone-containing OC versus nonusers, indicating a more than sixfold increase in the risk of VTE. When comparing patients using drospirenone-containing OCs with those using levonorgestrel-containing OCs, the investigators found an OR of 1.7 (95% CI, 0.7–3.9) for the risk of VTE. Short-term risk of VTE, defined as a VTE occurring in three months or less after beginning treatment, was also analyzed. A comparison between short-term use of drospirenone-containing OCs and levonorgestrel-containing OCs resulted in an OR of 1.9 (95% CI, 0.2–21.3) regarding the risk of VTE among women using a drospirenone-containing OC. The investigators stated that the wide CI was due to the small number of women using each type of progestin for the study period, thereby decreasing the reliability of these findings.

Similar to the previous studies, a limitation of this report was the lack of *p* values. While the investigators obtained patients' diagnostic information from hospital and general practitioner records, only those patients cared for in one of the six participating anticoagulation clinics were included in this study. The investigators selected the majority (59.5%) of the participants in the control group through the use of random-digit telephone dialing. This constitutes a selection bias, since only those people who were able to be reached by telephone were considered for participation. Furthermore, the investigators did not provide any specific information about what time of day they called each telephone number, the use of voicemail, or the

number of attempts. Of those people reached via random-digit telephone dialing, 1048 were chosen to serve as controls; however, the investigators did not indicate how each person was selected. Recall bias may have also been a factor, since patients had to complete a questionnaire about risk factors and OC use. Furthermore, the study design only allowed the investigators to determine that an association existed between the use of OCs and the risk of VTE, not a cause-and-effect relationship. While certain risk factors were assessed, the demographics were not compared to determine homogeneity between groups. Additionally, the investigators did not state whether they asked patients or participants to report any malignancies or recent surgeries. Few patients in this study actually took a drospirenone-containing OC (19 in the VTE group and 14 in the control group), despite the large number of participants. Also, the height and weight used to calculate BMI were reported by the patients themselves; this was a potential source of bias. Furthermore, the CI contained the value of 1 in the analyses comparing women using a drospirenone-containing OC with those using a levonorgestrel-containing OC and those using both of these OCs for the short term, suggesting a decreased risk, no difference in risk, or an increased risk of VTE. However, the small number of patients using OCs for this period of time may have affected the results. Also, the results showed a wide CI for the risk of VTE in those women using drospirenone-containing OCs compared with nonusers (95% CI, 2.9–13.7), indicating that the sample may not have truly represented the population. Although the total number of women in this study was reported, the number of patients taking each type of hormonal contraception was not indicated. The investigators concluded that with regard to VTE risk, the safest OC is one that contains levonorgestrel and a low dose of estrogen.

Dinger et al. (2010). A community-based, case–control study was conducted by Dinger et al.[19] to assess the incidence of VTE in OC users compared with matched controls. Women age 15–49 years who were diagnosed with VTE were identified through communication with 250 health care practitioners in all federal states of Germany. A questionnaire was administered to assess patients' various risk factors for VTE (e.g., use of OCs, body weight or height, smoking, family and personal history of VTE, varicose veins, immobility, pregnancy, history of surgery or trauma, genetic risk factors). Four community-based controls were randomly identified for each woman with VTE. The controls lived in the same town as the women with VTE and were contacted by trained interviewers. A total of 3400 patients were analyzed (680 women with VTE and 2720 controls). Twenty-five cases of VTE were identified among users of drospirenone-containing OCs, compared with 60 cases in women taking low-dose levonorgestrel-containing OCs and 35 cases in users of dienogest-containing OCs. The overall crude OR associated with current OC use was 1.9 (95% CI, 1.5–2.5), and the adjusted OR was 2.3 (95% CI, 1.7–3.0). When drospirenone-containing OCs were compared with low-dose levonorgestrel-containing OCs, the crude OR was 1.0 (95% CI, 0.6–1.6), and the adjusted OR was 1.0 (95% CI, 0.6–1.8). The investigators concluded that the use of drospirenone-containing OCs was not associated with a higher risk of VTE.

The investigators controlled for many confounders, though some were not explicitly discussed (e.g., chronic diseases, concomitant medications). Limitations of this study included the random selection of patients from only 250 health care practitioners in Germany and the possibility of recall bias due to the retrospective collection of patient data. In addition, *p* values were not provided for the assessment of baseline characteristics. Furthermore, evaluating the risk of VTE associated with drospirenone-containing OCs was a secondary objective of the study.

International Active Surveillance Study of Women Taking Oral Contraceptives. This currently ongoing, prospective, noninterventional, multinational, cohort, noninferiority study is assessing the safety of the 24-day combination of drospirenone 3 mg and ethinyl estradiol 20 µg as part of a Phase IV study for the Food and Drug Administration.[20] The study began in the United States in August 2005 and in Europe in the fall of 2008. The follow-up period will be three to five years in the United States and two to four years in Europe. Participants include all women beginning therapy with a new OC (either for the first time or switching to a different product) who are willing to join the study. The investigators estimate that there will be approximately 80,000 participants with an estimated 220,000 woman-years, which would give the study 90% power to exclude a twofold risk of VTE. The primary outcome is the hazard ratio of VTE (i.e., DVT and PE) associated with the 24-day regimen of drospirenone–ethinyl estradiol compared with other OCs. Follow-up questionnaires will be completed at six-month intervals, and serious adverse events will be confirmed through the patients' physician. This study is funded by Bayer Schering Pharma AG.

Hemostatic outcomes studies

Klipping and Marr. An open-label, randomized controlled study involving healthy women age 18–35 years was conducted by Klipping and Marr[21] to compare various outcomes in participants taking either ethinyl estradiol 20 µg–drospirenone 3 mg (24 active pills) or ethinyl estradiol 20 µg–desogestrel 150 µg (21 active

pills). Women up to age 30 years who were smokers were also allowed to participate in the study. The exclusion criteria were extensive; some included pregnancy and lactation, a BMI of >30 kg/m^2, uncontrolled thyroid conditions, diabetes, use of medications that affect the kinetic profile of OCs, use of an OC within two cycles before initiating the OC used during the study, uncontrolled hypertension, and malignant or premalignant tumors. Hemostatic outcomes, as secondary objectives, were assessed in women using these two types of OCs.

The full analysis set, which included patients who used at least 1 tablet of their randomized OC and with at least one observation, included a total of 29 women in the drospirenone-containing OC group and 30 women in the desogestrel-containing OC group. The results indicated an increase in prothrombin fragments 1 and 2 and in D-dimer levels. The mean rise in levels of prothrombin fragments 1 and 2 was lower in the drospirenone-containing OC group; however, the mean increase in D-dimer levels was higher in the drospirenone-containing OC group. The investigators stated that the mean difference between the groups was not significant for either prothrombin 1 and 2 levels (–0.06 nmol/L; 95% CI, –0.18 to 0.06) or D-dimer levels (15.26 ng/mL; 95% CI, –45.91 to 76.43). The mean absolute difference in procoagulatory factors (i.e., factors VII and VIII and fibrinogen) in the drospirenone-containing OC group was higher than that in the desogestrel-containing OC group. For the anticoagulation variables, the mean absolute change for users of drospirenone-containing OCs suggested less of a decrease in antithrombin activity but demonstrated a greater increase in protein C activity. The drospirenone-containing OC group had a greater decrease in mean absolute change for free and total protein S levels. An increase in the profibrinolytic values (e.g., plasminogen, plasmin–antiplasmin complex) was observed in both groups; however, the increase was greater in the drospirenone-containing OC group. The antifibrinolytic measure (i.e., plasminogen activator inhibitor-1 [PAI-1] antigen) decreased for both groups, though there was a greater decrease in the mean absolute change in the desogestrel-containing OC group. The investigators concluded that the drospirenone-containing OC and the desogestrel-containing OC were associated with similar hemostatic changes.

A limitation of this report was the lack of *p* values for both the baseline characteristics and the results. Also, the investigators did not assess whether any of the women had undergone recent surgery, which is a risk factor for VTE[17] and may have affected the hemostatic changes. In addition, the study did not have adequate statistical power to detect a difference in the hemostatic outcomes, since these were secondary outcomes. Based on these factors, it is not clear whether the hemostatic changes between the two groups were similar. Furthermore, the results from this study cannot be extrapolated to all patients taking drospirenone-containing OCs due to the extensive exclusion criteria and because nearly all the study participants were Caucasian.

Kluft et al. An open-label, randomized, prospective study was conducted by Kluft et al.[22] to compare the hemostatic effects of drospirenone 3 mg–ethinyl estradiol 30 µg, drospirenone 3 mg–ethinyl estradiol 20 µg, and desogestrel 150 µg–ethinyl estradiol 30 µg. The study was conducted from October 1992 through July 1993 and included healthy women age 18–35 years from one outpatient clinic who were either new users of combined OCs or were changing from their current OC. Smokers age 30 years or younger who smoked no more than 10 cigarettes daily were included in the study. The criteria for exclusion "were similar to the known contraindications for combined OC use" and included the use of "coagulation-relevant preparations," a family history of coagulation disorders, use of a parenteral depot contraceptive within the previous six months, "specified concomitant pathology," unclassified genital bleeding, and a history of migraines with menstruation.

Seventy-five women were randomized to one of the three treatment groups (25 per group). Participants underwent a one-cycle washout period, a cycle in which no treatment was given, six cycles of treatment, and a 28-day follow-up period with no treatment. Baseline body weight values were higher in the drospirenone–ethinyl estradiol 20-µg group compared with the desogestrel–ethinyl estradiol 30-µg and drospirenone–ethinyl estradiol 30-µg groups (by 4.5 and 4.6 kg, respectively). Procoagulatory, anticoagulatory, fibrinolytic, antifibrinolytic, and global clotting tests were conducted at baseline; at cycles 1, 3, and 6; and twice during the follow-up period. The results demonstrated that each of the procoagulatory measures (i.e., platelet count, fibrinogen, factor VII, and thrombin–antithrombin complex) increased; however, the only significant increase among the groups from baseline to cycle 6 was for fibrinogen ($p = 0.0329$). Further analysis with a two-sided Wilcoxon test indicated a significant increase in fibrinogen for drospirenone–ethinyl estradiol 20-µg when compared with desogestrel–ethinyl estradiol 30-µg ($p = 0.0078$). Regarding anticoagulatory measures, antithrombin and protein C antigen nonsignificantly increased among all three groups from baseline to cycle 6. Furthermore, reduced protein S antigen and activity levels were noted in all three groups. Use of a two-sided Kruskal–Wallis test revealed a significant change in protein S activity among the groups

($p = 0.0183$). Additional analysis with a two-sided Wilcoxon test indicated a significant change in protein S activity between the drospirenone–ethinyl estradiol 20-µg and drospirenone–ethinyl estradiol 30-µg groups ($p = 0.0198$) and between the drospirenone–ethinyl estradiol 20-µg and desogestrel–ethinyl estradiol 30-µg groups ($p = 0.0111$). The differences in the profibrinolytic, antifibrinolytic, and global clotting test results and in D-dimer levels among the groups were not significant. The investigators stated that the results signified similar changes in the hemostatic variables among all three groups and concluded that the use of drospirenone–ethinyl estradiol 20 µg yielded changes in hemostatic values that were not as marked as those seen with the other two regimens.

One of the limitations of this report is that the investigators did not provide *p* values for the differences between the demographic characteristics and baseline laboratory data, and there was no indication that the statistical tests were selected a priori. Also, the investigators did not explicitly state the contraindications for OC use that were part of the exclusion criteria. Furthermore, the data derived from this study apply to women receiving 21 days of drospirenone–ethinyl estradiol 20 µg and are not necessarily indicative of findings in women taking 24 days of active tablets.

Machado et al. In an open-label, prospective, randomized study, Machado et al.[23] assessed the effects of ethinyl estradiol 30 µg–drospirenone 3 mg given continuously (daily administration for 168 days) and cyclically (six 28-day cycles with a one-week hormone-free period) on metabolic and coagulation variables. Participants included sexually active women age 18–35 years desiring to use contraception who were not receiving hormonal contraception for at least two months before study entry or who had an intrauterine contraceptive device. The study also required participants to have a BMI of 19–30 kg/m^2, at least eight years of education, and the ability to comprehend written and oral instructions. Exclusion criteria included pregnancy, abnormal findings on a cervicovaginal colposcopy, use of drugs that may interact with OCs (e.g., barbiturates, carbamazepine, rifampicin), and personal history of conditions such as breast or genital cancer, cardiovascular disease, VTE or arterial thromboembolism, diabetes, alcoholism, acute or chronic liver disease, and arterial hypertension. A total of 78 women were included, with 39 allocated to each treatment group.

When assessing coagulation variables, both thrombin time and activated partial thromboplastin time levels were reduced significantly from baseline in both groups; however, no significant difference was noted between treatment groups. No significant changes in fibrinogen, antithrombin III, PAI-1, protein C antigen, or D-dimer levels were observed in baseline and intergroup comparisons. The mean free protein S antigen level was significantly lower in the cyclic treatment group compared with the continuous-treatment group ($p = 0.0232$). The investigators concluded that comparable changes with no negative effects could be expected with cyclic and continuous administration of drospirenone-containing OCs.

The findings from this study should be interpreted cautiously. Because assessment of the hemostatic variables was a secondary outcome, the study was not adequately designed or powered to determine a difference in these values. In addition, the investigators mentioned that three patients tested positive for the activated protein C resistance test, "constituting a criterion for exclusion." Interestingly, coagulation disorders were not listed as part of the exclusion criteria. The external validity of this study is somewhat limited by the numerous diseases that were excluded. Thus, the data may not be extrapolated to patients with diabetes or cardiovascular disease.

Discussion

A review of the current literature revealed that data are conflicting regarding the risk of VTE associated with drospirenone-containing OCs. Two studies found that when compared with nonuse of OCs, use of drospirenone-containing OCs was associated with a fourfold to over sixfold increased risk of having a thrombotic event.[4,18] In addition, when compared with OCs containing levonorgestrel, the adjusted rate ratios suggested an almost twofold risk of VTE with drospirenone-containing OCs. One of these studies found an increased risk associated with short-term use (three months or less) of drospirenone-containing OCs.[4] However, this study was limited by the small number of participants who were taking drospirenone ($n = 19$) despite the large number of study participants ($n = 3284$).

Three studies did not find an increased risk of VTE with drospirenone.[2,16,19] One of these studies assessed medical health claims, limiting the patient population evaluated.[16] In addition, the investigators did not explain how they calculated the reported NNH. Based on study design, only an association between VTE and drospirenone use could be established, not a cause-and-effect relationship. In another study, the investigators stated that noninferiority was established; however, this statement was based on an adjusted hazard ratio, as the crude hazard ratio did not establish noninferiority.[2] Lastly, in a case–control study, the use of drospirenone-containing OCs was not found to increase the risk of VTE.[19] However, the data should be interpreted cautiously, as assessment of drospirenone-containing OCs was a secondary objective of the study.

Data from two of the hemostatic outcomes studies suggested that changes in hemostatic variables were similar between drospirenone- and desogestrel-containing OCs.[21,22] Comparable findings were noted in a study that assessed continuous versus cyclic drospirenone-containing OCs.[23] The findings from two of the studies were limited given that the results were secondary outcomes; thus, the studies were not powered to determine a statistical difference.[21,23] Moreover, these studies included extensive exclusion criteria, and one study included predominantly Caucasian females, reducing its external validity.[21] Based on these limitations, it is uncertain if the changes in hemostatic variables would be similar between drospirenone- and desogestrel-containing OCs as well as between cyclic and continuous drospirenone-containing OCs.

Taken collectively, the data from these outcomes studies should be interpreted cautiously given their numerous limitations. Most of the study reports did not include *p* values, which are imperative for determination of homogeneity among treatment groups. In addition, though some confounders were controlled for, other known risk factors for VTE, such as recent surgery, immobility, and obesity, were not.[17] Some of the studies did not provide total numbers of participants and types of other combined OCs used. Studies that incorporated questionnaires were subject to recall bias, though investigators attempted to minimize this.

Given the findings from the medical literature, it appears that drospirenone-containing OCs remain a viable method of oral contraception for some women. The provision of adequate patient counseling is important to help patients identify signs and symptoms of VTE. Patients should also be encouraged to seek immediate help in the event of a suspected adverse effect. Patients prone to hyperkalemia (i.e., those with hepatic insufficiency, with adrenal insufficiency, or taking medications that can raise potassium levels) should be identified to help avoid this adverse effect with concomitant administration of drospirenone-containing OCs.

Conclusion

The majority of available data does not support the conclusion that drospirenone-containing OCs pose an increased risk of VTE compared with other OCs.

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