



The American College of
Obstetricians and Gynecologists

WOMEN'S HEALTH CARE PHYSICIANS

COMMITTEE OPINION

Number 540 • November 2012

Reaffirmed 2018

Committee on Gynecologic Practice

This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.

Risk of Venous Thromboembolism Among Users of Drospirenone-Containing Oral Contraceptive Pills

ABSTRACT: Although the risk of venous thromboembolism is increased among oral contraceptive users compared with nonusers who are not pregnant and not taking hormones, and some data have suggested that use of drospirenone-containing pills has a higher risk of venous thromboembolism, this risk is still very low and is much lower than the risk of venous thromboembolism during pregnancy and the immediate postpartum period. When prescribing any oral contraceptive, clinicians should consider a woman's risk factors for venous thromboembolism and refer to the *U.S. Medical Eligibility Criteria for Contraceptive Use* issued by the Centers for Disease Control and Prevention. Patient education materials, including product labeling, should place information regarding oral contraceptive use and venous thromboembolism risks in context by also providing information about overall venous thromboembolism risks and venous thromboembolism risks during pregnancy and the postpartum period. Decisions regarding choice of oral contraceptive should be left to clinicians and their patients, taking into account the possible minimally increased risk of venous thromboembolism, patient preference, and available alternatives.

Combined oral contraceptives (OCs) that contain drospirenone have been widely used in the United States for several years and in Europe for longer. Early safety reports have suggested a higher risk of venous thromboembolism associated with the use of OCs that contain drospirenone compared with OCs that contain other progestins, such as levonorgestrel (1, 2). Two large studies (one large Dutch case-control study and one cohort study from Denmark) also reported increased risks of venous thromboembolism with use of drospirenone-containing OCs compared with levonorgestrel-containing OCs (3, 4). However, these studies had several methodological limitations, such as potential misclassification of venous thromboembolism and the duration of use of the OCs, inadequate control of confounding variables, and potential information and detection biases (5). Despite these limitations, it is biologically plausible to consider an increased risk of complications from venous thromboembolism with the use of drospirenone-containing OCs as compared with other progestin-containing OCs. Aldosterone may be involved with hemostasis, leading to a decrease in coagulability. Therefore, the antimineralocorticoid properties of drospirenone could in turn lead to

hypercoagulability, creating a possible mechanism for the increased risk of venous thromboembolism with the use of drospirenone-containing OCs (6).

After reviewing the data in these as well as other studies, the U.S. Food and Drug Administration (FDA) issued a *Drug Safety Communication* in which it concluded that use of drospirenone-containing OCs may be associated with a higher risk of blood clots than other progestin-containing OCs (7). Because the studies did not provide consistent estimates of the comparative risk of blood clots between drospirenone-containing OCs and other progestin-containing OCs and because the studies failed to account for important patient characteristics, such as smoking status and body mass index, that may influence prescribing and likely affect the risk of blood clots, the FDA was unable to conclude causality.

Two nested case-control studies that used United States and United Kingdom clinical databases found the risk of nonfatal idiopathic venous thromboembolism to be two to three times higher among new current users of drospirenone-containing OCs compared with users of levonorgestrel-containing OCs (8, 9). Information regarding OC use was ascertained from a pharmacy database

recorded from drug claims in one study (8) and from a research database in the other study (9). All identified patients with venous thromboembolism had to have received long-term anticoagulation therapy. In contrast, a German case-control study found similar risks of confirmed venous thromboembolism between users of drospirenone-containing OCs and levonorgestrel-containing OCs (10). Although some known potential confounders were identified and adjusted for in these studies, case-control studies remain susceptible to confounding by unknown variables, selection bias, and diagnostic referral bias, among other factors.

The European Active Surveillance Study prospectively evaluated the risks of cardiovascular complications among 59,674 new users of OCs, including women who were taking drospirenone-containing OCs, who were actively observed for 142,475 woman-years (11). Cases of venous thromboembolism were verified with medical records; loss to follow-up was less than 2.5%. In this 5-year multinational study, the risk of venous thromboembolism among new users of drospirenone-containing OCs was 9.1 per 10,000 woman-years compared with 8 per 10,000 woman-years among new users of levonorgestrel-containing OCs and 9.9 per 10,000 woman-years among new users of other progestin-containing OCs. The adjusted hazard ratios (HRs) were 1 (95% confidence interval [CI], 0.6–1.8) for users of drospirenone-containing OCs compared with users of levonorgestrel-containing OCs and 0.9 (95% CI, 0.5–1.3) for users of drospirenone-containing OCs compared with users of other progestin-containing OCs. A U.S. study of 67,000 new OC users, one third of whom were using drospirenone-containing OCs, did not find significant differences in the incidence of venous thromboembolism among users of drospirenone-containing OCs (1.3/1,000 woman-years; 95% CI, 0.8–2) compared with users of other progestin-containing OCs (1.4/1,000 woman-years; 95% CI, 1.–1.9) (12).

Another large multinational prospective cohort study assessing the risk of drospirenone use and venous thromboembolism, the International Active Surveillance Study of Women Taking Oral Contraceptives, will conclude in 2012 (13). Preliminary safety data from this study, based on 105,000 woman-years of observation, showed that the risk of venous thromboembolism was not significantly different among users of 24-day regimens of drospirenone-containing OCs (8.7/10,000 woman-years), 21-day regimens of drospirenone-containing OCs (5.4/10,000 woman-years), and regimens of other progestin-containing OCs (8/10,000 woman-years) (13). Initial data from this study also showed that women who took 24-day regimens of drospirenone-containing OCs had lower pregnancy rates with typical use than users of 21-day regimens of other progestin-containing OCs (14).

In contrast with these studies, an FDA-funded study released in October 2011 concluded that all use (ie, new use, switching from another combined OC, or

continuing use of a current contraceptive) of the drospirenone-ethinyl estradiol pill (3 mg of drospirenone and 30 micrograms of ethinyl estradiol) was associated with a 1.74-fold increased risk of venous thromboembolism relative to the other low-dose combined OCs (0.1 mg of levonorgestrel and 20 micrograms of ethinyl estradiol; 0.15 mg of levonorgestrel and 30 micrograms of ethinyl estradiol; 1 mg of norethindrone acetate and 20 micrograms of ethinyl estradiol; and 0.18–0.25 mg of norgestimate and 35 micrograms of ethinyl estradiol) (15). The FDA study of more than 800,000 U.S. women reported an increased age-adjusted incidence rate of venous thromboembolism of 10.22 per 10,000 women-years in users of drospirenone-containing OCs versus 5.96 per 10,000 women-years in the comparison group of users of second-generation combined OCs (15). However, this study is limited by the lack of adjusting for confounders, such as smoking and obesity. Furthermore, diagnoses of venous thromboembolism were established based on computerized data with partial verification from review of medical records. Additionally, the increased risk of venous thromboembolism demonstrated in this study is seen within the first 12 months of drospirenone-containing OC use only. The elevated incidence ratio in the first 3 months is 1.93 (1.26–2.95) and from 7 months to 12 months is 2.9 (1.59–5.28). However, after 12 months of use, the risk of venous thromboembolism in patients who use drospirenone-containing OCs is equivalent to that of users of other second-generation combined OCs, with an incidence rate ratio of 1.17 (0.63–2.18). The increased risk of venous thromboembolism with all use of drospirenone-containing OCs as compared with all use of other OCs is found in women aged 10–34 years. The relative HR in this age range is 1.86 (1.41–2.46) compared with the relative HR of 1.35 (1–1.82) for women aged 35–55 years. Older “new” users of the drospirenone-containing OCs are less likely to be naïve users of combined OCs and are more likely to have had previous hormonal exposure without complications.

Conclusions

The risk of venous thromboembolism is increased among OC users (3–9/10,000 woman-years) compared with nonusers who are not pregnant and not taking hormones (1–5/10,000 woman-years) (7), and some data have suggested that the use of drospirenone-containing OC pills has a higher risk (10.22/10,000) than the use of other progestin-containing OCs (15). However this risk is still very low and is much lower than the risk of thromboembolism during pregnancy (approximately 5–20/10,000 woman-years) and the postpartum period (40–65/10,000 woman-years) (7) (Figure 1).

Recommendations

Based on recent reports regarding the increase of venous thromboembolism in users of drospirenone-containing OCs, the American College of Obstetricians

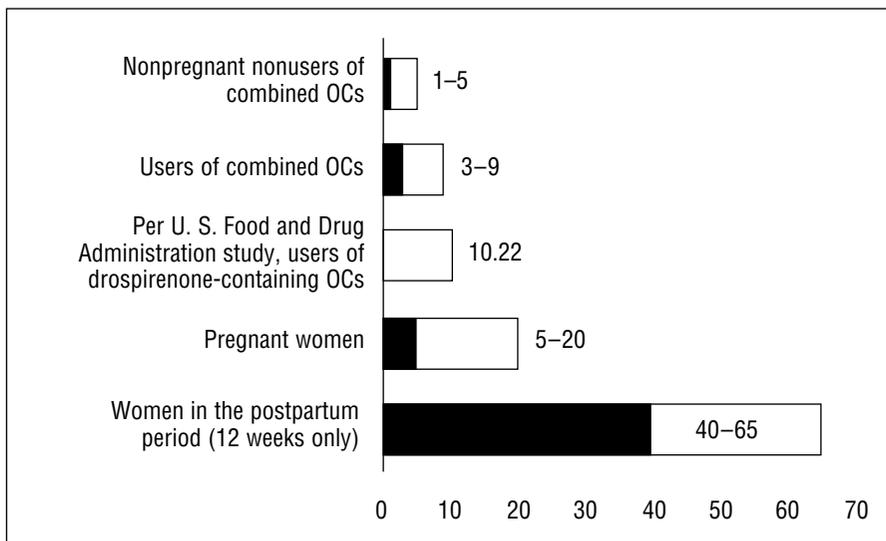


Fig. 1. Likelihood of developing a blood clot (number of women with a blood clot per 10,000 women-years). Abbreviation: OC indicates oral contraceptives. Adapted from Food and Drug Administration. FDA drug safety communication: updated information about the risk of blood clots in women taking birth control pills containing drospirenone. Silver Spring (MD): FDA; 2012. Available at: <http://www.fda.gov/Drugs/DrugSafety/ucm299305>. Retrieved July 5, 2012. Additional information from Food and Drug Administration. Combined hormonal contraceptives (CHCs) and the risk of cardiovascular disease endpoints. Silver Spring (MD): FDA; 2011. Available at: <http://www.fda.gov/downloads/Drugs/DrugSafety/UCM277384.pdf>. Retrieved July 5, 2012. ↩

and Gynecologists' Committee on Gynecologic Practice makes the following recommendations:

- Decisions regarding the choice of OC should be left to clinicians and their patients, taking into account the following factors:
 - The possible minimally increased risk of venous thromboembolism in new users of drospirenone-containing OCs compared with users of combined OCs (10.22/10,000 woman-years compared with 3–9/10,000 woman-years) (Fig. 1)
 - Patient preference
 - Available alternatives
- Women should have a wide range of contraceptive options, including drospirenone-containing OCs.
- If a patient is using a drospirenone-containing OC and is tolerating the regimen, there is no need to discontinue that OC.
- When prescribing any OC, clinicians should consider a woman's risk factors for venous thromboembolism (Box 1) and refer to the *U.S. Medical Eligibility Criteria for Contraceptive Use* (16, 17).
- Patient education materials, including product labeling, should place information regarding risks of venous thromboembolism in context by also providing information about overall venous thromboembolism risks and venous thromboembolism risks during pregnancy and the postpartum period.

Box 1. High-Risk Factors for Venous Thromboembolism in Users of Combined Oral Contraceptives* ↩

- Smoking and age 35 years or older
- Less than 21 days postpartum or 21–42 days postpartum with other risk factors
- Major surgery with prolonged immobilization
- History of deep vein thrombosis or pulmonary embolism
- Hereditary thrombophilia (including antiphospholipid syndrome)
- Inflammatory bowel disease with active or extensive disease, surgery, immobilization, corticosteroid use, vitamin deficiencies, or fluid depletion
- Systemic lupus erythematosus with positive (or unknown) antiphospholipid antibodies

*Oral contraceptive use in women with these conditions is classified as U.S. Medical Eligibility Criteria Category 3 (theoretical or proven risks usually outweigh the advantages of using the method) or Category 4 (condition that represents an unacceptable health risk if the contraceptive method is used).

Data from U.S. Medical Eligibility Criteria for Contraceptive Use, 2010. Centers for Disease Control and Prevention (CDC). *MMWR Recomm Rep* 2010;59(RR-4):1–86 [PubMed] [Full Text] and Update to CDC's U.S. Medical Eligibility Criteria for Contraceptive Use, 2010: revised recommendations for the use of contraceptive methods during the postpartum period. Centers for Disease Control and Prevention (CDC). *MMWR Morb Mortal Wkly Rep* 2011;60:878–83. [PubMed] [Full Text]

References

1. Sheldon T. Dutch GPs warned against new contraceptive pill. *BMJ* 2002;324:869. [PubMed] [Full Text] ↵
2. van Grootheest K, Vrieling T. Thromboembolism associated with the new contraceptive Yasmin. *BMJ* 2003;326:257. [PubMed] [Full Text] ↵
3. Lidegaard O, Lokkegaard E, Svendsen AL, Agger C. Hormonal contraception and risk of venous thromboembolism: national follow-up study. *BMJ* 2009;339:b2890. [PubMed] [Full Text] ↵
4. van Hylckama Vlieg A, Helmerhorst FM, Vandenbroucke JP, Doggen CJ, Rosendaal FR. The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case-control study. *BMJ* 2009;339:b2921. [PubMed] [Full Text] ↵
5. Shapiro S, Dinger J. Risk of venous thromboembolism among users of oral contraceptives: a review of two recently published studies. *J Fam Plann Reprod Health Care* 2010;36:33–8. [PubMed] [Full Text] ↵
6. Ducros E, Berthaut A, Mirshahi SS, Faussat AM, Soria J, Agarwal MK, et al. Aldosterone modifies hemostasis via upregulation of the protein-C receptor in human vascular endothelium. *Biochem Biophys Res Commun* 2008;373:192–6. [PubMed] ↵
7. Food and Drug Administration. FDA drug safety communication: updated information about the risk of blood clots in women taking birth control pills containing drospirenone. Silver Spring (MD): FDA; 2012. Available at: <http://www.fda.gov/Drugs/DrugSafety/ucm299305>. Retrieved July 5, 2012. ↵
8. Jick SS, Hernandez RK. Risk of non-fatal venous thromboembolism in women using oral contraceptives containing drospirenone compared with women using oral contraceptives containing levonorgestrel: case-control study using United States claims data. *BMJ* 2011;342:d2151. [PubMed] [Full Text] ↵
9. Parkin L, Sharples K, Hernandez RK, Jick SS. Risk of venous thromboembolism in users of oral contraceptives containing drospirenone or levonorgestrel: nested case-control study based on UK General Practice Research Database. *BMJ* 2011;342:d2139. [PubMed] [Full Text] ↵
10. Dinger J, Assmann A, Mohner S, Minh TD. Risk of venous thromboembolism and the use of dienogest- and drospirenone-containing oral contraceptives: results from a German case-control study. *J Fam Plann Reprod Health Care* 2010;36:123–9. [PubMed] [Full Text] ↵
11. Dinger JC, Heinemann LA, Kuhl-Habich D. The safety of a drospirenone-containing oral contraceptive: final results from the European Active Surveillance Study on oral contraceptives based on 142,475 women-years of observation. *Contraception* 2007;75:344–54. [PubMed] [Full Text] ↵
12. Seeger JD, Loughlin J, Eng PM, Clifford CR, Cutone J, Walker AM. Risk of thromboembolism in women taking ethinylestradiol/drospirenone and other oral contraceptives. *Obstet Gynecol* 2007;110:587–93. [PubMed] [Obstetrics & Gynecology] ↵
13. Dinger J, Bardenheuer K, Moehner S. The risk of venous thromboembolism in users of a drospirenone-containing oral contraceptive with a 24-day regimen – results from the INAS-OC Study [abstract]. *Fertil Steril* 2010;94:S3. ↵
14. Dinger J, Minh TD, Buttman N, Bardenheuer K. Effectiveness of oral contraceptive pills in a large U.S. cohort comparing progestogen and regimen. *Obstet Gynecol* 2011;117:33–40. [PubMed] [Obstetrics & Gynecology] ↵
15. Food and Drug Administration. Combined hormonal contraceptives (CHCs) and the risk of cardiovascular disease endpoints. Silver Spring (MD): FDA; 2011. Available at: <http://www.fda.gov/downloads/Drugs/DrugSafety/UCM277384.pdf>. Retrieved July 5, 2012. ↵
16. U. S. Medical Eligibility Criteria for Contraceptive Use, 2010. Centers for Disease Control and Prevention (CDC). *MMWR Recomm Rep* 2010;59(RR-4):1–86. [PubMed] [Full Text] ↵
17. Update to CDC's U.S. Medical Eligibility Criteria for Contraceptive Use, 2010: revised recommendations for the use of contraceptive methods during the postpartum period. Centers for Disease Control and Prevention (CDC). *MMWR Morb Mortal Wkly Rep* 2011;60:878–83. [PubMed] [Full Text] ↵

Copyright November 2012 by the American College of Obstetricians and Gynecologists, 409 12th Street, SW, PO Box 96920, Washington, DC 20090-6920. All rights reserved.

ISSN 1074-861X

Risk of venous thromboembolism among users of drospirenone-containing oral contraceptive pills. Committee Opinion No. 540. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2012;120:1239–42.