Combined hormonal contraception and the risk of venous thromboembolism: a guideline

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While venous thromboembolism (VTE) is rare in young women of reproductive age, combined oral contraceptives increase the risk of VTE. In the patient in whom combined hormonal contraception is appropriate, it is reasonable to use any currently available preparation. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)

BACKGROUND

Venous thromboembolism (VTE) refers to the formation of a blood clot in a deep vein and is a rare but potentially preventable cause of death in women of reproductive age. Deep venous thromboses, which commonly occur in the legs, may break off and move into the pulmonary vasculature, which can be life-threatening. However, most venous thromboses do not result in death. Common risk factors for VTE include hypercoagulability and vascular injury. Pregnancy and the postpartum period in particular are associated with an increased risk of VTE compared with the non-pregnant state: The incidence of VTE is 5–20/10,000 woman-years in pregnancy and 40–65/10,000 woman-years postpartum, compared with 1–5/10,000 woman-years outside of pregnancy (1).

Overall, it appears that combined hormonal contraceptives (CHCs) are associated with an increased risk of VTE compared with non-use (3–15/10,000 woman-years in users vs. 1–5/10,000 risk in non-users), but this risk is still smaller than the risk in pregnancy and appears to decline over time (1). In general, the risk of VTE while on hormonal contraception must be weighed against potential contraceptive benefits and the risks of VTE during pregnancy and postpartum to determine whether a woman should take CHCs.

While there is good evidence that CHCs are associated with an increased risk of VTE, there has been substantial controversy surrounding the actual risk associated with various different formulations of CHCs. A variety of CHC methods are available with different doses of estrogen and types of progestin, which are delivered through various routes of administration.

METHODS

This clinical practice guideline was based on a systematic review of the literature. A systematic literature search of relevant articles was performed in the electronic database MEDLINE through PubMed (February and June 2015), with a filter for human subject research. This electronic search and examination of reference lists from primary and review articles yielded 1,254 studies, of which 86 studies were included.

A combination of the following medical subject headings or text words/keywords were used: birth control; contraception; combined hormonal contraception; combined oral contraceptive; combined oral contraceptives; contraceptives, oral; contraceptives, oral/administration and dosage; contraceptives, oral, combined; contraceptives, oral, combined/administration and dosage; hormonal contraception; oral contraceptive; oral contraceptives; desogestrel; drospirenone; estradiol; estrogen; oestrogen; ethynodiol diacetate; etynodiol diacetate; levonorgestrel; nomegestrol; norethisterone; norethisteron; norethindrone; norethindron; norethynodrel; norgestimat; norgestimate; norgestrel; AND ethinyl estradiol; ethinyl estradiol; ethinylestradiol; mestranol; progesterone; progestin; progestins; progestogen; progestogens; AND

Received September 13, 2016; accepted September 13, 2016.

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Fertility and Sterility® Vol. ■, No. ■, ■ 2016 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2016.09.027

cerebral vein thrombosis; clot; deep vein thrombosis; deep venous thrombosis; DVT; embolism; hepatic thrombosis; mesenteric venous thrombosis; pulmonary emboli*; pulmonary embolism; thrombosis; thrombus; thromboembolism; thrombophlebitis; vein embolism; vein thrombosis; venous embolism; venous thromboembolism; venous thrombosis; venous thrombosis; venous thrombotic; first generation, second generation, third generation, fourth generation; AND obese; obesity; body weight; body weight; body mass index; BMI; PCOS; polycystic ovaries; polycystic ovary; polycystic ovary syndrome; polycystic ovarian syndrome; smoking; age; risk, risks, risk factor, risk factors.

An independent panel of experts reviewed the full articles of all citations that possibly matched the predefined selection criteria. Final inclusion or exclusion decisions were made on examination of the articles in full. Disagreements about inclusion among reviewers were discussed and solved by consensus or arbitration after consultation with an independent reviewer/epidemiologist. Studies were eligible if they met one of the following criteria: primary evidence (clinical trials) that assessed the effectiveness of a treatment correlated with an outcome measure (VTE); meta-analyses; and relevant articles from bibliographies of identified articles.

The quality of the evidence for each reference in the bibliography was evaluated using the following grading system:

Level I: Evidence obtained from at least one properly designed randomized, controlled trial.

Level II-1: Evidence obtained from well-designed controlled trials without randomization.

Level II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.

Level II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.

Level III: Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

Systematic reviews/meta-analyses were individually considered and included if they followed a strict methodological process and assessed relevant evidence.

The strength of the evidence was evaluated as follows:

Grade A: There is good evidence to support the recommendations, either for or against.

Grade B: There is fair evidence to support the recommendations, either for or against.

Grade C: There is insufficient evidence to support the recommendations, either for or against.

OVERVIEW OF THE LITERATURE

There are no large, prospective randomized studies comparing the risk of VTE among various doses of estrogen, types of progestin, or routes of administration. Only level II-2 studies exist, including large cohort and case-control studies that are limited by a number of methodological issues which may skew results. For example, without randomization, it is difficult to control for different patient populations and prescriber bias (2). It is also important to recognize that VTE risk is greater in new hormonal contraceptive users during the first year (3), in older women, and in obese women. Many studies do not adequately account for imbalances in these risk factors between treatment groups. In addition, the diagnosis of venous thrombosis may not always be accurate in studies since cases are not always confirmed by hospital records or radiologic studies. Finally, given that the incidence of VTE is low, large numbers of observations are required to compare cases among various treatment groups.

CLASSIFICATION OF COMBINED HORMONAL CONTRACEPTIVES

Combined hormonal contraceptives (CHCs) are classified into several categories. Combined oral contraceptives (COCs) with 50 μg of ethinyl estradiol (EE) are considered first generation. Second-generation combined oral contraceptive pills contain lower doses of estradiol (20, 30, or 35 μg) and the progestin norethindrone and its derivatives, including levonorgestrel (4). Third-generation combined oral contraceptive pills containing the progestins desogestrel and gestodene were formulated to be less androgenic than the second-generation progestins (5). Norgestimate is technically a third-generation progestin; however, its bioactivity is mediated mainly through levonorgestrel, which distinguishes it from other third-generation progestins (6). Finally, fourth-generation contraceptive pills include, among others, the progestin drospirenone, which is derived from spironolactone and has anti-androgenic activity (7). In addition, CHCs are available in several routes of administration including pills, transdermal patches, and vaginal ring. For the purpose of this document, only preparations available in the United States will be discussed.

SCIENTIFIC QUESTIONS

Does the Dose of Estrogen Affect VTE Rates?

Modern combined oral contraception may contain 10, 15, 20, 30, or 35 μg of EE administered continuously for 21 or 24 out of 28 days. In addition, semicontinuous oral contraceptive pills are available, which contain 84 days of EE followed by a 7-day progestin-free window. It is difficult to compare the effect of EE dose since preparations often differ with respect to the progestin component. Despite this limitation, there is a good deal of evidence that increased estrogen dose is associated with VTE risk. The best evidence suggests that by lowering the estrogen content of the pill to $\leq$50 μg of EE, VTE incidence decreases (8–17). A number of large studies found that preparations of COCs with 50 μg EE have a higher risk of thrombosis compared with sub-50 μg EE formulations (12–14), which likely informed conclusions made in subsequent reviews/meta-analyses that there is an overall increased risk of VTE in COCs containing 50 μg EE and select progestins

(15–17). A 2014 Cochrane review concluded that a 50 μg EE pill containing levonorgestrel was associated with relative risks (RR) for VTE of 2.1 (95% CI, 1.4–3.2) and 2.3 (95% CI, 1.3–4.2) compared with a 30 μg and 20 μg pill containing levonorgestrel, respectively (16, 17). However, a number of studies did not find that reductions in dose from 50 μg to <50 μg EE COC decreased the risk of VTE (18–26). There is no evidence that lowering the estrogen content of the COCs below 35 μg further lowers the risk of VTE (Table 1) (12, 14, 15, 18–20, 23, 24, 26, 27, 29, 30).

Summary statement. There are no randomized trials large enough to compare thrombosis risk in patients on oral contraceptives containing different doses of EE. Only level II-2 studies exist, including large cohort and case-control studies. It is difficult to compare the effect of the EE dose since preparations differ with respect to the progestin component. In addition, observational studies are limited by a number of unmeasured confounders and bias. The following may be concluded from the literature:

- While no longer available in the United States, high-dose combined oral contraception (>50 μg) is associated with higher risks of VTE than lower-dose formulations. (Grade B)
- There is fair evidence that combined oral contraception with 50 μg EE has a higher risk of thrombosis compared with sub-50 μg EE formulations. (Grade B). However, data are conflicting and difficult to interpret due to the variable progestin component of the pills studied.
- There is fair evidence that COCs containing EE doses lower than 35 μg have similar VTE risk to 35 μg formulations. (Grade B)

Does Type of Progestin Contribute to VTE Risk?

A particular area of controversy is whether the type of progestin in COCs affects VTE rates. Specifically, there have been conflicting results from large epidemiologic studies, none of which are randomized, as to whether there is an increased risk of VTE rates in COCs containing the newer progestins desogestrel, gestodene (not available in the United States), norgestimate, and drospirenone compared with the progestins levonorgestrel and norethindrone.

Beginning in the mid-1990s, cohort and case-control studies reported a 2-fold increased risk of VTE with COCs containing the third-generation progestins desogestrel and gestodene compared with second-generation preparations (21, 31, 32). However, further studies questioned the initial findings, attributing the increased risk to confounding factors including new-user and prescriber bias (3, 4, 23–26, 33–40). It is known that new users of oral contraception have a higher rate of VTE that gradually decreases as the length of time taking combined oral contraception increases (3). Therefore, the increased risk seen in early studies of third-generation progestins may have been the result of differences in the populations taking the second- vs. third-generation progestins (2, 4, 40, 41). However, additional studies have shown an increased risk of VTE with third-generation progestins (with the exception of norgestimate, which has been found to have a risk similar to levonorgestrel) even when potential confounders are taken into account (Table 1) (9, 10, 12–14, 28, 42–51).

Cohort and case-control studies have also shown an increased VTE risk with the fourth-generation progestin drospirenone (12, 13, 30, 51–55). A recent large US cohort study of over 100,000 women who were new users of drospirenone

TABLE 1

Relative risk compared with absolute risk for venous thromboembolism by characteristic (1, 16, 17, 27, 28).

Variable	Relative risk compared with non-pregnant women without the risk factor	Absolute risk
Nonpregnant, not taking hormones	1.0	VTE: 1–5/10,000 woman-years (1)
Pregnancy	4.29 (95% CI, 3.49–5.22; $P<.001$) compared with non-pregnant women (27)	VTE: 5–20/10,000 woman-years (1) PE: 1/10,000 woman-years
Postpartum	4.29 (95% CI, 3.49–5.22; $P<.001$) compared with non-pregnant women (27)	VTE: 40–65/10,000 woman-years (1) PE: 16 per 10,000 woman-years
Progestin type	RR of VTE (16, 17): Non-use vs. 1st generation (norethindrone COC) users: 3.2 (95% CI, 2.0–5.1) Non-use vs. 2nd generation (levonorgestrel COC) users: 2.8 (95% CI, 2.0–4.1) Non-use vs. 3rd generation (desogestrel COC users): 3.8 (95% CI, 2.7–5.4) 2nd vs. 1st generation: 0.9 (95% CI, 0.6–1.4) 3rd vs. 1st generation: 1.2 (95% CI, 0.8–1.9) 3rd generation vs. 2nd generation: 1.3 (95% CI, 1.0–1.8)	
Estrogen dose	20 μg ethinyl estradiol with levonorgestrel vs. non-use: 2.2 (95% CI, 1.3–3.6) 30 μg ethinyl estradiol with levonorgestrel vs. 20 μg ethinyl estradiol with levonorgestrel: 1.1 (95% CI, 0.7–1.7) 50 μg ethinyl estradiol with levonorgestrel vs. 20 μg ethinyl estradiol with levonorgestrel: 2.3 (95% CI, 1.3–4.2) (16, 17)	
Thrombophilias	Factor V Leiden: 2.6 no OC, 64.7 1st/2nd generation, 29.6 3rd generation Other heritable thrombophilia: 2.6 no OC, 63.3 1st/2nd generation; 52.5 3rd generation (28)	

Note: CI = confidence interval; COC = combined oral contraceptives; OC = oral contraceptives; PE = pulmonary embolism; RR = relative risk; VTE = venous thromboembolism.

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compared with over 300,000 women who were new users of second-generation combined oral contraception noted an increased risk of VTE in the drospirenone group (hazard ratio [HR] 1.77; 95% CI, 1.33–2.35) (55). However, other studies, including large cohort and case-control studies controlling for multiple factors including the new-user effect, show no increased risk with drospirenone (56–60). Similarly, the International Active Surveillance Study of Women Taking Oral Contraceptives did not find a difference in VTE rates among different progestins. This large, European, prospective observational study found VTE incidence rates of approximately 7.2–9.8/10,000 woman-years among combined oral contraception users, with similar rates for drospirenone and third-generation progestins compared with levonorgestrel, and an adjusted HR of 0.8 (95% CI, 0.5–1.3) between drospirenone and levonorgestrel (61). Another case-control study, which included 311 combined oral contraception users with first-time VTE, found an increased risk, the adjusted odds ratio (OR) of 2.5 (95% CI, 1.2–5.1) for desogestrel compared with levonorgestrel. However, there were no significantly higher risks with other progestin types, including drosperinone (OR 1.9; 95% CI, 0.9–4.1) (62).

Recent meta-analyses and systematic reviews have consistently shown a small but significant increased risk of VTE among users of third-generation progestins and drospirenone compared with second-generation progestins (15–17, 63–65). One meta-analysis, which included 23 studies, reported that COCs increased the risk of venous thrombosis 4-fold. The relative risk of VTE compared with non-use in norethindrone COC users was 3.2 (95% CI, 2.0–5.1), levonorgestrel COC users 2.8 (2.0–4.1), and desogestrel COC users 3.8 (2.7–5.4) (16). Similarly, a Cochrane review of 26 studies showed a 50%–80% increased relative risk of VTE among third-generation or drosperinone COC users compared with levonorgestrel COC users at the same dose of EE (30–35 μg). The relative risk for third-generation compared with second-generation users was 1.3 (95% CI, 1.0–1.8). Overall, the relative risk of VTE among COC users was 3.5 (95% CI, 2.9–4.3) (Table 1) (17).

Since none of the studies were randomized, they may be limited by confounding VTE risk factors such as new use, older age, obesity, family history of VTE, or prolonged immobilization. They may also be subject to bias including the healthy-user effect, misclassification bias of VTE events, and prescriber bias (39, 41). The EE dose is also not consistent among combined oral contraception preparations, making direct comparisons of the progestin component difficult. Finally, it is important to note that even in the studies that have found an increased risk of VTE with newer progestins, the absolute increase in risk is very small relative to the overall increased risk with combined oral contraception. The absolute risk of third-generation or drospirenone-containing COCs was estimated in one meta-analysis to be 10–15 VTE/10,000 women per year compared with 8 VTE/10,000 women in levonorgestrel COC users and 2 VTE/10,000 women with no use (63). This is still lower than the overall risk in pregnancy (5–20/10,000 woman-years).

Summary statement. There are no randomized trials large enough to compare the risk of VTE in patients on different types of oral contraceptives. Only level II-2 studies exist, including large cohort and case-control studies. It is difficult to compare the effect of the progestin component alone, as some studies include preparations with different doses of EE. In addition, observational studies are limited by a number of confounders and bias (including differences in users and non-users of COCs, duration of combined oral contraception use, and misclassification of VTE due to differences in diagnostic criteria used).

Because of the lack of high-quality level I studies comparing progestins, it is possible that methodological problems in the present studies are responsible for the small increased risk in VTE events, and that there is actually no increased risk with third- or fourth-generation progestins, such as desogestrel or drospirenone. If there is indeed an increased RR, the absolute risk increase is extremely small. Therefore, in the appropriately selected patient, the choice of COC method does not need to be made based on the type of progestin. If a woman has estrogen-related COC risk for VTE, then no route of administration or dose of estrogen has been found to be safer. All estrogen-containing hormonal methods are contraindicated in that setting.

- There is fair evidence that all available CHC preparations increase the risk of VTE over the non-pregnant state.
- There is fair evidence that women using preparations of COC with drospirenone or third-generation progestins have a slightly higher risk of VTE compared with those using norethindrone or levonorgestrel. (Grade B). These results may in part be related to characteristics of the populations using these preparations.

Does Route of Administration of CHC Contribute to VTE Risk?

CHC is commonly delivered by an oral route but may also be administered by vaginal ring, which is a transmucosal route, or as a transdermal preparation. Although it has been suggested that transdermal estradiol for hormone therapy in postmenopausal women may confer a lower risk of VTE due to the first-pass effect in the liver, this has not been noted with non-oral hormonal contraceptive preparations. There have been reports that the non-oral route of administration increases the risk of VTE. However, there are no prospective, randomized trials large enough to determine a difference in VTE risk of transdermal or vaginal ring CHC compared with oral administration.

The only currently available contraceptive vaginal ring (NuvaRing®, Merck) contains 11.7 mg etonogestrel (the biologically active metabolite of desogestrel, a third-generation progestin) and 2.7 μg EE, with approximately 120 μg mg of etonogestrel and 15 μg of EE released per day. Users of the ring have the same systemic exposure to the progestin component but approximately half of the systemic exposure to EE when compared with users of an oral preparation of 150 μg desogestrel and 30 μg EE (66).

Observational studies have shown that similar to users of COCs, ring users have an elevated risk of VTE compared with

non-users of hormonal contraception (67). A retrospective cohort study from Denmark found a slightly increased risk of VTE among users of the vaginal ring compared with users of COCs containing levonorgestrel (RR 1.9; 95% CI, 1.3 to 2.7) (67). However, a large retrospective cohort study, using data from four US health plans, which separated new from established users, showed no difference in VTE risk among vaginal ring users compared with COC users; the incidence of VTE events among vaginal ring users was 11.3 per 10,000 women per year (55). A large, European prospective observational study similarly found no increased risk of VTE among vaginal ring users compared with COC users (HR 0.8; 95% CI, 0.5–1.5) (68). The evidence, therefore, suggests that the risk of VTE related to the vaginal ring is similar, neither decreased nor increased, from oral CHC.

There has been controversy as well regarding the transdermal CHC patch which contains 6 mg norelgestromin (the active metabolite of norgestimate, a third-generation progestin) and 0.75 mg EE, and delivers approximately 150 μg of norelgestromin and 20 μg of EE per day (69). The amount of estradiol and progestin delivered has been considered equivalent to an oral pill containing 250 μg norgestimate and 35 μg EE; however, pharmacokinetic studies have shown that the systemic exposure is higher but the peak levels are lower with the transdermal patch (70, 71).

Post-marketing studies comparing the risks of VTE among users of the transdermal patch and combined oral contraception have shown conflicting results. Three case-control studies (including a follow-up to the first study that added 56 additional cases) showed no difference in VTE risk between users of the transdermal patch compared with users of comparable combined oral contraception containing the progestins norgestimate and levonorgestrel (72–75). However, a third case-control study found a higher risk in transdermal patch users, with an incidence rate of 2.2 (95% CI, 1.3–3.8) (76). More recent studies have also demonstrated inconsistent results. A case-control study of 152 women with thrombotic or cardiovascular events and 606 matched controls found a 2-fold higher increase in transdermal patch users compared with users of COCs containing norgestimate (RR 2.0; 95% CI, 1.2–3.3) (77). However, the same large, US retrospective cohort study discussed above (which found no difference in VTE risk among vaginal ring users) also found no increased risk of VTE among transdermal patch users, with an overall incidence of VTE of 12.3 per 10,000 woman-years for patch users (55).

Summary statement. All of the studies addressing this question were Level II-III.

- There is insufficient evidence that the contraceptive patch or contraceptive vaginal ring has a different risk of VTE compared with COCs. (Grade C)

Are Smoking, Obesity, or Inherited Thrombophilias Risk Factors for VTE in CHC Users?

Several Level II and III studies have identified risk factors associated with VTE. However, determining to what degree a specific risk factor increases the risk of VTE is difficult as these studies are heterogeneous, are often affected by biases, and analyze risk factors as confounders rather than as primary predictors of outcomes. But, a number of risk factors have been found in multiple studies examining the risk of VTE in oral contraceptive users, including prolonged immobilization, age over 35 years, increased body mass index (BMI) in patients over 35 years, personal history of VTE, family history of deep vein thrombosis (DVT), inherited thrombophilia (most commonly factor V Leiden or prothrombin G20210A) mutation, antiphospholipid syndrome, active systemic lupus, and current cancer diagnosis. None of these risk factors increases the risk of VTE more than pregnancy (5–20/10,000 woman-years); however, they are additive.

The overall likelihood of VTE is greatest in the postpartum period for 6 weeks (approximately 40–65 per 10,000 woman-years, and is increased until 12 weeks) (1, 78). Women with familial thrombophilia syndromes, including factor V Leiden mutation, prothrombin G20210 A mutation, protein C, protein S, or antithrombin deficiency, have a several-fold increased risk of VTE (depending on the type of thrombophilia), and oral contraceptive use further increases the risk of thrombosis in these patients (9, 15, 28, 43, 62, 65, 79–84). One population-based case-control study found that among women with thrombophilia, the risk of developing DVT during the first 6 months of oral contraceptive use (compared with prolonged use) was increased 19-fold (95% CI, 1.9–175.7), and in the first year of use, it was increased 11-fold (95% CI, 2.1–57.3) (83). Given the rarity of fatal VTE, one group of investigators concluded that screening more than 1 million CHC candidates for thrombophilia would at best prevent two oral contraceptive-associated deaths (85). Therefore, the Centers for Disease Control and Prevention (CDC) does not recommend screening for thrombophilias with laboratory testing during routine care (Table 1) (86).

Other factors associated with VTE in those women who use CHCs include smoking, age, and obesity, although smoking and obesity alone are weak risk factors for VTE. Women who smoke, particularly more than 15 cigarettes daily, have a greater risk (18, 20, 26, 31, 32, 34, 37, 39, 40, 49, 54, 87, 88). This risk increases substantially if women are over age 35 years and smoke, as age has been found to be an independent risk factor for VTE in several studies (10, 12–14, 18, 20, 23, 31, 39, 43, 44, 51, 80, 87). Given the increasing epidemic of obesity in the United States and even worldwide, the association between obesity and thrombosis is particularly important. Some studies have revealed that oral contraceptive use further increases the effect of obesity on the risk of thrombosis leading up to a 10-fold increased risk of VTE among obese oral contraceptive users compared with non-users (12, 22, 24, 26, 31, 32, 34, 40, 49, 54, 59, 60, 64, 65, 88–91).

Summary statement. Several level II and III studies have identified risk factors associated with VTE; however, determining to what degree a specific risk factor increases the

risk of VTE is difficult as these studies are heterogeneous and are often confounded by biases.

- There is fair evidence that tobacco use, age (>35 years), obesity, and the presence of hereditary thrombophilias (including factor V Leiden mutation, prothrombin G20210A mutation and protein C, protein S, or antithrombin deficiency) increase the risk of thrombotic events in the setting of CHC use. (Grade B)

CONCLUSIONS

While VTE is a rare event in young women of reproductive age (1–5/10,000 woman-years), COCs increase the risk of VTE. Women taking preparations containing drospirinone and third-generation progestins appear to be at slightly increased risk of VTE compared with those taking first- and second-generation preparations. Nonetheless, the overall risk of VTE even with these preparations is low, approximately 10–15 VTE/10,000 women. The benefits of any currently available COC to prevent pregnancy outweighs the risks for most women. It is important to recognize that the risk of VTE is substantially higher in pregnancy (5–20/10,000 woman-years) and postpartum (40–65/10,000 women years) than in women on CHC. Nonetheless, when selecting a particular CHC preparation, any potential increased risk of VTE should be balanced with the potential benefits associated with each preparation.

SUMMARY

- High-dose combined oral contraception (>50 μg) is associated with higher risks of VTE than lower-dose formulations. (Grade B)
- Evidence is conflicting whether preparations of COC with 50 μg EE have a higher risk of thrombosis compared with sub-50 μg EE formulations, although several large studies have seen an increased risk of VTE in 50 μg EE COCs. (Grade B)
- There is no reliable evidence that EE doses lower than 35 μg have less VTE risk than 35 μg formulations. (Grade B)
- There is fair evidence that preparations of COCs with drospirenone or third-generation progestins have only a slightly higher risk of VTE compared with those containing norethindrone or levonorgestrel. (Grade B)
- There is insufficient evidence that the contraceptive patch or contraceptive vaginal ring has a different risk of VTE compared with COCs. (Grade C)
- There is fair evidence that tobacco use, age (>35 years), obesity, hypertension, and the presence of hereditary thrombophilias (including factor V Leiden mutation, prothrombin G20210A mutation and protein C, protein S, or antithrombin deficiency) increase the risk of thrombotic events in the setting of CHC use. (Grade B)

RECOMMENDATION

- In the patient in whom combined hormonal contraception is appropriate, it is reasonable to use any currently available preparation.

Acknowledgments: This report was developed under the direction of the Practice Committee of the American Society for Reproductive Medicine as a service to its members and other practicing clinicians. Although this document reflects appropriate management of a problem encountered in the practice of reproductive medicine, it is not intended to be the only approved standard of practice or to dictate an exclusive course of treatment. Other plans of management may be appropriate, taking into account the needs of the individual patient, available resources, and institutional or clinical practice limitations. The Practice Committee and the Board of Directors of the American Society for Reproductive Medicine have approved this report.

This document was reviewed by ASRM members and their input was considered in the preparation of the final document. The Practice Committee acknowledges the special contribution of Steven Sondheimer, MD, Kathleen O'Neill, MD, and Rachel Weinerman, MD, in the preparation of this document. The following members of the ASRM Practice Committee participated in the development of this document. All Committee members disclosed commercial and financial relationships with manufacturers or distributors of goods or services used to treat patients. Members of the Committee who were found to have conflicts of interest based on the relationships disclosed did not participate in the discussion or development of this document.

Samantha Pfeifer, M.D.; Samantha Butts, M.D., M.S.C.E.; Daniel Dumesic, M.D.; Gregory Fossum, M.D.; Clarisa Gracia, M.D., M.S.C.E.; Andrew La Barbera, Ph.D.; Jennifer Mersereau, M.D.; Randall Odem, M.D.; Alan Penzias, M.D.; Margareta Pisarska, M.D.; Robert Rebar, M.D.; Richard Reindollar, M.D.; Mitchell Rosen, M.D.; Jay Sandlow, M.D.; Rebecca Sokol, M.D., M.P.H.; Michael Vernon, Ph.D.; Eric Widra, M.D.

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