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Oral Contraceptives and the Risk of Venous Thromboembolism: An Update

This clinical practice guideline has been reviewed by the Clinical Practice Gynaecology Committee and approved by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

PRINCIPAL AUTHOR

Robert Reid, MD, Kingston, ON

CLINICAL PRACTICE GYNAECOLOGY COMMITTEE

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Vyta Senikas, MD, Ottawa ON

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Abstract

Objective: To provide current and emerging evidence on oral contraceptives and the risk of venous thromboembolism.

Evidence: Articles published in English from 2005 were retrieved through searches of PubMed and Medline, using the following terms: venous thromboembolism, VTE, contraception, oral contraceptives, hormonal contraception. Results were restricted to systematic reviews, randomized control trials/controlled clinical trials, and observational studies. Searches were updated on a regular basis and incorporated in the guideline to May 2010. Grey (unpublished) literature was identified through searching the websites of health technology assessment and health technology assessment-related agencies, clinical practice guideline collections, clinical trial registries, and national and international medical specialty societies.

Values: The quality of evidence was rated using the criteria described by the Canadian Task Force on Preventive Health Care (Table).

Summary Statements

1. Modern oral contraceptives offer highly effective contraception and a range of non-contraceptive benefits. (I)
2. Venous thromboembolism, although rare, remains one of the serious adverse consequences of hormonal contraception. Best evidence indicates that venous thromboembolism rates in non-users of reproductive age approximate 4–5/10 000 women per year; rates in oral contraceptive users are in the range of 9–10/10 000 women per year. For comparison, venous thromboembolism rates in pregnancy approach 29/10 000 overall and may reach 300–400/10 000 in the immediate postpartum period. (II-1)
3. Research demonstrates that oral contraceptives with ≤ 35 µg of ethinyl estradiol carry a lower risk of venous thromboembolism than oral contraceptives with 50 µg. (II-2) Although preliminary data suggest a possible further reduction in venous thromboembolism with oral contraceptives with < 35 µg ethinyl estradiol, robust data to support this conclusion are presently lacking.
4. Recent contradictory evidence and the ensuing media coverage of the venous thromboembolism risk attributed to the progestin component of certain newer oral contraceptive products have led to fear and confusion about the safety of oral contraceptives in general and drospirenone-containing oral contraceptives in particular. “Pill scares” of this nature have occurred in the past, with panic stopping of the pill, increased rates of unplanned pregnancy, and no subsequent decrease in venous thromboembolism rates. (II-3)
5. Two high quality research studies that addressed the venous thromboembolism risk associated with various oral contraceptives found comparable venous thromboembolism rates with drospirenone-containing oral contraceptives and other approved products. (II-1)
6. Two reports suggesting an increased risk of venous thromboembolism with drospirenone-containing oral contraceptives have significant

Key Words: Venous thromboembolism, VTE, contraception, oral contraceptives, hormonal contraception

Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care

Quality of evidence assessment*	Classification of recommendations†
I: Evidence obtained from at least one properly randomized controlled trial	A. There is good evidence to recommend the clinical preventive action
II-1: Evidence from well-designed controlled trials without randomization	B. There is fair evidence to recommend the clinical preventive action
II-2: Evidence from well-designed cohort (prospective or retrospective) or case–control studies, preferably from more than one centre or research group	C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category	D. There is fair evidence to recommend against the clinical preventive action
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	E. There is good evidence to recommend against the clinical preventive action
	L. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

*The quality of evidence reported in these guidelines has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.[35]
†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the The Canadian Task Force on Preventive Health Care.[35]

methodological flaws that render their conclusions suspect. It seems likely that residual confounding could have distorted both the results and the conclusions of these reports. (II-3)

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INTRODUCTION

Modern oral contraceptives afford not only excellent contraception but also a variety of non-contraceptive benefits, ranging from regulation and reduction of both menstrual bleeding and dysmenorrhea to treatment of premenstrual syndrome, menstrual migraines, acne, and hirsutism. Long-term benefits include reduced rates of endometrial, ovarian, and colorectal cancer.[1] Modern OCs are well tolerated (serious side effects are rare), and adherence to prescribed regimens is generally excellent. As a result, OC users are able to prevent pregnancy and the considerable risks associated with being pregnant while enjoying the non-contraceptive benefits of hormonal contraception.

ABBREVIATIONS

FDA	US Food and Drug Administration
OC	oral contraceptives
VTE	venous thromboembolism

VENOUS THROMBOEMBOLISM

Risk Factors

Venous thromboembolism is a rare but potentially serious condition, usually involving a blood clot in the deep veins of the legs or pelvis. If the clot breaks away into the circulation it may block blood flow to the lungs (pulmonary embolism) with potentially fatal consequences. Known risk factors for VTE include advancing age,[2] cigarette smoking,[3] immobility (such as that associated with travel or hospitalization),[4] obesity,[5] and pregnancy and the peripartum period.[6,7]

Hormonal Effects on Venous Thromboembolism

Hormonal contraceptives increase the risk of VTE above the background rate (from 5/10 000 woman years in non-users[8] to 9–10/10 000 woman years in OC users[9]).

To keep the risks of VTE for OC users in perspective, it is important to remember that the risk of VTE in pregnancy may reach 29/10 000,[9,10] and in the peripartum period the risk has been reported to be as high as 300–400/10 000.[6,7] Among the most widely used and effective contraceptive methods, OCs reduce rates of unplanned pregnancies and actually decrease the overall rate of VTE in the population compared with rates in populations without access to effective contraception.[11]

Older OCs, which contained higher levels of estrogen, carried a slightly greater risk than currently available OCs, most of

which contain < 50 μg of ethinyl estradiol. Sub-50 μg pills have a lower risk of VTE than pills with ≥ 50 μg.[12] Although, in theory, greater reductions in the dosage of estrogen might further decrease the risk of VTE, this benefit has not been clearly established. A non-significant decrease in VTE was noted in the European Active Surveillance Study when OCs containing 30μg ethinyl estradiol were compared with those containing 20μg.[9] Lidegaard et al.[13] also reported that "a reduction in estrogen dose from 30–40 μg to 20 μg for OCs containing desogestrel or gestodene reduced the risk of venous thromboembolism by 18%"; however, the validity of the VTE diagnoses in the Danish National Patient Registry (1 of 4 registries used by the Lidegaard et al. study) has been questioned.[14]

Many pills with ethinyl estradiol levels lower than 35 μg are currently on the market, and although they may be associated with fewer estrogen-related nuisance side effects (such as nausea or breast tenderness) in the first months of use, no conclusive data exist to establish that they result in a lower risk of VTE. Pills with ≤ 20 μg of ethinyl estradiol have the potential to cause more breakthrough (unscheduled) bleeding, and this may be a deterrent to consistent use for some women.[15]

Innovations in hormonal contraception in recent years have largely involved the use of new progestins, and this has brought the progestin component of the OC under increasing scrutiny. New progestins are, in part, responsible for some of the most desired non-contraceptive benefits, while maintaining a low risk of serious side effects.

Third generation pills have been promoted as being less androgenic and as possibly having fewer adverse effects on cardiovascular and metabolic parameters and therefore as being safer than existing pills. Shortly after the introduction of these third generation pills, reports of a possible increased risk of VTE began to appear, bringing the progestin component of these pills under scrutiny. A phenomenon called "stimulated reporting" occurred: physicians with patients on these new pills were more likely to send their patients for assessment of any leg pain and more likely to report any VTE episodes to regulatory authorities because of heightened awareness of the possible risk. What followed was the "pill scare" in 1995, when regulatory authorities issued an alert about the possible increased risk of VTE with third generation pills. The abrupt rise in births and abortions[16,17] (each associated with an increased risk of VTE) that resulted from unplanned pregnancies indicated that many women stopped taking OCs because of this scare. The history of this unfortunate episode is well-documented.[18,19] Subsequent analysis and/or replication has shown systematic error in the epidemiological studies that examined VTE risks. The precise effects of different hormonal contraceptives on the hemostatic system continue to be studied and debated,[20] but because there were no compelling data demonstrating an increased risk, third generation pills remain on the market and are widely prescribed.[21]

Assessing Venous Thromboembolism Risks of Oral Contraceptives

VTE remains one of the few serious side effects of OC use. Because VTE is so rare, valid information about the risks associated with a given pill cannot be adequately gleaned from pre-marketing research, which may involve only 1000 to 3000 women. Information on serious but rare side effects like VTE must come from post-marketing surveillance.

The current Canadian system requires that health care providers voluntarily report unexpected or severe adverse reactions to drugs to Health Canada. Although such a system can alert regulatory authorities to rare unexpected side effects of a medication, it cannot provide valid information about the rates of complications or inform consumers about the comparative risks of available products. This is because newer products tend to be prescribed for women who already have risk factors. For example, drospirenone-containing pills, which are effective in reducing acne and hair growth, tend to be prescribed for women who are obese and who therefore already have an independent risk factor for a blood clot. Isolated reports of serious side effects of a specific OC may motivate health care providers to be more vigilant in looking for and reporting similar cases (stimulated reporting). Numerators in adverse event reporting are therefore selectively biased towards certain products, which may give a misleading impression of risk. Since denominators (the number of women using a particular product) and risk factors in the entire population of women prescribed a specific type of OC are unknown, voluntary reports of individual cases cannot provide valid information on comparative risks for rare but serious side effects.

Another suggested methodology is to try to obtain more comprehensive data by retrospectively searching large databases for use of specific products and establish links between their use and complications like VTE. These techniques may be useful if the original data set includes information on age, weight, duration of use, etc., which are important independent risk factors that might influence risks for VTE. In the absence of quality data on such variables, it is possible that a risk apparently associated with a specific OC is actually associated with the characteristics of the women who were taking that OC. Databases, especially those developed for administrative purposes, may lack adequate validation of discharge diagnoses. A 2010 study has shown that conditions signed out as VTEs in an administrative database are often found to be something else when testing is completed.[14] A valid comparison of VTE risk with

different OCs must consider the fact that the risk for VTE is greatest in the first months of use and declines thereafter.[9,22–24] This same effect was noted in the largest randomized clinical trial to examine VTE in menopausal women receiving hormone therapy at the time of menopause.[25] Comparisons of the VTE risks for different OCs must account for duration of use and ensure that new users of one pill are truly being compared with new users of the other pill.

RECENT RESEARCH

Legitimate information on these rare risks is most likely to come from research that uses a prospective approach with subjects who are all new users of various OCs. Careful follow-up by active surveillance (regular patient contact) and validation of all suspected cases (through examination of the medical records) is critical.

The European Active Surveillance Study was conducted by the manufacturer of a new drospirenone-containing OC with an independent advisory board and after approval by European regulatory authorities. This prospective non-interventional active surveillance study followed 59 674 new users of different OCs for a total of 142 475 woman years, with a loss to follow-up of only 2.4%. The study demonstrated that drospirenone-containing OCs were prescribed more often to heavier women and that despite this there was no difference in VTE rates between users of this new drospirenone- containing OC and other OCs.

Another large prospective study used a propensity (risk factor) scoring system to match new users of different pills according to baseline VTE risk.[26,27] This study matched new OC prescriptions (drospirenone-containing OCs vs. other OCs in a 2:1 ratio) and evaluated the medical records of all potential VTE episodes. No differences in VTE rates were found between drospirenone-containing OCs and other OCs.

Recent publicity about class action litigation in the US and Canada over complications related to drospirenone-containing OCs has again raised questions about whether VTE rates are higher with drospirenone-containing OCs. Critical analysis of the 2 studies responsible for this adverse publicity,[13,28] however, suggests that the conclusions could have resulted from methodologic flaws and/or misinterpretation of findings, a view shared by the FDA.[29]

The Dutch Mega Study,[28] a retrospective case-control study, was designed to evaluate environmental and genetic factors influencing VTE and the effects of different OCs on VTE. Controls were found in an unusual way: many were the partners of men who were seen in a thrombosis clinic, and the remainder were recruited through random-digit dialling. The authors showed hazard ratios for various OCs with wide and overlapping 95% confidence intervals indicating no statistically significant differences between drospirenone and so-called second generation progestins. Duration of use information was not available on all women, so it is not clear that all were new users. In addition, the risk estimates were not adjusted for important risk factors (such as obesity). Despite this the authors concluded that second generation OCs were safer than third generation as far as VTE was concerned. The FDA has recently revised the product labelling for a drospirenone-containing OC, and with respect to the Dutch Mega Study notes that "The number of [drospirenone-containing OC] cases (in the Dutch Mega Study) was very small (1.2% of all cases) making the risk estimates unreliable."[29]

The other study reporting increased rates of VTE with drospirenone-containing and other third generation OCs was a large Danish national cohort study.[13] It consisted of a retrospective examination of Danish women who had prescriptions for hormonal contraception and subsequent hospital diagnostic codes for deep vein thrombosis between 1995 and 2005 in a number of interrelated databases maintained by the Danish national health service. This comprehensive data set included 3.4 million woman years of hormonal contraceptive use. The investigators identified 2045 hormonal contraceptive-related VTEs during this time period. In keeping with prior reports, they found that the risk of VTE decreased with duration of use and with pills containing lower estrogen dosages. In contrast to the prospective studies reported above, they found that drospirenone-containing OCs and other third generation OCs (those containing desogestrel, gestodene) carried an increased risk of VTE compared with levonorgestrel-containing OCs. Several significant methodological weaknesses have been identified since the publication of that report.[13] First, detailed information on confounders such as obesity was not available for the analysis. This is important: obesity rates in the Danish population have almost tripled in the past decade, and evidence from other research suggests that obese women are more likely to be prescribed drospirenone-containing OCs because of the perceived beneficial effects on androgenic symptoms that affect many obese women and on body weight (diuretic effect). In addition, the investigators had no information on OC use before 1995. Therefore, they classified all levonorgestrel use in 1995 as short-term use, but others have estimated that 60% of those levonorgestrel users should have been classified as long-term users.[30] Supporting this premise was the finding that the expected first year elevation of VTE risk was seen with all OCs except the levonorgestrel products.

More importantly, the incidence of VTE could not reliably be assessed in the Danish registry.[14] Severinsen et al.[14] examined the medical records of patients with a diagnosis of

VTE in the same Danish registry used for the Lidegaard et al.[13] study and could confirm only 31% of diagnoses made through emergency room visits and only 71% of those made in women admitted to the ward for diagnostic testing. The Danish database was designed as an administrative database rather than as a medical research database, and the diagnostic codes were primarily intended to capture costs related to hospitalization. Many physicians were incorrectly entering a diagnostic code for VTE rather than the intended code of "admitted for evaluation of possible VTE."[14]

The increased rate ratio of VTEs with drospirenone-containing OCs compared with levonorgestrel containing OCs was 1.64 (95% CI 1.27 to 2.10). With the potential methodological issues identified above and with rate ratios that in epidemiological terms are very small (relative risks of ≤ 2), it is extremely difficult to exclude bias or residual confounding as the explanation for the findings.[30–33] Despite the recent serious allegations about the validity of the VTE diagnostic codes in the Danish database, the authors of this research have yet to acknowledge the possibility that their data were invalid and their conclusions incorrect.[34] The new FDA-endorsed product labelling for a drospirenone-containing OC addresses the Lidegaard et al. study and concludes, "The risk estimates may not be reliable because the analysis may include women of varying risk levels."[29]

CONCLUSION

The highest quality scientific studies evaluating the risk of VTE in OC users show a baseline risk of approximately 4–5/10 000 woman years in women who do not use hormonal contraception. In the absence of reliable contraception, women of reproductive age face risks of VTE associated with pregnancy of up to 29/10 000 woman years, and in the immediate postpartum period this risk is as high as 300–400/10 000 woman years. Prospective observational studies have shown that all currently available OCs increase the risk of VTE to the range of 9–10/10 000 woman years of use and that this risk is highest in the first months of use, with a fall towards baseline risk thereafter. Modern OCs offer excellent contraceptive efficacy, and adherence is good because of their many non-contraceptive benefits. The occurrence of serious risks such as VTE, including pulmonary embolism, are rare with contemporary OCs, but individualized risk assessment should always be unertaken to identify women who would be better advised to use other forms of contraception. For most healthy women of reproductive age, the benefits of OCs will outweigh the risks.

Summary Statements

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6. Two reports suggesting an increased risk of venous thromboembolism with drospirenone-containing oral contraceptives have significant methodological flaws that render their conclusions suspect. It seems likely that residual confounding could have distorted both the results and the conclusions of these reports. (II-3)

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