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Review article

Superficial venous disease and combined hormonal contraceptives: a systematic review☆

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Abstract

Background: Superficial venous disease, which includes superficial venous thrombosis (SVT) and varicose veins, may be associated with a higher risk of venous thromboembolism (VTE). Use of combined hormonal contraceptives (CHCs) has been associated with an increased risk of VTE compared with nonuse. Little is known about whether use of CHCs by women with superficial venous disease may further elevate the risk of VTE.

Objectives: To investigate evidence regarding risk of VTE in women with SVT or varicose veins who use CHCs compared with non-CHC users.

Methods: We searched the PubMed database for all English-language articles published from database inception through September 2014. We included primary research studies that examined women with SVT or varicose veins who used CHCs compared to women with these conditions who did not use CHCs. Outcomes of interest included VTE (among women with SVT or varicose veins) and SVT (for those with varicose veins).

Results: Two studies were identified that met inclusion criteria. One fair-quality case–control study reported an odds ratio (OR) for VTE of 43.0 (95% confidence interval [CI] 15.5–119.3) among women with SVT using oral contraceptives (OCs) compared with nonusers without SVT. The OR for VTE was also increased for women with SVT not using OCs (OR 5.1; 95% CI 2.8–9.5) and for women without SVT using OCs (OR 4.0; 95% CI 3.3–4.7), compared with nonusers without SVT. One fair-quality cohort study demonstrated that women with varicose veins had an increased rate of VTE with use of OCs (1.85 per 1000 women-years [WY]), compared with users without varicose veins (0.84 per 1000 WY), nonusers with varicose veins (0.31 per 1000 WY) and nonusers without varicose veins (0.19 per 1000 WY). This study also demonstrated that women with varicose veins had an increased rate of SVT with use of OCs (10.63 per 1000 WY), compared with nonusers with varicose veins (7.59 per 1000 WY), users without varicose veins (1.89 per 1000 WY) and nonusers without varicose veins (0.77 per 1000 WY).

Conclusion: Two studies suggest increased risk of VTE among OC users with superficial venous disease; however, no definitive conclusions can be made due to the limited number of studies and limitations in study quality. Theoretical concerns need to be clarified with further research on whether the risk of significant sequelae from superficial venous disease among CHC users is related to clinical severity of disease and underlying factors.

Keywords: Superficial venous disease; Superficial venous thrombosis; Varicose veins; Oral contraceptives; Systematic review

1. Introduction

Superficial venous disease includes varicose veins and superficial venous thrombosis (SVT) [1]. The prevalence of varicose veins among women ranges widely in published literature from less than 1% to 73%, with more recent studies demonstrating prevalences of approximately 30% [2]. The incidence of SVT is not well studied, but the preponderance (60%–80% of cases) occurs in women [3–5]. Although once thought to be fairly benign, SVT has increasingly been found to be associated with venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE) [1]. Use of combined hormonal contraceptives (CHCs) increases the risk of VTE in healthy women compared with nonusers [6]. Given that SVT and CHCs may be independent risk factors for VTE, there is theoretical

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concern that use of CHCs in women with SVT might further elevate the risk of VTE.

The World Health Organization's (WHO) Medical Eligibility Criteria for Contraceptive Use (MEC) currently recommends that women with varicose veins can use CHCs (MEC Category 1) and women with superficial thrombophlebitis generally can use CHCs (MEC Category 2) [7]. This systematic review was conducted as part of the process of updating the MEC. We sought evidence regarding whether CHCs increase the risk of VTE in women with superficial venous disease. Our specific question was whether women with superficial venous disease who use CHCs have a higher risk of VTE than women with superficial venous disease who do not use CHCs.

2. Materials and methods

We conducted this systematic review according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [8].

2.1. Literature search

We searched the PubMed database for all relevant articles published from database inception through September 2014 using the following search strategies:

Search strategy for SVT:
((“Thrombophlebitis”[Mesh] OR superficial thrombophlebitis OR superficial vein thrombosis OR superficial venous thrombosis)) AND (((((((((“Contraceptives, Oral”[Mesh]) OR “oral contraceptives”)) OR oral contracept*))) OR (“Ortho Evra”[Supplementary Concept] OR ortho evra OR “contraceptive patch” OR “transdermal patch”)) OR (“NuvaRing”[Supplementary Concept] OR nuvaring OR “vaginal ring”)) OR (((once a month OR monthly) AND inject*) AND contracept* OR cyclofem OR lunelle OR mesigyna OR cycloprovera))

Search strategy for varicose veins:
((“Varicose Veins”[Mesh] OR varicose vein* OR varicosit*)) AND ((((((((((“Contraceptives, Oral”[Mesh]) OR “oral contraceptives”)) OR oral contracept*))) OR (“Ortho Evra”[Supplementary Concept] OR ortho evra OR “contraceptive patch” OR “transdermal patch”)) OR (“NuvaRing”[Supplementary Concept] OR nuvaring OR “vaginal ring”)) OR (((once a month OR monthly) AND inject*) AND contracept* OR cyclofem OR lunelle OR mesigyna OR cycloprovera)) AND Humans[Mesh])

We searched for all primary research articles published in any language. We excluded articles published in non-English languages that did not have an English abstract. We also searched reference lists of identified articles and relevant review articles for additional citations of interest. We did not consider unpublished studies, abstracts of conference presentations or dissertations.

2.2. Selection criteria

Articles were included in this review if they were primary reports on studies examining women with SVT or varicose veins using CHCs (pills, patches, rings and injectables containing both ethinyl estradiol and a progestin). Outcomes of interest among women with SVT included venous thromboembolic complications, including DVT and PE. Outcomes of interest among women with varicose veins included VTE and SVT. We included studies that examined women using unspecified formulations of oral contraceptives (OCs); while some of these women may have been using progestin-only formulations, we assume that the great majority of women would have been using combined formulations.

2.3. Study quality assessment and data synthesis

Two authors (N.T. and K.C.) summarized and systematically assessed the evidence. We assessed the quality of each individual piece of evidence using the system developed by the United States Preventive Services Task Force (USPSTF) [9,10]. Summary measures were not calculated.

3. Results

3.1. Women with SVT

The search identified 572 articles, of which one article met the criteria for inclusion (Table 1) [11]. The remaining articles were excluded because they addressed DVT but not SVT, were review articles, or otherwise did not address the question of interest. The included study examined the risk of VTE in women with SVT using OCs (not further specified). The analysis was a substudy of the Multiple Environmental and Genetic Assessment (MEGA) study, a large case–control study examining risk factors for VTE conducted in the Netherlands. For this analysis, cases were premenopausal women aged 18–50 years with a first episode of VTE recruited from anticoagulation clinics. Partner controls were female partners of male VTE cases; these controls were also aged 18–50 years with no history of VTE. Community controls were recruited by random digit dialing and matched by age and sex. Information on OC use in the month before and SVT at any time before VTE (cases) or before interview (controls) was obtained by participant questionnaires. DVT and PE diagnoses were obtained by review of hospital discharge reports and general practitioner records, including confirmatory radiologic studies. Odds ratios (ORs) for VTE were highest in women with a history of SVT who used OCs, compared with non-OC users with no history of SVT. Among women with SVT using OCs, OR for VTE was 43.0 (95% confidence interval [CI] 15.5–119.3) compared with nonusers without SVT. The OR for VTE was also increased for women with SVT not using OCs (OR 5.1; 95% CI 2.8–9.5) and for women without SVT using OCs (OR 4.0; 95% CI 3.3–4.7), compared with nonusers without SVT. Similar trends were seen for DVT alone, PE alone and DVT with

Table 1
Evidence for risk of VTE in users of CHCs who have superficial venous disease.

<table>
<tr><th>Author, year, location, support</th><th>Study Design</th><th>Population</th><th>Contraceptive</th><th>Results</th><th>Strengths</th><th>Weaknesses</th><th>Quality Grading</th></tr>
<tr><td>RCGP [12], 1978

United Kingdom

Medical Research Council, Royal College of General Practitioners, Organon Laboratories Ltd, Ortho Pharmaceutical Corp, Schering Chemicals Ltd, G.D. Searle and Co. Ltd, Syntex Pharmaceuticals Ltd, and John Wyeth and Brother Ltd</td><td>Prospective cohort</td><td>OC users: Women currently using OCs recruited from general practitioners

Controls: Non–users matched for age and marital status</td><td>OCs (not further specified)</td><td>Risk of DVT:
<table><tr><th>Varicose veins</th><th>Users (N)</th><th>Users (Rate/1000 WY)</th><th>Non–users (N)</th><th>Non–users (Rate/1000 WY)</th><th>Rate ratio*</th></tr><tr><td>Yes</td><td>9</td><td>1.85</td><td>3</td><td>0.31</td><td>5.97</td></tr><tr><td>No</td><td>30</td><td>0.84</td><td>9</td><td>0.19</td><td>4.42</td></tr><tr><td>Rate ratio</td><td></td><td>2.20 (p<0.05)</td><td></td><td>1.66 (NS)</td><td></td></tr></table>* Calculated by review authors

Risk of SVT:
<table><tr><th>Varicose veins</th><th>Users (N)</th><th>Users (Rate/1000 WY)</th><th>Non–users (N)</th><th>Non–users (Rate/1000 WY)</th><th>Rate ratio*</th></tr><tr><td>Yes</td><td>54</td><td>10.63</td><td>72</td><td>7.59</td><td>1.40</td></tr><tr><td>No</td><td>67</td><td>1.89</td><td>36</td><td>0.77</td><td>2.45</td></tr><tr><td>Rate ratio</td><td></td><td>5.62 (p<0.005)</td><td></td><td>9.87 (p<0.005)</td><td></td></tr></table>* Calculated by review authors</td><td>Excluded women with certain risks for VTE

Rates standardized for age, parity, smoking, and social class</td><td>Varicose veins, SVT and VTE diagnoses from general practitioners, not verified by review of radiologic studies

No information on OC type

OC use reported by general practitioners without additional verification

Small numbers for comparisons of interest</td><td>II–2, fair</td></tr>
<tr><td>Roach [11], 2013

Netherlands

Netherlands Heart Foundation, Dutch Cancer Foundation, Netherlands Organization for Scientific Research</td><td>Case–control</td><td>Women ages 18–50

Cases: from anticoagulation clinic with first DVT or PE

Partner controls: partners of male patients

Community controls: random digit dialing, age and sex matched</td><td>OCs (not further specified)

Use in month before VTE (cases) or interview (control)</td><td>Odds of VTE:
<table><tr><th>SVT history</th><th>OC use</th><th>Cases (N)</th><th>Controls (N)</th><th>VTE aOR* (95% CI)</th></tr><tr><td>Negative</td><td>No</td><td>416</td><td>1046</td><td>Ref</td></tr><tr><td>Negative</td><td>Yes</td><td>902</td><td>642</td><td>4.0 (3.3–4.7)</td></tr><tr><td>Positive</td><td>No</td><td>41</td><td>18</td><td>5.1 (2.8–9.5)</td></tr><tr><td>Positive</td><td>Yes</td><td>86</td><td>5</td><td>43.0 (15.5–119.3)</td></tr></table><table><tr><th>SVT history</th><th>OC use</th><th>DVT aOR* (95% CI)</th></tr><tr><td>Negative</td><td>No</td><td>Ref</td></tr><tr><td>Negative</td><td>Yes</td><td>4.4 (3.6–5.4)</td></tr><tr><td>Positive</td><td>No</td><td>5.1 (2.5–10.5)</td></tr><tr><td>Positive</td><td>Yes</td><td>46.8 (16.5–133.0)</td></tr></table><table><tr><th>SVT history</th><th>OC use</th><th>DVT withPE aOR* (95% CI)</th></tr><tr><td>Negative</td><td>No</td><td>Ref</td></tr><tr><td>Negative</td><td>Yes</td><td>7.1 (4.1–12.5)</td></tr><tr><td>Positive</td><td>No</td><td>12.5 (3.6–43.3)</td></tr><tr><td>Positive</td><td>Yes</td><td>100.4 (24.2–416.0)</td></tr></table><table><tr><th>SVT history</th><th>OC use</th><th>PE aOR* (95% CI)</th></tr><tr><td>Negative</td><td>No</td><td>Ref</td></tr><tr><td>Negative</td><td>Yes</td><td>3.5 (2.7–4.5)</td></tr><tr><td>Positive</td><td>No</td><td>4.3 (1.9–10.0)</td></tr><tr><td>Positive</td><td>Yes</td><td>33.2 (10.9–101.5)</td></tr></table>* aOR adjusted for age, BMI, smoking, family history VTE.</td><td>VTE confirmed by radiology results from hospital discharge and general practitioners</td><td>Information on SVT obtained via questionnaire, not objectively verified

Information on OC use obtained via questionnaire

No information on timing, location or severity of SVT

No information on OC type

Small numbers and wide confidence intervals for some OR</td><td>II–2, fair</td></tr>
</table>

Abbreviations: aOR, adjusted OR; BMI, body mass index; NS, not significant; RCGP, Royal College of General Practitioners.

concomitant PE (Table 1). Among women with SVT, the OR of VTE (calculated for purposes of this review) was 8.4 among OC users compared with nonusers.

3.2. Women with varicose veins

The search identified 108 articles, of which one article met the criteria for inclusion (Table 1) [12]. The remaining articles were excluded because they addressed the development of varicose veins in healthy women, were review articles, or otherwise did not address the question of interest. The included study examined the risk of DVT or SVT in women with varicose veins using OCs (not further specified). The analysis used data from the Royal College of General Practitioners' (RCGP) Oral Contraception Study,

a prospective cohort study of OC users. Women using OCs were recruited from many general practices in the United Kingdom. Women not using OCs and matched for age and marital status were recruited from the same general practices. Information on varicose veins, SVT and DVT was obtained by report from the general practitioners, without medical record review by study authors (personal communication with study authors). Information on OC use was reported by the general practitioners [13]. The rate of DVT or SVT was highest among women with varicose veins who used OCs. For the outcome of DVT, among women with varicose veins without other thrombotic risk factors, the rate of DVT was 1.85 per 1000 women-years (WY) in OC users and 0.31 per 1000 WY in nonusers, for a rate ratio of 5.97 (calculated for purposes of this review). Among women without varicose veins, the rate of DVT was 0.84 per 1000 WY in OC users and 0.19 per 1000 WY in nonusers, for a rate ratio of 4.42 (calculated for purposes of this review). For the outcome of SVT, among women with varicose veins, the rate of SVT was 10.63 per 1000 WY in OC users and 7.59 per 1000 WY in nonusers, for a rate ratio of 1.40 (calculated for purposes of this review). Among women without varicose veins, the rate of SVT was 1.89 per 1000 WY in OC users and 0.77 per 1000 WY in nonusers, for a rate ratio of 2.45 (calculated for purposes of this review).

4. Discussion

This systematic review identified minimal evidence on VTE risk in women with superficial venous disease who used CHCs compared with nonusers. One fair-quality case–control study demonstrated that women with SVT had an increased odds of VTE with use of OCs [11]. In decreasing order of magnitude, the odds of VTE was elevated in OC users with SVT, nonusers with SVT and users without SVT, compared with nonusers without SVT, although CIs were sometimes wide and overlapping. While the point estimates suggest an interaction between SVT and CHC use on the risk of VTE, no formal testing for statistical interaction was reported. One fair-quality cohort study demonstrated that women with varicose veins had an increased rate of VTE with use of OCs [12]. In decreasing order of magnitude, the rate of VTE was highest in OC users with varicose veins, users without varicose veins and nonusers with varicose veins, compared with nonusers without varicose veins. This study also demonstrated an increased rate of SVT in women with varicose veins using OCs.

Both studies provided USPSTF Level II-2 evidence because they were cohort studies. Both studies were rated as fair quality, because they demonstrated strengths in study design, and although both had limitations, there were no fatal flaws. Neither study specified OC type or estrogen dose. It is likely that the OCs used were predominantly combined OCs. While the RCGP study reported few users of OCs with >50 mcg estrogen and the MEGA study likely also had few high-dose users given timing of data collection (1999–2004), neither study examined different estrogen doses for OCs containing <50 mcg. It is possible that any potential relationship between superficial venous disease and VTE would be attenuated by the progressively decreasing estrogen levels in modern COCs. Both studies had small numbers for comparisons of interest. In the MEGA study, information on OC use and SVT history was obtained by self-reported questionnaire and thus may be subject to recall bias. The MEGA study also did not collect information on timing, location or severity of SVT. In the RCGP study, information on varicose veins, SVT and VTE was obtained from the general practitioners but not verified by review of medical records or radiologic studies; information on OC use was also reported by general practitioners with no other source of verification.

In considering the potential impact of CHC use by women with SVT or varicose veins, it is important to take into account the separate influences of CHC use and superficial venous disease. Studies have demonstrated that healthy women using CHCs have an incidence of VTE of approximately 9–10 per 10,000 WY [14]. This risk is increased compared with nonusers, by approximately 2- to 3-fold [6].

Several studies have reported increased risks of VTE in individuals with SVT, with varying degrees of magnitude. Some studies found that risk of VTE was 4- to 7-fold higher in individuals with SVT; however, most of these studies did not separately report these risks by gender and age [11,15–17]. The frequency of concurrent DVT in individuals with SVT varies from 6% to 53%, and concurrent PE varies from 0.5% to 10% for symptomatic cases and up to 33% diagnosed on lung scans [4,5,18–20]. Although results have been inconsistent, some studies have found that the risk of VTE was approximately 4- to 6-fold higher in individuals with varicose veins [15,21]. It is likely that the risk of significant sequelae from superficial venous disease is related to clinical severity and underlying risk factors, such as thrombophilias [1,4,5,22]. In individuals with SVT, concurrent DVT most often is found in the same limb as the SVT, but in a small number of cases (2%), the DVT develops in the opposite limb, suggesting that the association may be due either to progression of the clot or to a hypercoagulable state [5]. Absence of varicose veins has been associated with concurrent DVT in patients with SVT [20]. Nonetheless, additional studies are needed in order to better understand the predictors of development of DVT in patients with superficial venous disease and to explore how hormones might interact with these thrombotic mechanisms.

In summary, minimal evidence from two observational studies of fair quality was identified regarding the risk of VTE in women with superficial venous disease who use CHCs. One case–control study demonstrated a higher risk of VTE in women with SVT who used OCs, and one cohort study demonstrated a higher rate of VTE in women with varicose veins who used OCs. No evidence on other CHCs

was identified. Future studies should examine the risk of VTE among women of reproductive age with varying degrees of superficial venous disease and the possible interaction with CHCs; if there are significant sequelae from superficial venous disease among CHC users, it may be related primarily to clinical severity of disease and other underlying factors. The information in this review was presented to an expert review panel in March 2014 at a meeting convened by WHO. The findings of this systematic review will be incorporated into the forthcoming update of the WHO MEC.

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