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Progestin-only contraception and thrombosis: an updated systematic review

Naomi K. Tepper, MD, MPH^a, Antoinette T. Nguyen, MD, MPH^a, Maura K. Whiteman, PhD^a, Kathryn M. Curtis, PhD^a

^aDivision of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, GA, USA

Abstract

Objective: Evidence is limited on whether use of progestin-only contraception (POC) is associated with risk of thrombosis. Our objective was to update an earlier systematic review on POC and thrombosis risk.

Methods: We searched for articles that examined risk of venous thromboembolism (VTE) (e.g., deep venous thrombosis or pulmonary embolism) or arterial thromboembolism (ATE) (e.g., myocardial infarction or stroke) among women with thrombogenic conditions or characteristics or in the general population using POC, compared with women using non-hormonal or no contraception, published during February 1, 2016 – November 30, 2022. We also included articles from a previous systematic review with articles published through January 2016. We assessed quality for each study and certainty of evidence for all outcomes.

Results: Thirty-three articles met inclusion criteria; one was good quality, 20 were fair quality, and 12 were poor quality. Seven articles were newly identified, and 26 were included in the previous review. Risk of VTE, but not ATE, was generally elevated with depot medroxyprogesterone acetate (DMPA) use among women with certain thrombogenic conditions or characteristics (e.g., diabetes or postpartum) and women in the general population. Risks of VTE and ATE were generally not elevated with use of other POC, including levonorgestrel intrauterine devices, implants, or progestin-only pills.

Conclusion: Evidence suggests that risk of VTE, but not ATE, is increased with DMPA use compared with non-use among women with certain thrombogenic conditions and women in the general population. Evidence does not suggest increased risk of VTE or ATE with use of other POC. While several studies examined thrombosis risk with POC use and thrombogenic conditions or characteristics, data are limited for individual conditions or characteristics and no evidence was identified for most conditions. The certainty of evidence is low or very low for all outcomes.

Corresponding author: Naomi Tepper: ntepper@cdc.gov.

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Keywords

contraception; progestin-only contraception; thromboembolism; systematic review

1. Introduction

Although relatively rare among women of reproductive age, venous thromboembolism (VTE) (including deep venous thrombosis [DVT] and pulmonary embolism [PE]) and arterial thromboembolism (ATE) (including stroke and acute myocardial infarction [AMI]) can lead to significant morbidity [1–4]. The association between combined hormonal contraceptives (i.e., containing estrogen and progestin) and increased risk for thrombosis, both VTE and ATE, is well established [5, 6]. Emerging evidence has suggested that some progestin-only contraception (POC), specifically depot medroxyprogesterone acetate (DMPA) injectables, may also be associated with VTE [7]. Studies have generally not found an increased risk of VTE or ATE with use of other POC, i.e., levonorgestrel intrauterine devices (LNG-IUDs), progestin-only implants, and progestin-only pills (POPs) [8].

Certain characteristics (e.g., postpartum status) and medical conditions (e.g., thrombophilias, sickle cell disease, systemic lupus erythematosus, diabetes, and hypertension) confer an increased risk of thrombosis [9–11]. Women with these thrombogenic conditions are at additional increased risk for thrombosis and associated morbidity during pregnancy [12]. It is important that women with thrombogenic conditions are able to select and use contraceptive methods safely. However, there is theoretical concern that women with thrombogenic conditions might be at additional increased risk of thrombosis with use of certain hormonal contraceptives. Knowledge is limited on whether POC use might further elevate thrombosis risk in women with most thrombogenic conditions. The U.S. Centers for Disease Control and Prevention (CDC) publishes the *U.S. Medical Eligibility Criteria for Contraceptive Use* (US MEC) [13], which provides evidence-based guidance on the safety of contraceptive methods for patients with certain characteristics or medical conditions, including patients with thrombogenic conditions. As part of a process to update the US MEC, the objective of this systematic review was to evaluate the evidence on risk of thrombosis with POC use, among women with thrombogenic conditions or in the general population. This review updates a previous systematic review on POC and risk of thrombosis, which included studies published through January 2016 [8]. The previous review identified only 9 studies of women with thrombogenic conditions or characteristics, with generally only 1 or 2 studies per condition, thereby limiting conclusions that could be made about most thrombogenic conditions.

2. Methods

We conducted this systematic review according to the methods of a previously published systematic review on this topic [8]. The results are reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14].

2.1. Eligibility criteria

Studies were eligible for inclusion if they examined thrombosis risk among women using POC. The population of interest was women with characteristics or medical conditions that confer an increased risk for VTE or ATE, e.g., postpartum, hypertension, or diabetes. We also included studies of women in the general population (those without thrombogenic conditions or not specified), to further examine thrombosis risk with use of POC. The exposure of interest was any POC, i.e., LNG-IUDs, progestin-only implants, progestin-only injectables (DMPA or norethisterone enanthate [NET-EN]), POPs, or emergency contraceptive pills. We also included articles examining progestin-only medications with unspecified or non-contraceptive formulations or used for therapeutic purposes, as the dose of progestin might have been higher than contraceptive dosing. The comparison was use of non-hormonal or no contraception. The outcomes of interest were VTE (DVT or PE) or ATE (stroke or AMI). We included randomized controlled trials (RCTs), non-randomized trials, cohort studies, and case-control studies. We excluded non-comparative studies, e.g., case series, case reports and review articles.

2.2. Literature search

We worked with a research librarian at the U.S. Centers for Disease Control and Prevention to develop the search strategy (Appendix A). The search was conducted in MEDLINE, Embase, Cochrane, CINAHL, Scopus, and [ClinicalTrials.gov](https://www.clinicaltrials.gov) databases. The previous systematic review included articles published from database inception through January 31, 2016 [8]; therefore this updated search included articles published from February 1, 2016, through November 30, 2022. We considered articles in all languages. We did not consider abstracts from scientific conferences.

2.3. Study selection and data extraction

Among articles identified by the search strategy, all titles and abstracts were screened independently by at least two co-authors, using the Covidence platform [15]. Two co-authors then reviewed full-text articles to determine if they met inclusion criteria. Any conflicts were resolved by discussion. Standardized evidence tables were used to summarize information on each study.

2.4. Study quality assessment

Study quality was assessed in the previous review using the United States Preventive Services Task Force (USPSTF) system [16]. Therefore, we assessed the quality of each newly identified study using the USPSTF system. RCTs are level I evidence, non-randomized trials are level II-1 evidence, and cohort or case control studies are level II-2 evidence. Internal validity (risk of bias) of studies is considered based on criteria that are specific to the study design, such as participant selection, measurement of contraceptive use and outcomes, and assessment of confounding. Studies were assessed as being of good, fair, or poor quality. Two co-authors independently assessed study quality, and conflicts were resolved by discussion.

2.5. Data synthesis

We summarized descriptive statistics, unadjusted and adjusted point estimates, and results of significance tests. We did not conduct meta-analyses due to heterogeneity of study populations, exposures, and outcomes.

2.6. Certainty of evidence methods

We assessed the certainty of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [17–19]. For each outcome, we considered risk of bias, directness, precision, and consistency to be not serious, serious, or very serious. Based on these assessments, the certainty of evidence was rated as high, moderate, low, or very low. At baseline, RCTs are considered to have high certainty, and non-randomized trials and observational studies are considered to have low certainty; ratings are then adjusted based on the criteria previously listed. Outcomes related to use of unspecified or non-contraceptive progestins were not included in GRADE.

3. Results

We identified 1114 articles through our updated database search (February 2016 through November 2022), from which 50 articles were identified for full-text review (Figure 1). Among these articles, 43 were excluded (22 wrong study design, 12 wrong intervention, 5 wrong outcomes, 3 wrong comparison, and 1 abstract only). Seven newly identified articles met inclusion criteria [20–26]; one article [26] was written by the authors of this systematic review. Twenty-six articles are also included from the previous review [27–52], for a total of 33 included articles. These 33 articles represent 30 studies, as results from 3 studies were reported in more than one article [27, 29, 30, 38, 39, 46].

The articles all described cohort or case-control studies and reported on women using the following contraceptive methods (Table 1, Figures 2–4, Appendix B). Regarding LNG-IUDs there were 3 articles on women with thrombogenic conditions [23, 24, 30] and 7 articles on women in the general population [20, 30, 40–43, 51]. Regarding implants there were 3 articles on women with thrombogenic conditions [21, 23, 25] and 5 articles on women in the general population [20, 30, 40, 42, 45]. Regarding DMPA there were 6 articles on women with thrombogenic conditions [23, 25–27, 30, 44] and 4 articles on women in the general population [20, 27, 30, 51]). Regarding POPs there were 7 articles on women with thrombogenic conditions [23, 25, 27, 32, 34, 44, 50] and 15 articles on women in the general population [20, 22, 27, 30, 33, 34, 36–41, 43, 48, 49]. Regarding POC (e.g., methods combined, not specified, or non-contraceptive formulations) there were 5 articles on women with thrombogenic conditions [24, 25, 30, 31, 35] and 5 articles on women in the general population [20, 28, 29, 46, 52].

3.1. Study quality

All studies provided level II-2 evidence from cohort or case-control studies. Most studies were deemed to be of fair or poor quality, with the exception of 1 study that was deemed to be of good quality (Appendix B.1 and Appendix B.2) [34]. Eighteen studies (19 articles) [20–22, 24–27, 30, 33, 36–43, 45, 51] were deemed to be of fair quality because: there were

different participation rates between groups [30, 33]; contraceptive types and/or thrombosis outcomes were obtained from diagnosis codes and were not confirmed by medical records [20–22, 25, 26, 36, 37, 40–43]; contraceptive types were obtained by patient self-report soon after outcome but were not verified by medical records [27, 38, 39, 45, 51]; or analyses did not account for age [24]. Thirteen studies [23, 28, 29, 31, 32, 35, 44, 46–50, 52] were deemed to be of poor quality because: source population was not described [44]; participation rates were not described [32, 44]; progestin formulation and dose were not specified [46]; contraception and/or outcome ascertainment and verification were not described [35, 44]; POC types were not separated in analyses [28, 29, 31, 35, 52]; statistical testing was not reported [23, 44, 47, 48]; or analyses did not account for any confounders [49, 50].

3.2. Women using LNG-IUDs

3.2.1. Women with thrombogenic conditions or characteristics: Three studies examined LNG-IUD use among women with thrombogenic conditions, including history of VTE (2 studies [23, 24]) or factor V Leiden (FVL) mutation (1 study [30]) (Table 1, Figure 2, Appendix B.1). Two cohort studies of women with history of VTE found that incidence of VTE was lower with use of LNG-IUDs compared with non-use (5.3% in LNG-IUD users vs. 13.5% in non-users; 0% per year in LNG-IUD users vs. 4.7% per year in non-users) (statistical testing not reported) [23, 24]. One case-control study of women with FVL mutation found that odds of VTE were statistically significantly increased with LNG-IUD use compared with women without the mutation not using HC (odds ratio [OR] 3.2 [95% confidence interval (CI) 1.2–10.4]) [30].

3.2.2. Women in the general population: Seven studies examined LNG-IUD use among women in the general population, 4 cohort studies [40–43] and 3 case-control studies [20, 30, 51] (Table 1, Figure 4, Appendix B.2). None of the studies found statistically significantly increased risk estimates of VTE, stroke, or AMI with use of LNG-IUD compared with non-use (adjusted OR [aOR] and adjusted relative risk [aRR] or adjusted rate ratio range 0.3–1.0).

3.3. Women using implants

3.3.1. Women with thrombogenic conditions or characteristics: Three cohort studies examined implant use among women with thrombogenic conditions or characteristics including: history of VTE, 1 study [23]; postpartum, 1 study [21]; and diabetes, 1 study [25] (Table 1, Figure 2, Appendix B.1). One study of women with history of VTE reported VTE incidence of 33.3% in etonogestrel implant users compared with 13.5% in non-users (statistical testing not reported) [23]. One study of postpartum women found that risk of VTE in etonogestrel implant users compared with non-users was not statistically significantly increased (aOR 1.8, 95% CI 0.4–7.5) [21]. One study of women with diabetes found no thrombotic events in etonogestrel implant users [25].

3.3.2. Women in the general population: Five studies examined implant use among women in the general population, consisting of 2 cohort studies [40, 42] and 3 case-control studies [20, 30, 45] (Table 1, Figure 4, Appendix B.2). Among the 3 studies that reported

on VTE, none found statistically significantly increased risk of VTE with use of implants (etonogestrel or levonorgestrel) compared with non-use (aOR 0.9, 95% CI 0.5–1.6; aOR 1.1, 95% CI 0.7–1.8; and aRR 1.4, 95% CI 0.6–3.4) [20, 30, 42]. Among the 2 studies that reported on stroke, neither found statistically significantly increased risk estimates of stroke with use of implants (levonorgestrel or type unspecified) compared with non-use (aRR 0.9, 95% CI 0.3–2.7; and aOR 1.0, 95% CI 0.1–9.2) [40, 45]. Two studies found that risk of AMI with use of implants (levonorgestrel or type unspecified) compared with non-use was increased but not statistically significantly (aRR 2.1, 95% CI 0.7–6.7; and aOR 3.5, 95% CI 0.2–56.5) [40, 45].

3.4. Women using DMPA

3.4.1. Women with thrombogenic conditions or characteristics: Six studies examined DMPA use among women with thrombogenic conditions or characteristics [23, 25–27, 30, 44], including: FVL mutation or history of VTE, 2 studies [23, 30]; postpartum, 1 study [26]; diabetes, 1 study [25]; smoking, 1 study [27]; and lupus, 1 study [44] (Table 1, Figure 2, Figure 3, Appendix B.1). One cohort study of women with a history of VTE found no recurrent VTEs in DMPA users and 5 (13.5%) recurrent VTEs in non-users [23]. One case-control study of women with FVL mutation found that risk of VTE with DMPA use compared with non-users without the mutation was significantly increased (OR 16.7, 95% CI 2.4–714) [30]. One cohort study of postpartum women found that risk of VTE in DMPA users compared with non-users was statistically significantly increased (incidence rate ratio [IRR] 1.9, 95% CI 1.4–2.7) [26]. One retrospective cohort study of women with diabetes found that risk of ATE or VTE (41% of outcomes were stroke, 26% AMI, 33% VTE) in DMPA users compared with IUD users (type not specified) was significantly increased (adjusted hazard ratio [aHR] 4.7, 95% CI 2.5–8.8) [25]. One case-control study of women who smoked found that odds of VTE in progestin-only injectables (mostly DMPA) compared with non-users who did not smoke was increased but not statistically significant (aOR 7.0, 95% CI 0.4–138) [27]. One cohort study of women with lupus found an incidence of AMI in women using NET-EN of 10% compared with 0% in non-users and an incidence of PE in women using NET-EN of 0% compared with 5.6% in non-users; no statistical testing was reported [44].

3.4.2. Women in the general population: Four case-control studies examined DMPA use among women in the general population [20, 27, 30, 51] (Table 1, Figure 4, Appendix B.2). Three studies found that odds of VTE with DMPA use compared with non-use were statistically significantly increased (aOR 2.2, 95% CI 1.3–4.0; aOR 2.4, 95% CI 2.0–2.9; and aOR 3.0, 95% CI 1.2–7.5) [20, 30, 51]. One study found that odds of VTE with use of injectables (mostly DMPA) compared with non-use were increased but not statistically significant (aOR 2.2, 95% CI 0.7–7.3) [27]. One study found that odds of ATE with use of injectables (mostly DMPA) compared with non-use were not increased (stroke aOR 0.9, 95% CI 0.5–1.5; AMI aOR 0.7, 95% CI 0.1–6.0) [27].

3.5. Women using POPs

3.5.1. Women with thrombogenic conditions or characteristics: Seven studies examined POP use among women with thrombogenic conditions or characteristics [23, 25,

27, 32, 34, 44, 50], including: thrombophilia or history of VTE, 3 studies [23, 32, 50]; hypertension, 2 studies [27, 34]; diabetes, 1 study [25]; smoking, 2 studies [27, 34]; and lupus, 1 study [44] (Table 1, Figure 2, Figure 3, Appendix B.1). Three cohort studies of women with thrombophilia or history of VTE found that risk of VTE in POP users compared with non-users was not statistically significantly increased (aRR 0.8, 95% CI 0.2–3.9; HR 1.3, 95% CI 0.5–3.0; 1 [5.6%] in POP users vs. 5 [13.5%] in non-users) [23, 32, 50]. Two case-control studies of women with hypertension found that odds of VTE in POP users compared with non-users without hypertension were not statistically significantly increased (aOR 2.3, 95% CI 0.2–28.1; and aOR 1.2, 95% CI 0.1–23.7) [27, 34]. One of these studies found that odds of stroke in POP users with hypertension compared with non-users without hypertension were statistically significantly increased (aOR 10.9, 95% CI 3.6–33.8) [27], while the other study found no strokes among POP users with hypertension [34]. Both studies found that odds of AMI in POP users with hypertension compared with non-users without hypertension were not statistically significantly increased (aOR 0.8, 95% CI 0.03–20.4 [34]; and aOR 1.9, 95% CI 0.1–38.4 [27]). One retrospective cohort study of women with diabetes found that the risk of ATE or VTE (41% of outcomes were stroke, 26% AMI, 33% VTE) in POP users compared with IUD users (type not specified) was statistically significantly increased (aHR 3.69, 95% CI 2.10–6.48) [25]. Two case-control studies of women who smoked found that odds of VTE in POP users compared with non-users who did not smoke were not statistically significantly increased (aOR 0.95, 95% CI 0.2–6.0; and aOR 2.4, 95% CI 0.7–8.3) [27, 34]. One of these studies found that odds of stroke in POP users who smoked compared with non-users who did not smoke was not statistically significantly increased (aOR 2.5, 95% CI 0.5–13.2) [27]. The other study found a higher percentage of stroke in POP users (50%) than non-users (27%), although statistical testing was not reported [34]. Both studies found an increased odds of AMI in POP users who smoked compared with non-users who did not smoke, with odds statistically significant in one study (aOR 10.4, 95% CI 1.1–98.8) [34] but not in the other study (aOR 7.2, 95% CI 0.7–74.6) [27]. One cohort study of women with lupus found that the number of PEs was not higher in women using POPs (1 event [6.7%]) compared with non-use (1 event [5.6%]), but no statistical testing was done [44]. The same study found no AMIs in POP users [44].

3.5.2. Women in the general population: Fourteen studies (15 articles) examined POP use among women in the general population [20, 22, 27, 30, 33, 34, 36–41, 43, 48, 49]: 3 cohort [40, 41, 43] and 11 case-control studies (12 articles) [20, 22, 27, 30, 33, 34, 36–39, 48, 49] (Table 1, Figure 4, Appendix B.2). Among 9 studies that reported on VTE, none found that risk of VTE with use of POPs compared with non-use was statistically significantly increased (aRR, adjusted rate ratio, and aOR range 0.6–2.6) [20, 22, 27, 30, 34, 37, 38, 41, 43]. Among the 6 studies that reported on stroke, none found that risk of stroke with use of POPs compared with non-use was significantly increased (aRR and aOR range 0.4–1.6) [27, 34, 36, 39, 40, 49]. Among the 5 studies that reported on AMI, none found that risk of AMI with use of POPs compared with non-use was statistically significantly increased (aRR and aOR range 0.8–1.5) [27, 33, 34, 40, 48].

3.6. Women using POC (methods combined, not specified, or non-contraceptive formulations)

3.6.1. Women with thrombogenic conditions or characteristics: Five studies examined POC use among women with thrombogenic conditions [24, 25, 30, 31, 35], including: thrombophilia or history of VTE, 4 studies [24, 30, 31, 35]; and diabetes, 1 study [25] (Table 1, Figure 2, Figure 3, Appendix B.1). Four of these were cohort studies [24, 25, 31, 35] and 1 was a case-control study [30]. Among 4 studies of women with thrombophilia or history of VTE, risk of VTE in POC users (not separated by type) compared with non-users with and without the condition was not statistically significantly increased (aOR and IRR range 0.6–3.6; incidence density 3.8% per year in POC users vs. 4.7% per year in non-users) [24, 30, 31, 35], with the exception of higher odds in women with FVL mutation using POC compared with non-users without the mutation (OR 5.4, 95% CI 2.5–13) [30]. One study of women with diabetes found that risk of ATE or VTE (41% of outcomes were stroke, 26% AMI, 33% VTE) in POC users compared with non-hormonal users was statistically significantly increased in women <35 years (aHR 2.02, 95% CI 1.51–2.70) but not in women >35 years (aHR 1.33, 95% CI 0.99–1.79) [25].

3.6.2. Women in the general population: Five case-control studies examined POC use broadly (methods combined, not specified, or non-contraceptive formulations) among women in the general population [20, 28, 29, 46, 52] (Table 1, Figure 2, Appendix B.2). Three studies found that odds of VTE with use of POC (methods combined or not specified) compared with non-use was not increased (aOR 1.2, 95% CI 0.4–3.6; aOR 1.0, 95% CI 0.6–1.6; and aOR 1.3, 95% CI 0.3–6.8) [28, 29, 52]. Three studies found that odds of VTE with use of non-contraceptive progestins (oral or type unspecified) for therapeutic reasons was statistically significantly increased compared with non-use (aOR range 2.0–5.9, 95% CI range 1.2–30.1) [20, 46, 52]. One of these studies did not find increased odds of stroke (aOR 1.1, 95% CI 0.2–7.1) or AMI (aOR 0.9, 95% CI 0.1–15.3) with use of oral therapeutic progestins compared with non-use [46].

3.7 Certainty of evidence

Because all included studies were observational (cohort or case-control studies), the certainty of evidence for all outcomes was deemed to be low or very low [53]. For all outcomes, the risk of bias was considered to be serious or very serious due to concerns about selection bias (e.g., different participation rates between groups or rates were not reported), information bias (e.g., contraceptive type was not specified or confirmed, outcomes were not confirmed), lack of statistical testing, or concerns for confounding. For some outcomes, inconsistency was considered to be serious or very serious due to varying results between studies. For most outcomes, imprecision was considered to be serious or very serious due to wide CIs that included significantly decreased and significantly increased levels of risk. For some outcomes, indirectness was considered to be serious because analyses compared POC users with thrombogenic conditions to non-users without thrombogenic conditions (rather than non-users with thrombogenic conditions).

4. Discussion

This updated systematic review found that relative risk of thrombosis varied by POC type when compared with non-POC use. Risk of VTE was generally increased with DMPA use among women with certain thrombogenic conditions or characteristics, e.g., diabetes or postpartum, and women in the general population when compared with non-use; however, risk of ATE was not increased with DMPA use. Risks of VTE and ATE were generally not elevated with use of LNG-IUDs, implants, or POPs among women with certain thrombogenic conditions or women in the general population. Newly identified evidence was consistent with evidence included in the previously published systematic review [8].

The prior review included 3 studies on DMPA that found risk of VTE was statistically significantly increased [30, 51] or elevated to a similar degree but not statistically significant [27]. In this updated review, we identified 4 new studies on DMPA and risk for VTE, one among women with a history of VTE [23], one among postpartum women [26], one among women with diabetes [25], and one in the general population of DMPA users [20]. Three of these new studies also found increased relative risk for VTE [20, 25, 26]. One new study of DMPA use among women with history of VTE found a lower incidence of recurrent VTE in DMPA users than non-HC users, but no statistical testing was done [23]. An additional study found that risk of VTE was increased with use of DMPA compared with LNG-IUDs (age-adjusted IRR 3.7, 95% CI 1.3–10.4); although this study did not meet inclusion criteria for this review because the comparison group was LNG-IUD users, it lends support to the general body of evidence on DMPA [54].

Several meta-analyses have examined risk of thrombosis with POC use [7, 55–58]. In the most recent meta-analysis, risk of VTE was increased with use of DMPA compared with non-hormonal use (aOR 2.6, 95% CI 1.7–3.9) [7]. Risk of VTE was not statistically significantly increased with use of LNG-IUDs. Risk of VTE and ATE were not statistically significantly increased with use of POPs. Our systematic review differs from this meta-analysis because we separately describe studies on women with thrombogenic conditions and women in the general population. We also included several additional studies not included in the meta-analysis and studies published since the meta-analysis.

It is important to consider any increases in relative risk in the context of absolute risk. Although the relative risk of VTE may be increased 2–3 fold with use of DMPA, this represents a small increase in absolute numbers due to the rarity of VTE among women of reproductive age, at 5–10/10,000 women-years [4]. The absolute risk of stroke and MI are even lower among women of reproductive age: 19/100,000 women-years, and 10/100,000 women-years, respectively [40, 59]. Nonetheless, these outcomes might result in mortality or severe morbidity and incidence might be further increased in the setting of thrombogenic characteristics and medical conditions. The relative risk of VTE among postpartum women is 2.5–84 [60]. The relative risks of VTE in individuals with thrombophilias range from approximately 10 to 80 [61]. Approximately 25% of patients with sickle cell disease have a stroke by age 45 [62]. There is concern that use of certain hormonal contraceptives by women with thrombogenic conditions could further elevate their risk to a concerning level. Three of the studies that were identified in this review found that VTE risk was increased

with use of DMPA compared with no use of DMPA among women who are postpartum or have diabetes [25, 26], and VTE was increased among DMPA users who smoke compared with non-users who do not smoke [27].

Reasons for the increased risk with DMPA may be related to the higher dose of progestin delivered or may be due to an interaction of DMPA and other thrombogenic changes. Three studies found an increased risk of VTE with progestins in non-contraceptive formulations or doses or used for non-contraceptive purposes (e.g., menstrual disorders) [20, 46, 52]; doses of progestin were likely higher than contraceptive doses. This finding suggests a potential dose response for thrombosis risk with POC that could explain some of the risk associated with DMPA, which is a relatively higher dose of progestin. In addition, DMPA has been found to have certain biological effects that may contribute to thrombogenesis. Several, mostly small, studies have found DMPA to be associated with increased total cholesterol, triglycerides, and low-density lipoprotein; decreased high-density lipoprotein; and reduced endothelial function [63–65]. DMPA does not appear to have deleterious effects on coagulation parameters [66–68]. However, the mechanism of thrombosis is complex and further study is needed to better understand impacts of DMPA on the hemostatic system and correlations with clinical outcomes.

In addition to further study of DMPA, future research on the drospirenone (DRSP) POP can provide additional evidence. No VTEs were reported in the Phase 3 clinical trials of the DRSP POP [69], however combined oral contraceptives (COCs) containing DRSP are associated with increased risk of VTE compared with COCs containing levonorgestrel [70]. Different progestins may have different effects on the coagulation system or may counteract the procoagulant effect of estrogen to varying degrees [71]. Additional study of DRSP POP use by women with thrombogenic conditions would advance understanding of any potential risks.

The body of evidence has several limitations. Most of the studies were deemed to be of fair or poor quality. The certainty of evidence was deemed to be low or very low for all outcomes, generally due to concerns about risk of bias and imprecision. A limited number of studies examined women with certain thrombogenic conditions or characteristics using POC, and most of these studies had relatively small numbers of women, limiting generalizability. Although the certainty of evidence was deemed to be low or very low, consistency across studies lends some confidence to the findings, e.g., increased risk with DMPA and lack of risk with POPs. Evidence remains limited on safety of these methods in women with most thrombogenic conditions and characteristics, with no studies for most conditions. Given that mechanisms of thrombosis differ between conditions, it is not possible to extrapolate evidence across different thrombogenic conditions and characteristics.

In conclusion, evidence suggests that risk of VTE is increased with use of DMPA compared with non-use. Evidence does not suggest an increased risk of VTE or ATE with use of other POC, including LNG-IUDs, implants, and POPs. Further study is needed on safety of POC use among women with thrombogenic conditions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Implications

Use of DMPA might increase risk of VTE among women with medical conditions associated with thrombosis and among women in the general population. Evidence does not suggest an increased risk of thrombosis with other POC. Further study is needed on safety of POC use by women with thrombogenic conditions.

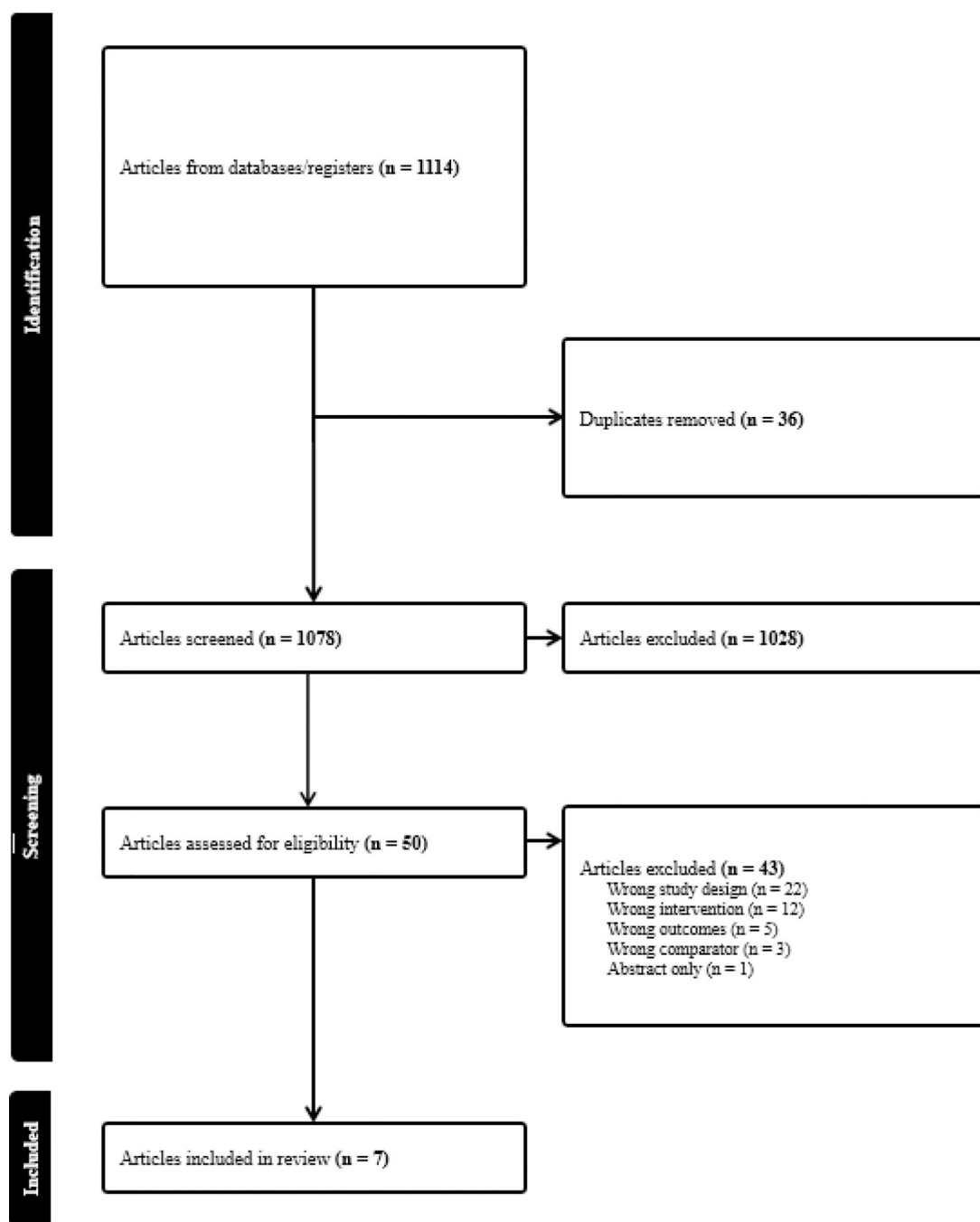


Figure 1.

PRISMA flow chart for updated search^a for evidence on progestin-only contraception and thrombosis

^a Updated search included articles published from February 1, 2016, through November 30, 2022. The previous systematic review included articles published from database inception through January 31, 2016 [8].

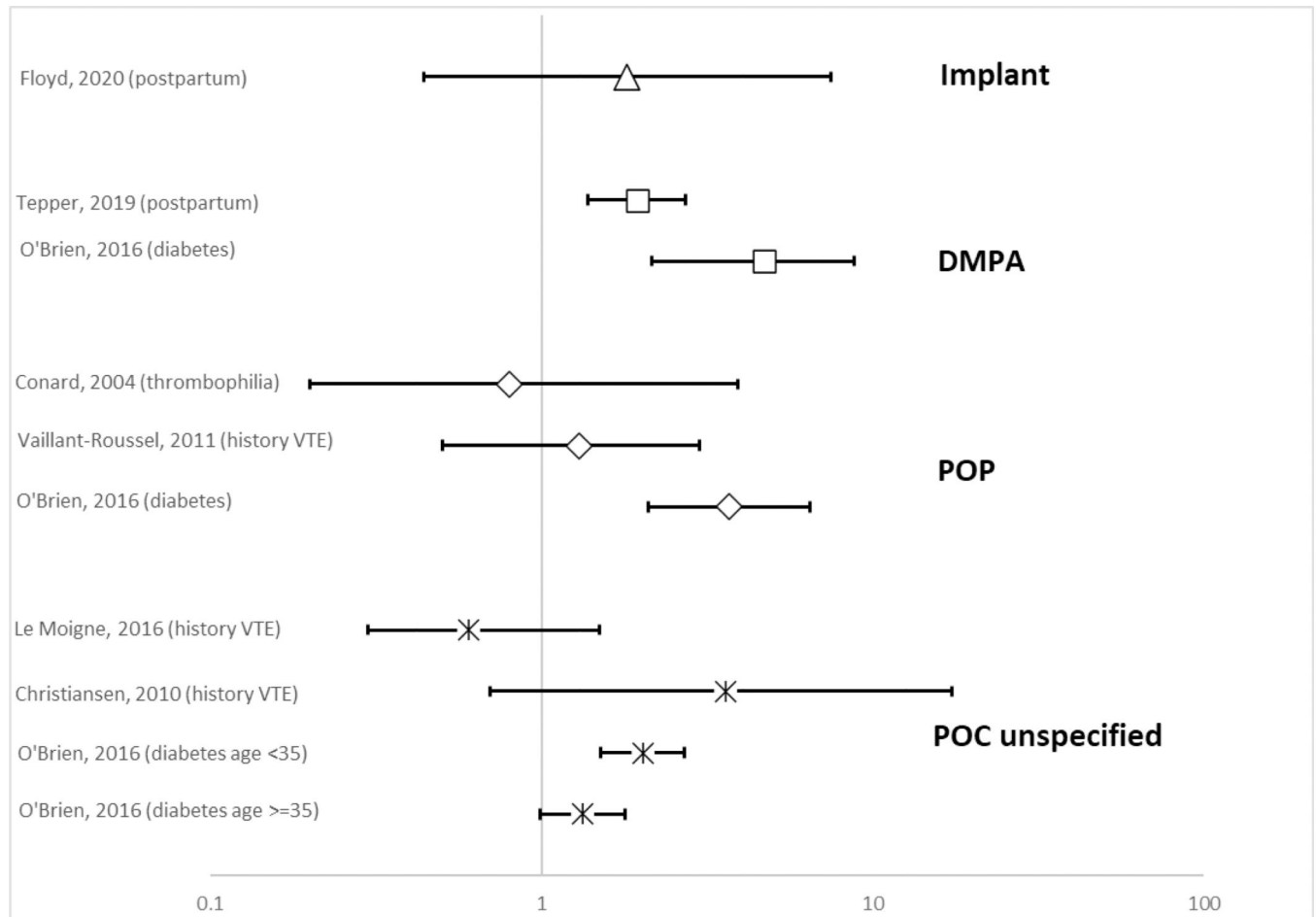


Figure 2.
 Risk of venous thromboembolism among women with thrombogenic conditions using progestin-only contraception compared with non-use^a
 DMPA, depot medroxyprogesterone acetate; POC, progestin-only contraception; POP, progestin-only pill; VTE, venous thromboembolism.
^a Reference group is use of non-hormonal or no contraception among women with the condition.

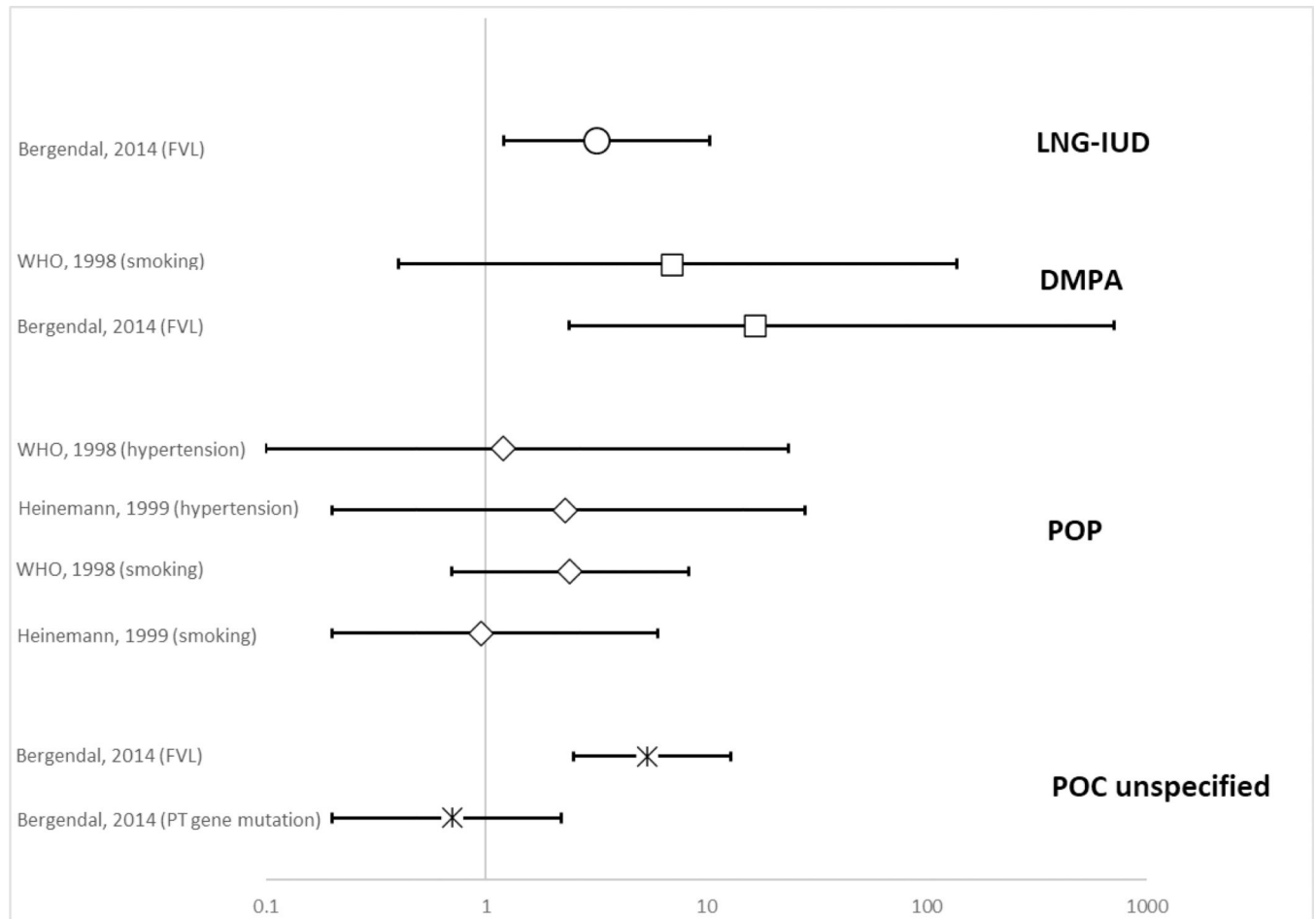


Figure 3. Risk of venous thromboembolism among women with thrombogenic conditions using progestin-only contraception compared with non-users without thrombogenic conditions^a DMPA, depot medroxyprogesterone acetate; FVL, factor V Leiden; IUD, intrauterine device; LNG, levonorgestrel; POC, progestin-only contraception; POP, progestin-only pill; PT, prothrombin.
^a Reference group is use of non-hormonal or no contraception among women without the condition.

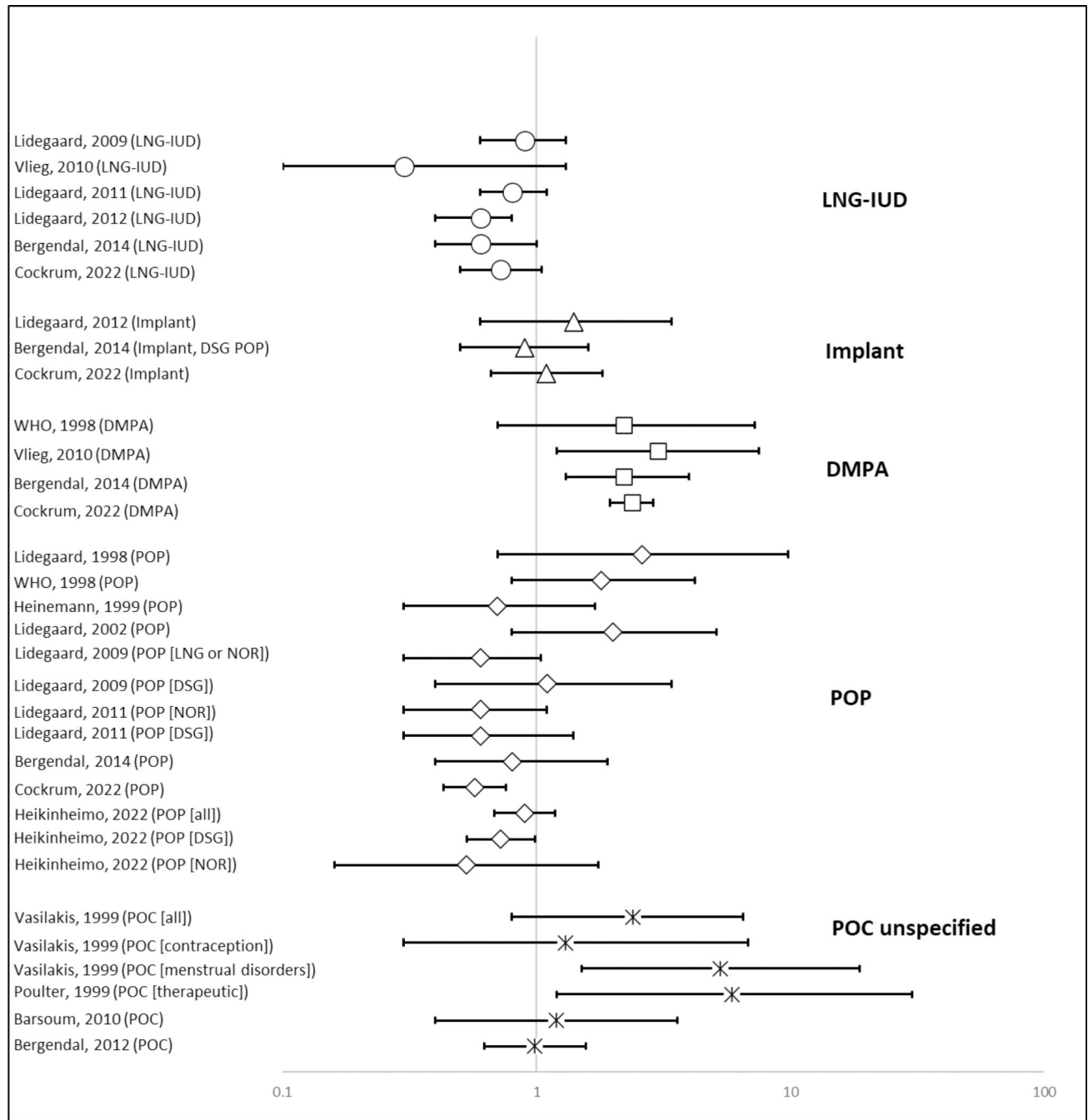


Figure 4.
 Risk of venous thromboembolism among women in the general population using progestin-only contraception^a
 DMPA, depot medroxyprogesterone acetate; DSG, desogestrel; IUD, intrauterine device; LNG, levonorgestrel; NOR, norethisterone; POC, progestin-only contraception; POP, progestin-only pill.
^a Reference group for most studies is use of non-hormonal or no contraception.

Table 1.
Summary of evidence on progestin-only contraception and thrombosis

Study	Population	Contraception	Comparison group	Outcome	Risk of thrombosis (95% CI)
<i>LNG-IUD use among women with thrombogenic conditions or characteristics</i>					
Maher, 2022 [23]	History VTE	LNG-IUD	+ history VTE, – HC	VTE	5.3% (LNG-IUD) vs 13.5% (non-use)
Martinelli, 2016 [24]	History VTE	LNG-IUD	+ history VTE, – HC	VTE	Incidence density/year: 0 (LNG-IUD) vs. 4.7% (non-use)
Bergendal, 2014 [30]	FVL	LNG-IUD	– FVL, – HC	VTE	OR 3.2 (1.2–10.4)
<i>LNG-IUD use among women in general population</i>					
Lidegaard, 2009 [41]	General population	LNG-IUD	– HC	VTE	Adjusted rate ratio 0.9 (0.6–1.3)
Vlieg, 2010 [51]	General population	LNG-IUD	– HC	VTE	aOR 0.3 (0.1–1.3)
Lidegaard, 2011 [43]	General population	LNG-IUD	– HC	VTE	aRR 0.8 (0.6–1.1)
Lidegaard, 2012 [42]	General population	LNG-IUD	– HC	VTE	aRR 0.6 (0.4–0.8)
Bergendal, 2014 [30]	General population	LNG-IUD	– HC	VTE	aOR 0.6 (0.4–1.0)
Cockrum, 2022 [20]	General population	LNG-IUD	– HC	VTE	aOR 0.72 (0.50–1.05)
Lidegaard, 2012 [40]	General population	LNG-IUD	– HC	Stroke	aRR 0.7 (0.5–0.98)
Lidegaard, 2012 [40]	General population	LNG-IUD	– HC	AMI	aRR 1.0 (0.7–1.5)
<i>Implant use among women with thrombogenic conditions or characteristics</i>					
Maher, 2022 [23]	History VTE	Implant (ETG)	+ history VTE, – HC	VTE	33.3% (implant) vs. 13.5% (non-use)
Floyd, 2020 [21]	Postpartum	Implant (ETG)	+ postpartum, – HC	VTE	aOR 1.81 (0.44–7.45)
O'Brien, 2017 [25]	Diabetes	Implant (ETG)	+ diabetes, + IUD (type unspecified)	VTE/A TE	0 (implant) vs 3.4/1000 WY (non-use)
<i>Implant use among women in general population</i>					
Bergendal, 2014 [30]	General population	Medium dose (implants [ETG or LNG], oral DSG)	–HC	VTE	aOR 0.9 (0.5–1.6)
Cockrum, 2022 [20]	General population	Implant (ETG)	–HC	VTE	aOR 1.09 (0.66–1.82)
Lidegaard, 2012 [42]	General population	Implant (ETG)	–HC	VTE	aRR 1.4 (0.6–3.4)
Lidegaard, 2012 [40]	General population	Implant (type unspecified)	–HC	Stroke	aRR 0.9 (0.3–2.7)
Petitti, 1998 [45]	General population	Implant (LNG)	–HC	Stroke	aOR 1.0 (0.1–9.2)
Lidegaard, 2012 [40]	General population	Implant (type unspecified)	–HC	AMI	aRR 2.1 (0.7–6.7)
Petitti, 1998 [45]	General population	Implant (LNG)	–HC	AMI	aOR 3.5 (0.2–56.5)
<i>DMPA use among women with thrombogenic conditions or characteristics</i>					
WHO, 1998 [27]	Smokers	Injectables (mostly DMPA)	– smoking, – HC	VTE	aOR 7.0 (0.4–138)
Maher, 2022 [23]	History of VTE	DMPA	+ history VTE, – HC	VTE	Incidence: 0% (DMPA) vs. 13.5% (non-use)
Bergendal, 2014 [30]	FVL	DMPA	– FVL, – HC	VTE	OR 16.7 (2.4–714)
Tepper, 2019 [26]	Postpartum	DMPA	+ postpartum, – HC	VTE	IRR 1.94 (1.38–2.72)
O'Brien, 2017 [25]	Diabetes	DMPA	+ diabetes, – HC	VTE or ATE	aHR 4.69 (2.51–8.77)
Mintz, 1984 [44]	Lupus	DMPA	+ lupus, – HC	PE	0% (DMPA) vs. 5.6% (non-use)

Study	Population	Contraception	Comparison group	Outcome	Risk of thrombosis (95% CI)
Mintz, 1984 [44]	Lupus	DMPA	+ lupus, – HC	AMI	10% (DMPA) vs. 0% (non-use)
<i>DMPA use among women in general population</i>					
WHO, 1998 [27]	General population	Injectables (mostly DMPA)	– HC	VTE	aOR 2.2 (0.7–7.3)
Vlieg, 2010 [51]	General population	DMPA	– HC	VTE	aOR 3.0 (1.2–7.5)
Bergendal, 2014 [30]	General population	DMPA	– HC	VTE	aOR 2.2 (1.3–4.0)
Cockrum, 2022 [20]	General population	DMPA	– HC	VTE	aOR 2.37 (1.95–2.88)
WHO, 1998 [27]	General population	Injectables (mostly DMPA)	– HC	Stroke	aOR 0.9 (0.5–1.5)
WHO, 1998 [27]	General population	Injectables (mostly DMPA)	– HC	AMI	aOR 0.7 (0.1–6.0)
<i>POP use among women with thrombogenic conditions or characteristics</i>					
Conard, 2004 [32]	Thrombophilia or history VTE	POP	+ thrombophilia or history VTE, – HC	VTE	aRR 0.8 (0.2–3.9)
Maher, 2022 [23]	History VTE	POP	+ history VTE, – HC	VTE	5.6% (POP) vs. 13.5% (non-use)
Vaillant-Roussel, 2011 [50]	History VTE	POP	+ history VTE, – HC	VTE	HR 1.3 (0.5–3.0)
Heinemann, 1999 [34]	Hypertension	POP	– HTN, – HC	VTE	aOR 2.3 (0.2–28.1)
WHO 1998 [27]	Hypertension	POP	– HTN, – HC	VTE	aOR 1.2 (0.1–23.7)
Heinemann, 1999 [34]	Smokers	POP	– smoking, – HC	VTE	aOR 0.95 (0.2–6.0)
WHO, 1998 [27]	Smokers	POP	– smoking, – HC	VTE	aOR 2.4 (0.7–8.3)
O'Brien, 2017 [25]	Diabetes	POP	+ diabetes, + IUD (type unspecified)	VTE/A TE	aHR 3.69 (2.10–6.48)
Mintz, 1984 [44]	Lupus	POP (LNG)	+ lupus, – HC	PE	6.7% (POP) vs. 5.6% (non-use)
Heinemann, 1999 [34]	Hypertension	POP	– HTN, – HC	Stroke	No strokes in POP users
WHO 1998 [27]	Hypertension	POP	– HTN, – HC	Stroke	aOR 10.9 (3.6–33.8)
Heinemann, 1999 [34]	Smokers	POP	– smoking, – HC	Stroke	50% (POP) vs. 27% (non-use)
WHO, 1998 [27]	Smokers	POP	– smoking, – HC	Stroke	aOR 2.5 (0.5–13.2)
Heinemann, 1999 [34]	Hypertension	POP	– HTN, – HC	AMI	aOR 0.8 (0.03–20.4)
WHO 1998 [27]	Hypertension	POP	– HTN, – HC	AMI	aOR 1.9 (0.1–38.4)
Heinemann, 1999 [34]	Smokers	POP	– smoking, – HC	AMI	aOR 10.4 (1.1–98.8)
WHO, 1998 [27]	Smokers	POP	– smoking, – HC	AMI	aOR 7.2 (0.7–74.6)
Rosenberg, 2001 [47]	Smokers	POP	+ smokers, – HC	AMI	50% (POP) vs. 17.9% (non-use)
Mintz, 1984 [44]	Lupus	POP (LNG)	+ lupus, – HC	AMI	0 vs 0
<i>POP use among women in general population</i>					
Lidegaard, 1998 [37]	General population	POP	–HC	VTE	aOR 2.6 (0.7–9.8)
WHO, 1998 [27]	General population	POP	–HC	VTE	aOR 1.8 (0.8–4.2)
Lidegaard, 2002 [38]	General population	POP	–HC	VTE	aOR 2.0 (0.8–5.1)
Lidegaard, 2009 [41]	General population	POP (LNG or norethisterone)	–HC	VTE	Adjusted rate ratio 0.6 (0.3–1.04)
Lidegaard, 2009 [41]	General population	POP (DSG)	–HC	VTE	Adjusted rate ratio 1.1 (0.4–3.4)

Study	Population	Contraception	Comparison group	Outcome	Risk of thrombosis (95% CI)
Lidegaard, 2011 [43]	General population	POP (norethisterone)	–HC	VTE	aRR 0.6 (0.3–1.1)
Lidegaard, 2011 [43]	General population	POP (DSG)	–HC	VTE	aRR 0.6 (0.3–1.4)
Heinemann, 1999 [34]	General population	POP	–HC	VTE	aOR 0.7 (0.3–1.7)
Bergendal, 2014 [30]	General population	POP	–HC	VTE	aOR 0.8 (0.4–1.9)
Cockrum, 2022 [20]	General population	POP (norethindrone)	–HC	VTE	aOR 0.57 (0.43–0.76)
Heikinheimo, 2022 [22]	General population	POP	–HC	VTE	aOR 0.90 (0.68–1.18)
Lidegaard, 1993 [36]	General population	POP	–HC	Stroke	aOR 0.9 (0.4–2.4)
Tzourio, 1995 [49]	General population	POP	–HC	Stroke	OR 1
WHO, 1998 [27]	General population	POP	–HC	Stroke	aOR 1.1 (0.6–1.9)
Lidegaard, 2002 [39]	General population	POP	–HC	Stroke	aOR 1.0 (0.3–3.0)
Lidegaard, 2012 [40]	General population	POP (norethindrone)	–HC	Stroke	aRR 1.4 (0.9–2.0)
Lidegaard, 2012 [40]	General population	POP (LNG)	–HC	Stroke	aRR 0.4 (0.1–3.1)
Lidegaard, 2012 [40]	General population	POP (DSG)	–HC	Stroke	aRR 1.4 (0.7–2.6)
Heinemann, 1999 [34]	General population	POP	–HC	Stroke	aOR 1.6 (0.2–10.7)
Thorogood, 1991 [48]	General population	POP	–HC	AMI	20% (POP) vs. 31.6% (non-use)
WHO, 1998 [27]	General population	POP	–HC	AMI	aOR 0.98 (0.2–6.0)
Dunn, 1999 [33]	General population	POP	–HC	AMI	aOR 1.5 (0.6–3.7)
Lidegaard, 2012 [40]	General population	POP (norethindrone)	–HC	AMI	aRR 0.8 (0.4–1.6)
Lidegaard, 2012 [40]	General population	POP (LNG)	–HC	AMI	Incidence rate/100,000 WY: 0 (POP) vs. 13.2 (non-use)
Lidegaard, 2012 [40]	General population	POP (DSG)	–HC	AMI	aRR 1.5 (0.6–3.9)
Heinemann, 1999 [34]	General population	POP	–HC	AMI	aOR 0.9 (0.3–2.9)
POC (combined, unspecified, or non-contraceptive formulations) use among women with thrombogenic conditions or characteristics					
Bergendal 2014 [30]	FVL mutation	POP, DMPA, implant, LNG-IUD	– FVL, – HC	VTE	aOR 5.4 (2.5–13)
Bergendal 2014 [30]	PT gene mutation	POP, DMPA, implant, LNG-IUD	– PT, – HC	VTE	aOR 0.7 (0.2–2.2)
Christiansen, 2010 [31]	History VTE	POP, DMPA	+history VTE, – HC	VTE	IRR 3.6 (0.7–17.3)
Le Moigne, 2016 [35]	History VTE	POP, implant, LNG-IUD	+history VTE, – HC	VTE	IRR 0.6 (0.3–1.5)
Martinelli, 2016 [24]	History VTE	POC	+history VTE, – HC	VTE	Incidence density/year: 3.8% (POC) vs. 4.7% (non-use)
O'Brien, 2017 [25]	Diabetes age <35	POC	+ diabetes, – HC	VTE/ATE	aHR 2.02 (1.51–2.70)
O'Brien, 2017 [25]	Diabetes age >35	POC	+ diabetes, – HC	VTE/A TE	aHR 1.33 (0.99–1.79)
POC (combined, unspecified, or non-contraceptive formulations) use among women in general population					
Barsoum, 2010 [28]	General population	POC	–HC	VTE	aOR 1.2 (0.4–3.6)
Bergendal, 2012 [29]	General population	DMPA, implant, LNG-IUD	–HC	VTE	aOR 0.98 (0.6–1.6)
Cockrum, 2022 [20]	General population	Oral progesterone	–HC	VTE	aOR 1.07 (0.75–1.54)
Cockrum, 2022 [20]	General population	Oral MPA	–HC	VTE	aOR 1.98 (1.41–2.80)
Cockrum, 2022 [20]	General population	POP (norethindrone acetate)	–HC	VTE	aOR 3.00 (1.96–4.59)

Study	Population	Contraception	Comparison group	Outcome	Risk of thrombosis (95% CI)
Vasilakis, 1999 [52]	General population	POC (for contraception)	–HC	VTE	aOR 1.3 (0.3–6.8)
Vasilakis, 1999 [52]	General population	POC (for menstrual disorders)	–HC	VTE	aOR 5.3 (1.5–18.7)
Poulter, 1999 [46]	General population	POC (therapeutic reasons)	–HC	VTE	aOR 5.9 (1.2–30.1)
Poulter, 1999 [46]	General population	POC (therapeutic reasons)	–HC	Stroke	aOR 1.1 (0.2–7.1)
Poulter, 1999 [46]	General population	POC (therapeutic reasons)	–HC	AMI	aOR 0.9 (0.1–15.3)

+, with condition; - without condition; aHR, adjusted hazard ratio; AMI, acute myocardial infarction; aOR, adjusted odds ratio; aRR, adjusted relative risk; ATE, arterial thromboembolism; DMPA, depot medroxyprogesterone acetate; DSG, desogestrel; ETG, etonogestrel; FVL, factor V Leiden; HC, hormonal contraception; HTN, hypertension; IRR, incidence rate ratio; IUD, intrauterine device; LNG, levonorgestrel; MPA, medroxyprogesterone acetate; PE, pulmonary embolism; POC, progestin-only contraception; POP, progestin-only pills; PT, prothrombin; VTE, venous thromboembolism; WY, women-years.