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Updates on progestin-only contraception and the risk of thromboembolism: A systematic review

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Abstract
Objectives: To summarize recent data on progestin-only contraception (POC) and the risk of thromboembolic events.
Methods: A total of 413 pertinent publications were found after a comprehensive search across four databases. 74 full-text publications were examined after duplicates were eliminated using Rayyan QCRI and relevance was checked; five studies finally satisfied the requirements for inclusion.
Results: We included five studies with a total of 380,134 women on hormonal contraception. Emerging evidence suggests an association between POCs and thromboembolic risk, though this risk is generally lower than that of combined hormonal contraceptives with estrogen. Not all POCs carry the same level of safety; injectables, in particular, may have a higher thromboembolic risk due to higher systemic progestin levels. The safety profile also varies by type and administration method, with levonorgestrel-releasing implants and intrauterine devices showing minimal impact on coagulation, while oral progestin-only pills have variable effects depending on the specific progestin used.
Conclusion: While estrogen containing contraceptives still come with the thrombotic risk, POCs tend to have a safer profile than these types of drugs in women at elevated thrombotic risk. Nevertheless, injectable POCs may have a slightly higher risk of thromboembolism than their fewer active forms. For example, women with diabetes and sickle cell disease, can safely been on POCs. These results highlight the need for individualised contraceptive counselling, particularly for women with a past medical history of thromboembolism. Additional longitudinal research with subgroup analysis is required to ascertain the unique risk of specific POC formulations.

Keywords: Progestin-only contraceptives; thromboembolic risk; coagulation parameters; contraceptive safety profile; systematic review

Introduction

It is commonly known that combination hormonal contraceptives increase the risk of thrombosis. When compared to nonuse, the risk of venous thromboembolism (VTE), which includes deep vein thrombosis and pulmonary embolism (PE), is two to three times higher for those who usage combined hormonal contraceptives, which contain estrogen and progestin [1, 2]. In addition, compared to not using them, combined hormonal contraceptives are linked to a two-fold higher risk of arterial thromboembolism (ATE), which includes stroke and acute myocardial infarction (AMI) [2, 3]. These events can have devastating sequelae linked to considerable morbidity, although being relatively uncommon among women of age at conception [VTE 5–10/10,000 women years (WY), strokes 21/100,000 WY, and AMI 10/100,000 WY] [2, 3].

Estrogen's actions on the coagulation system are most likely to be the cause of thrombosis [4]. Progestin-only contraceptives (POCs) were not previously believed to be associated with thrombosis. The progestin component may contribute to the development of thrombosis, nevertheless, as data has shown that combined oral contraceptives with the same estrogen dose but differing progestins are linked to a differential risk of VTE [1]. The use of POCs, particularly depot medroxyprogesterone acetate (DMPA), which provides a comparatively larger dose and potency of progestin, has also been linked to an increased risk of VTE in a small number of recent studies [5, 6].

The association of clonal hematopoiesis with thromboembolic complications is undergoing intense investigation and discussion because it could help healthcare providers design a safer form of contraception for women at higher thrombotic risk. POCs (eg, oral pills, injections, implants, and IUDs) are usually believed to be a safer choice as compared with estrogen-containing methods because they do not contain estrogen—a well-established thromboembolic risk factor. However, the growing use of progestin-only options—especially in women with contraindications to combined hormonal contraception—requires that we reconsider the thrombotic safety profile of POCs in light of emerging evidence. This systematic review aims to summarize recent data on progestin-only contraception and the risk of thromboembolic events to support safe contraceptive counseling and clinical decision-making in women identified as having increased risk for thromboembolic events.

Methods

Search strategy

The PRISMA and GATHER criteria were adhered to in the systematic review. To locate pertinent research on progestin-only contraception and the risk of thromboembolic events, a comprehensive search was carried out. Four electronic databases were searched by the reviewers: SCOPUS, Web of Science, Cochrane, and PubMed. We eliminated any duplicates and uploaded all of the abstracts and titles that we could find using electronic searches into Rayyan. After that, all of the study texts that met the requirements for inclusion based on the abstract or title were gathered for a thorough examination. Two reviewers independently assessed the extracted papers' suitability and discussed any discrepancies.

Study Population Selection

The PEO (Population, Exposure, and Outcome) factors were implemented as inclusion criteria for our review: (i)

Population: Women on contraception use, (ii) Exposure: POC, (iii) Outcome: Incidence of thromboembolism.

Data Extraction

Data from studies that satisfied the inclusion requirements were extracted by two objective reviewers using a predetermined and uniform methodology. The following information was retrieved and recorded: (i) First author (ii) Year of publication, (iii) Study design, (iv) Country, (v) Sample size, (vi) Age, (vii) Gender, (viii) Population type, (ix) Follow-up duration (years), (x) Main outcomes.

Quality Review

Since bias resulting from omitted factors is frequent in studies in this field, we used the ROBINS-I technique to assess the likelihood of bias since it enables a thorough examination of confounding. The ROBINS-I tool can be used for cohort designs where individuals exposed to different staffing levels are tracked over time and is designed to assess non-randomized studies. Each paper's risk of bias was evaluated independently by two reviewers, and any differences were settled by group discussion [7].

Results

The specified search strategy yielded 413 publications (Figure 1). After removing duplicates (n =206), 207 trials were evaluated based on title and abstract. Of these, 133 failed to satisfy eligibility criteria, leaving just 74 full-text articles for comprehensive review. A total of 5 satisfied the requirements for eligibility with evidence synthesis for analysis.

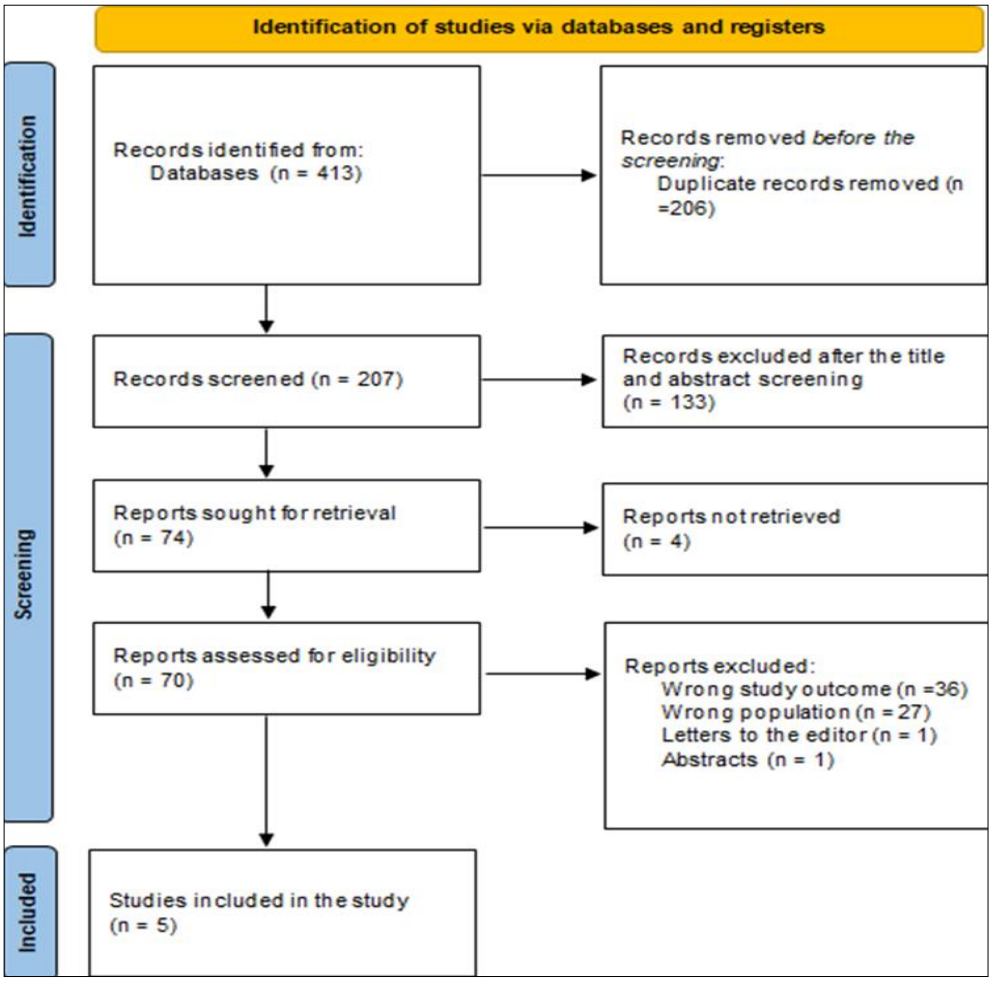

Fig 1. PRISMA flowchart [8]

Sociodemographic and clinical outcomes

We included five studies with a total of 380,134 women on hormonal contraception. Regarding study designs, three studies were retrospective cohorts [10, 11, 13] and two were case-controls [9, 12]. Two studies were implemented in the USA [10, 11], one in Finland [9], one in Poland [12], and one in Estonia [13].

Emerging data have highlighted an association between thromboembolic risk and progestin-only contraceptives. Overall, progestin-only methods (i.e., pills, injectables, implants, intrauterine devices) are thought to carry a lower risk of thromboembolism than combined hormonal contraceptives containing estrogen [9].

While the relative risk is generally lower, some findings indicate that not all progestin-only contraceptives are equally safe. Injectable progestins, for example, may pose a higher risk of thromboembolism than other methods of progestin-only contraception [10, 11]. Maybe because systemic levels of progestin are higher when using injectables formulations.

Moreover, the risk profile seems to be affected by both the kind of progestin used and method of administration. Levonorgestrel–releasing implants and intrauterine devices have good safety and tolerability profile with very little effect on the parameters of coagulation. In contrast, oral progestin-only pills have a heterogeneous effect based on the progestin compound [12, 13].

Table 1: Outcome measures of the included studies

Study ID	Study design	Country	Sociodemographic	Population type	Follow-up (years)	Main outcomes
Heikinheimo *et al*., 2022 [9]	Case–control	Finland	N= 6670 Age range: 15-49	Women using POC	1	The use of progestin-only contraception did not change the risk of VTE.
O'Brien *et al*., 2017 [10]	Retrospective cohort	USA	N= 146,080 Age range: 14-44	Women with DM	1	An elevated risk of thromboembolism (12.5 per 1,000 woman-years; adjusted hazard ratio 4.69 [95% CI 2.51–8.77]) was linked to injectable contraception that included just progestin.
Bala *et al*., 2023 [11]	Retrospective cohort	USA	N= 3976 Age range: 12-44	Women with SCD	1	In patients with sickle cell illness, this study did not find any appreciable variations in the incidence of thromboembolism among new progestin-only contraceptive users.
Piróg *et al*., 2019 [12]	Case–control	Poland	N= 96 Age range: 15-49	Women using POC	1	Participants with oral second-generation progestogen-induced VTE related to contraception show more adverse clotting characteristics.
Kurvits *et al*., 2021 [13]	Retrospective cohort	Estonia	N= 223,312 Age range: 15-49	Women using POC	1	Wider usage of progestogen-only contraceptives and a decrease in the prevalence of mixed hormonal contraceptives in Estonia are good trends with respect to the risk of thromboembolism. However, getting CHC in women with a history of thrombosis is a major risk.

Table 2: Risk of bias assessment using ROBINS-I

Study ID	Bias due to confounding	Bias in the selection of participants into	Bias in the classification of interventions	Bias due to deviations from the intended interval	Bias due to missing data	Bias in the measurement of outcomes	Bias in the selection of reported result	Overall bias
Heikinheimo *et al*., 2022 [9]	Mod	Mod	Low	Low	Low	Low	Low	Low
O'Brien *et al*., 2017 [10]	Low	Low	Low	Low	Low	Mod	Low	Low
Bala *et al*., 2023 [11]	Mod	Low	Mod	Mod	Low	Low	Low	Moderate
Piróg *et al*., 2019 [12]	Low	Low	Mod	Mod	Low	Low	Mod	Moderate
Kurvits *et al*., 2021 [13]	Mod	Mod	Low	Low	Low	Mod	Mod	Moderate

Discussion

Collectively, the newly published data regarding POC and thromboembolic risk emphasize important information around the relative safety of each of these POC methods. Although mostly progestin-only options are recommended for women at higher thrombotic risk, evidence shows that not all progestin-based methods may be equally safe. Higher systemic exposure to progestin may stimulate additional thromboevents, where applicable; thus, injectable progestins could be at a somewhat increased risk of VTE relative to other formulations.

Importantly, women with DM and SCD do not appear to have excess thromboembolic risk associated with POC use compared to non-users and other contraceptives in the studies addressed here. These results strengthen the case for advising progestin-only methods in this population, but caution against some types is prudent—especially where alternatives are available. The writing comes as certain second-creative medication progestogens are presumably protected, yet others may keep up some thrombotic risk and should be a point for additional examination and thought on clinical practice [9, 13].

Tepper *et al.* reported that the risk of venous and arterial thrombosis in women who use POCs and have medical disorders or traits linked to thrombosis risk was recognized as level II-2, good to low quality evidence. There was no evidence that women with lupus or hypertension who used POCs had a higher risk of arterial or venous thrombosis [14]. According to another study, women with FVL who used DMPA had noticeably higher odds of developing VTE than those who did not [5]. The same study also discovered that women with the MTHFR polymorphism who used POCs had considerably higher odds of developing VTE than those who did not; however, this risk was reduced and ceased to be significant when obese and severely immobile women were excluded. Two other studies that looked at non-DMPA POCs found no increased odds of recurrent VTE, while one research that suggested an elevated odd of recurrent VTE among women with a history of VTE using POCs (all of which happened among DMPA users) did not achieve statistical significance [15].

According to a meta-analysis of four studies on the risk of VTE in women who use POCs, the odds were not appreciably higher [15]. The use of all POCs, POPs, or LNG-IUDs did not significantly increase the risks of VTE, according to a more recent meta-analysis that included eight research on the subject [16]. However, when combined odds were derived from two trials, injectable use was linked to an increased incidence of VTE [6]. The combined OR was not raised, according to a meta-analysis of six studies on the risk of stroke in women who use POCs [17].

Thrombosis has a complicated mechanism that includes changes to numerous hemostatic system components. It is

unclear how POCs might affect the hemostatic system biologically. Progestins affect coagulation factors in different ways, and these effects probably change depending on the kind, potency, dosage, and mode of administration of the progestin. enhanced distensibility in veins and enhanced vasoconstriction in arteries are two possible vascular effects of progestins that may potentially lower blood flow [18]. Other biological parameters have been shown to be affected differently by progestins. According to studies, certain POCs can alter lipid parameters in both favorable and negative ways [19].

Strengths and Limitations

Encompassing a wide and diverse sample size from different countries, presents large-numbered data in this systematic review to increase the generalizability of findings. The variety of progestin-only methods, from oral to injectable and IUDs, enables a progression comparison for thromboembolic risk. Moreover, the study provides important information on patients with comorbidities; there are indeed patients who are complex but who receive POC tests for the management of diabetes or sickle cell disease.

Only few limitations should be kept in mind. Many of the studies included are observational in nature (e.g., helical CT analyses were nearly all case-control and retrospective cohort studies) and produce risk estimates that may be confounded. Moreover, the follow-up duration in studies was typically up to 1 year, which may have missed long-term effects on thromboembolism related to POC use.

Conclusion

While estrogen containing contraceptives still come with the thrombotic risk, POCs tend to have a safer profile than these types of drugs in women at elevated thrombotic risk. Nevertheless, injectable POCs may have a slightly higher risk of thromboembolism than their less active forms. For example, women with diabetes and sickle cell disease, can safely been on POCs. These results highlight the need for individualised contraceptive counselling, particularly for women with a past medical history of thromboembolism. Additional longitudinal research with subgroup analysis is required to ascertain the unique risk of specific POC formulations.

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