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Limited knowledge on progestogen-only contraception and risk of venous thromboembolism

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Abstract

Objective. To assess the current knowledge concerning progestogen-only contraception (POC) and risks of venous thromboembolism (VTE). *Design and setting*. Systematic review of the literature on observational and analytical studies reporting risk estimates for VTE in women exposed to POCs. *Methods and main outcome measures*. We performed a computerized literature search in the Pub Med, Embase, and the Cochrane Library for studies published between 1966 and February 13, 2008. Based on the evaluated studies we calculated an overall risk estimate for VTE in association with POC. *Results*. Four case-control studies and one cohort study were included. Of the case-control studies, three reported an increased risk and one a decreased risk of VTE. The cohort study found divergent results depending on the type of statistical analysis used. None of the results was statistically significant. The overall odds ratio for POC-associated VTE in the four case-control studies was 1.45 (95% CI = 0.92–2.26). *Conclusions*. The risk of VTE associated with use of POCs is poorly investigated. The slightly elevated overall risk estimate might suggest an association between POC and an increased risk for VTE. The results must, however, be interpreted with caution due to the possibility of residual confounding. Well-designed studies with sufficient statistical power to evaluate risks of VTE with POC are warranted.

Key words: *Progestogen-only contraception, venous thromboembolism, epidemiology, observational studies, systematic review*

Introduction

The use of exogenous hormones in women has been associated with an increased risk of venous thromboembolism (VTE). The well-established association between VTE and combined oral contraceptives (COC) has been attributed to the estrogen component, mainly because of its well-known effects on hemostasis (1,2). Progestogen-only contraception (POC) is assumed not to affect the risk of VTE. However, progestogens may affect both hemostasis and vessel walls, which are important etiological factors for VTE (3–5). Among POC, there are several regimens and methods of administration, using different progestogens, resulting in different systemic drug exposure. The different regimens have very variable effects on ovulatory function and contraceptive efficacy, and presumably, also on hemostasis (6). Oral POCs include the 'minipills' containing a low dose of progestogen, and the recently introduced medium-high dose oral progestogen-only pills (POPs). There are also high-dose, long-acting injectables and long-acting progestogen-only implants, delivering a medium-high daily dose. Finally, there is the levonorgestrel intrauterine device releasing a very low daily dose. All these different types of POC are available on the European market and hence used for contraception by many women (Table I). Consequently, it is important to review the

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Table I. Progestogen–only contraceptives available on the European market according to dose and route of administration. The general effect on ovulatory function is presented as footnotes.

Group according to dose	Progestogen intrauterine device	Progestogen-only pill	Progestogen implant	Progestogen injectables
High dose[a]				Medroxyprogesterone 150 mg/12 weeks Norethisterone enanthate 200 mg/8 weeks
Medium high dose[b]		Desogestrel 0.075 mg	Etonogestrel 68 mg (0.070–0.030 mg/24 h) Levonorgestrel 75 mg (0.100–0.030 mg/24 h)	
Low dose[c]		Lynestrenol 0.50 mg Levonorgestrel 0.030 mg Norethisterone 0.35 mg Etynodiol diacetate 0.50 mg Norethisterone 0.60 mg		
Very low dose[d]	Levonorgestrel 52 mg (0.020–0.011 mg/24 h)			

[a]High dose progestogens inhibit ovulation and result in low estrogen levels.
[b]Medium dose progestogens inhibit ovulation and result in early-mid follicular estrogen levels.
[c]Low dose progestogens affect ovulatory function only in some individuals, whereas many continue to have normal ovulations.
[d]Very low dose progestogens have no effect on ovulatory function.

present knowledge on VTE risk with different POC methods in larger populations. In this systematic review we summarize the available, published data from epidemiological studies assessing VTE risks in connection with use of POC.

Materials and methods

To identify publications on the association between POCs and the risk of VTE, we performed a computerized literature search in the electronic databases Pub Med, Embase, and the Cochrane Library. We set the criteria for eligibility as observational and analytical studies reporting risk estimates for VTE in women exposed to POCs. In the PubMed, the search was limited to studies in humans, reported in English, published between 1966 and February 13, 2008, and with an available abstract. The following single key words were used: 'Progestogen-only' or 'progestogens alone' or 'progestins' and 'VTE'. To search for further papers, we also used back-referencing (checking the reference list of the articles fulfilling our criteria). The same limitations and key words were used in the computerized literature search in the Embase and the Cochrane Library. To target the search in Embase, we included the substance names (lynestrenol, levonorgestrel, chlormadinone, desogestrel, norethisterone, etynodiol diacetate, medroxyprogesterone, etonogestrel).

The information from the reviewed case-control studies is presented in a forest plot (Figure 1), which also includes an overall risk estimate. For construction of the forest plot we used the Meta-analysis with Interactive eXplanations (MIX) software package (7). The overall odds ratio (OR) with a 95% confidence interval (CI) was calculated on the basis of risk estimates, CIs and the number of participants in each of the included studies.

Results

Using the key words, we identified 101 articles in the PubMed. After reading the abstracts, we were left with six studies fulfilling our criteria – i.e. observational and analytical studies of women exposed to POCs and including a risk estimate for VTE (8–13). Of these six studies, we excluded one case-control study since it contained data included in one of the other studies (8,10). All of the remaining five articles, reporting epidemiological studies, were published between 1998 and 2004. No relevant articles, not included among the 101 initially identified were found by back-referencing the five selected papers. In the Cochrane Library we identified 16 Cochrane reviews, five other reviews and 43 clinical trials, none of which included data on risk estimates for VTE for women using POC. Finally, in the Embase we identified 34 publications, but none of these fulfilled our inclusion criteria.

In the end we were left with five publications reporting observational and analytical studies of women exposed to POCs and including a risk estimate for VTE. There were four case-control studies and one cohort study (9–13). The main

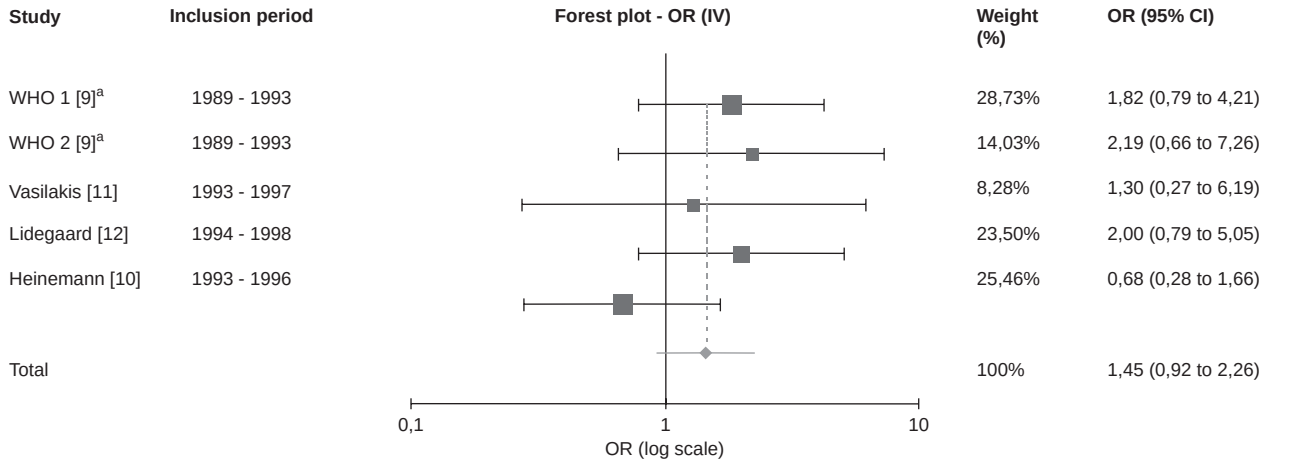

Figure 1. Forest plot with odd ratios from the reviewed case-control studies.
[a]The WHO study (9) presented risk estimates for progestogen-only pills (WHO 1) and progestogen-only injectables (WHO 2).

characteristics of the included studies are presented in Table II.

The WHO collaborative study of cardiovascular disease and steroid hormone contraception (9) was a case-control study evaluating risks of VTE, stroke and acute myocardial infarction (AMI) with POCs and combined injectable contraceptives. Cases and controls were recruited at 21 centers in 17 countries. Women aged 20–44 years (15–49 years of age in three centers), diagnosed with a first episode of VTE, AMI or stroke between February 1, 1989 and January 31, 1993, were included as cases. Controls were matched to cases by hospital and five-year age bands. There were 1,137 cases and 2,396 controls with VTE, of which 670 cases were included in the analyses. A modest, non-significant increased risk for VTE was reported among users of oral and injectable POCs. Neither current smoking nor hypertension was found to be significantly associated with VTE among users of POCs, and only Body Mass Index (BMI) was included in the adjusted analyses. Major limitations of the study include the small number of exposed cases and controls, the risk of recall bias of exposure selection bias due to use of hospital-based controls and the high number of exclusions. No overall analysis for POCs combined was presented, only analyses according to POC subtypes.

Vasilakis et al. (11) performed a nested case-control study including 49 cases and 275 controls. All women were identified through the General Practice Research Database (GPRD), and were women younger than 50 years of age with at least one prescription of a progestogen alone between January 1, 1993 and September 30, 1997. Current use was compared between cases and controls. Women with a first episode of VTE were included as cases. Those considered predisposed to cardiovascular diseases were excluded. Controls were matched to cases by age within one year and General Practice. A small, non-significant increase in relative risk (RR) for VTE was found among current users of POCs. Several analyses according to type of exposure were performed. The highest OR was found when progestogens had been prescribed for gynecological disorders. The study was limited by the small number of cases and controls that were exposed to POCs, which is reflected by the wide confidence intervals.

In a case-control study evaluating risks of VTE, stroke, and AMI by Heinemann et al. (10), 394 cases and 2,366 controls were included. Cases were women 16–44 years diagnosed with VTE, AMI, or stroke in one of 16 European hospitals between July 1993 and February 1996. Those considered predisposed to cardiovascular diseases were excluded. Controls were recruited at hospitals and from the community with an average of three controls to each case. At least one control was from the hospital and one from the community. The controls were matched to cases by five-year age bands. This was the only one of the included studies that found a decreased, non-significant risk of VTE with POCs. Although information on all POCs (POPs, injectables, and implants) was available, the authors only presented risks for POPs. Crude ORs were not presented, and of all investigated covariates, only BMI was included in the adjusted analyses, as it was the only variable that affected the risk estimate. Similar to the other studies, the major limitation of the study was the small number of cases and controls exposed to POCs, particularly as only POPs were included in the analyses.

A total of 987 cases and 4,054 controls were included by Lidegaard et al. (12) in a case-control study. Cases were identified through the Danish

Table II. Main characteristics of the included studies.

Study	Study design	Exposures	Numbers included in analyses for VTE	Number of women exposed to POC	Odds ratio or relative risk for POC together with 95% confidence intervals (CI)	
					Crude (95% CI)	Adjusted (95% CI)
WHO Collaborative Study (9) Contraception 1998	Case-control	All oral progestogens Continuous POP only Progestogen-only injectable Combined injectable	670 cases and 2,396 controls	32 cases and 97 controls	1.33 (0.77–2.31)[a] 1.27 (0.63–2.57)[b]	1.82 (0.79–4.22)[a,c] 2.19 (0.66–7.26)[b,c]
Vasilakis et al. (11) Lancet 1999	Nested case-control	All progestogens Progestogens for contraception Other progestogens COCs Pregnancy/post partum HRT	49 cases and 275 controls	Two cases and 26 controls	Not stated	1.3 (0.3–6.8)[d]
Heinemann et al. (10) The European Journal of Contraception and Reproductive Health Care 1999	Case-control	POP Progestogen-only injectable/implants	181 cases and 1,400 controls	Seven cases and 54 controls	Not stated	0.68 (0.28–1.66)[a,c]
Lidegaard et al. (12) Contraception 2002	Case-control	All oral contraceptives (COCs and POPs)	987 cases and 4,054 controls	Eight cases and 28 controls	1.6 (0.7–3.6)	2.0 (0.8–5.1)[a,e]
Conard et al. (13) Contraception 2004	Prospective cohort study	CMA	102 CMA-treated and 102 non-treated women	102 CMA-treated	1.3 (0.3–5.3)[f] 0.8 (0.2–3.5)[g]	Not stated[f] 0.8 (0.2–3.9)[g,h]

VTE: venous thromboembolism, COC: combined oral contraceptives, POP: progestogen-only pill, CMA: chlormadinone acetate, AMI: acute myocardial infarction.
[a]POP.
[b]Progestogen-only injectables.
[c]Adjusted for BMI.
[d]Adjusted for BMI and smoking status.
[e]Adjusted for age, year, family VTE, BMI, years of schooling, smoking, diabetes, coagulation disturbances, and previous birth.
[f]Poisson regression.
[g]Cox regression.
[h]Adjusted for age, BMI and thrombophilia.

National Patient Register as women 15–44 years with a first episode of VTE between 1994 and 1998. Controls were randomly selected from the Danish Central Person Register, and were matched to cases by age within one year. A two-fold, non-significant increased risk for VTE was found among users of POPs. As for the previously mentioned studies, the major limitation of this study was the small number of exposed cases and controls. Another important limitation was the possibility of recall bias of exposure, which might have been differential as use of hormonal contraceptives was evaluated about one year after diagnosis of VTE for cases, and in connection with study inclusion for the controls.

Conard et al. (13) performed a cohort study including 204 women of which 102 were exposed to chlormadinone acetate (CMA). The aim was to evaluate risks of VTE with POCs containing the 17α-hydroxyprogesterone derivate CMA in women at high risk of VTE. Apart from the limitation of the study to only evaluate CMA, a major difficulty for the interpretation was due to the divergent findings with the two different types of regression models used for statistical analyses. A RR of 1.3 was found when data were analyzed according to Poisson and a RR of 0.8 when data were analyzed using Cox regression. Based on the non-significant findings, the authors concluded that use of CMA as a contraceptive is not associated with an increased risk of VTE, and considered the contradictory results to be caused by the broader age classes used in Poisson regression compared with Cox regression. However, it should be noted that adjusting for age in the Cox regression model did not affect the risk estimate. The follow-up in the non-treated group was longer (mean: 35 months) compared with the treated group (mean: 31 months).

In the summary analysis including the four case-control studies, the overall OR was 1.45 (95% CI = 0.92–2.26, Figure 1). As the WHO collaborative study presented risks according to subtypes (oral or injectables), we included it as two separate studies.

When merging all included case-control studies, the total number of cases was 1,887 and the total number of controls was 8,117. By assuming an exposure frequency of 2.5%, which was the average frequency of exposure, we estimated the statistical power to be 70% to detect a RR of 1.45. For detecting a RR of 2, the merged data approached a power of 100%.

Discussion

We found that the risk of VTE associated with use of POCs is poorly investigated in larger populations, which is reflected by the fact that only five original studies evaluating risks of VTE and POC use were identified. Out of the five studies, three reported an increased risk of VTE (9,11,12), one found divergent results depending on type of statistical analysis used (13) and one showed a decreased risk (10). None of the risks was statistically significant.

After combining the data from the four case-control studies, the overall OR was found to be 1.45, but still not significant. We did not include the cohort study in this analysis because of the divergent results in the two statistical analyses that were presented, and as we deemed the cohort study to deviate too much from the other studies in terms of population and design (13).

In the past, POCs have not been as widely used as COCs. It could, however, be anticipated that in the future more women will be using POCs. Currently, there are many different and more effective POC methods available than in the past. Considering this and an increasing number of women with known risk factors for VTE, such as obesity, smoking, and previous VTE, it is not unlikely that larger number of women will be prescribed POCs instead of COCs (14–16).

The increased risk of VTE associated with sex hormones is predominantly explained by the effects on coagulation factors and fibrinolysis (1,4,17). However, effects on the vessel wall by estrogens and progestogens have also been reported (4,18,19). Such effects may depend on the type and dose of the progestogen, the route of administration, the duration of exposure, and, when combined with estrogens, the type and dose of the estrogen (20,21). It is disputed to what extent progestogens may affect primary hemostasis and platelet aggregation. Increased platelet counts and enhanced platelet aggregation have been reported, while others found no such associations (22,23). Furthermore, genetic variability might influence the risk of VTE associated with sex hormones as varying risks have been found in different ethnic groups (9,24). It is not known if the route of administration per se might affect the risk differently. In the WHO collaborative study, a somewhat higher risk estimate was found for injectables (adjusted OR = 2.19) compared with oral POCs (adjusted OR = 1.82), a finding that could be explained by the higher doses of progestogens in the injectables compared with the oral compounds, rather than by different routes of administration (9).

The elevated risk estimates in the summary analysis and in three out of five reviewed studies, together with risk estimates only slightly affected by adjustments for possible confounders, suggest an association between POC and an increased risk for

VTE (9–13). The results must, however, be interpreted with great caution as the precision of the risk estimates is low and since residual confounding, due to unrecognized or unmeasured factors, may render the results unreliable. Particularly in pharmacoepidemiological studies 'confounding by indication' should always be critically considered. It is not unlikely that women included in the reviewed studies were prescribed POC instead of COC because they were perceived to be carriers of risk factors for VTE. Such risk factors may well have been difficult to measure or too indistinct to be recognized and, therefore, not included in the adjusted analyses. In future studies it might be valuable to include information on genetic risk factors for VTE.

In summary, we found that scientific data concerning risks of VTE after use of POC is indeed sparse. The studies included here are few and none of them had sufficient statistical power to exclude moderate risks. Also in our meta-analysis, the power was not sufficient to detect smaller, but clinical significant risks. Accordingly, well-designed studies with sufficient power to evaluate risks of VTE with POC are warranted.

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