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Oral Contraceptives and Thrombotic Disease: Risk of Venous Thromboembolism

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Introduction

The history of the association between oral contraceptive (OC) use and venous thromboembolism (VT) began more than 35 years ago. Doctor Jordan, a general practitioner, reported on a 40-year-old woman who developed pulmonary embolism 10 days after stopping her mestranol and norethynodrel medication for endometriosis. He concluded the case-history in *The Lancet* (1) with the advice, "Because enavid may produce uncontrollable vomiting and provoke pulmonary embolism and infarction, I would counsel caution in the use of this widely advertised drug." Since then we are struggling with the association. Specialists and committees were reluctant to accept a relationship on the basis of case reports, until the more compelling report on the association between OC use and VTE was published by the Royal College of General Practitioners in 1967 (2). The major frustration during the last 35 years, however, has been lack of knowledge on how OC actually causes VTE, despite studies to elucidate its mechanism.

In this chapter we discuss epidemiological data gathered during 35 years of history, the search for pathophysiological understanding, with emphasis on recently found genetic and epidemiological data and we examine the clinical relevance and implications of these data.

Epidemiology

1967-1995

In order to estimate the risk of first venous thrombosis for women who used OCs as a method of birth control, a search for controlled trials published in English, French or German from 1960 to 1993 in which an index group was compared with a control group was conducted. The studies were identified by using Medline and by exploring references and reviews on this topic. A total of 588 articles or abstracts were reviewed (3), of which only 15 (2.6%)

were included in our examinations. These comprised one randomized controlled trial (4), 6 follow-up studies (5-10) and 8 case-control studies (2,11-17). The summary relative risk of first thrombosis during oral contraceptive use was 2.9 with a 95% confidence interval from 0.5 to 17.

Validity of the Studies

The 15 studies proved to be highly heterogeneous with regard to size and direction of the risk estimate (Fig. 1). Interpretation of the studies as a whole was therefore difficult. In these studies, objective diagnostic methods such as venography, ultrasound, impedance plethysmography, ventilation-perfusion scans, and postmortem examinations were either not explored at all or were only performed in some patients. The diagnostic problem could have led to numerous false-positive diagnosis, resulting in an overestimation of the RR. However, the more certain the diagnosis (10-12,18,19) or the more severe the VT events, the larger are the estimated relative risks. Thence, Katerndahl et al. (20) in their meta-analysis found that the method of diagnosis was not significantly related to RR.

Publication bias, caused by under-reporting smaller studies with no significant effect as a possible explanation of the outcome is less plausible, has seen the relative presence of smaller studies without a significant effect as depicted in Fig 1.

Five studies reported on the use of oral contraceptives containing 50 µg or more of ethinyl-estradiol (EE2), and four on doses less than 50 µg. In the remaining studies the dosage was not stated at all. Various case-control studies and cohort studies attribute the increased risk of VTE in OC users to the estrogen content of the OCs, but this effect has not consistently been shown to be related to dose (21,22).

The pooled summary estimate of case-control studies (RR 4.2) was higher than the pooled summary estimate of the cohort studies (RR 2.1). Cohort studies are considered methodologically stronger than case control studies because case-control studies can be affected by recall bias: a relative over-reporting of pill use is more likely when the patient suffered VTE as controls are likely to underreport pill use. Nevertheless, data from Glass et al. (23) and Stolley et al. (24) indicate that current or recent OC use is reported accurately. Interestingly, the only RCT, a study design least

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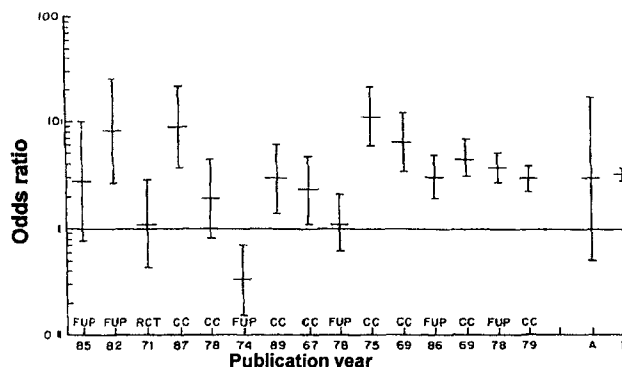


Fig. 1 Funnel plot of the relative risks and 95% confidence intervals ranked by standard error. FUP denotes follow-up study, CC case-control study and RCT randomized controlled trial. (A) represents the pooled unweighted relative risk; (B) represents the classical precision weighted (using inverse variance weights) pooled relative risk [from (3)].

likely to be biased, showed no difference in risk of VTE between 4965 OC users and 4933 vaginal barrier users (4). Although every study is likely to be affected by at least some bias, nearly all have reported elevated risk estimates of VTE after OC, increasing the plausibility of a causal relationship between current OC use and VT. Finally, it is characteristic of true association that this shows up whatever the shortcomings of studies set up to investigate it (albeit that an important flaw common to all studies can still produce erroneous conclusions.)

Smoking does not appear to be a risk factor for VTE (6,12,14,15,25); obesity (12,19) and varicose veins (6) are at most weak risk factors. Risk of VTE in pill users is unrelated to duration of OC use (11,12,18), and none of the studies have demonstrated an increased risk of VTE among past users or once the pill use has been stopped.

Recent Studies and Absolute Numbers

In recent studies in which the sub-50 (μg EE2 containing) pills were investigated comparing current users with non-users, the relative risk (RR) is 2.1 for fatal VT and pulmonary embolism (PE) (26), 3.8 for non-fatal deep venous thrombosis (DVT) (27), and 2.7 for superficial VT, DVT and PE (28). The data indicate that OCs containing less than 50 μg EE2 may still carry a risk of VTE. As the baseline incidence of deep VTE among young women who do not use OC is between 0.5–1 per 10,000 year (29–31), we can expect 20–40 cases annually with non fatal DVT per 100,000 women using sub-50 OCs [about one million women in the Netherlands use OCs throughout the year (32) and 10–20 cases with fatal VT and PE]. Case fatality of VTE is between 1–2% in young persons (33). The recurrence risk of VTE is not well known, especially among OC users. This is particularly remarkable since concern about recurrent venous thrombosis led many physicians to advise women to cease use of OCs after a first thrombotic episode (34). Our attempt at quantifying the difficult clinical decision whether or not to discontinue oral contraceptives after a first thrombosis has led to the startling result that we

lack the necessary data to answer this question (3). Only follow-up study on recurrence risk will settle the issue.

Coagulation

As a plausible mechanism behind the increased risk of VTE in OC users, it was suggested that in OC users activation of coagulation and fibrinolytic systems could alter the delicate dynamic hemostatic balance so that VTE can develop (35,36). Many studies indeed show changes in the activation of coagulation and fibrinolytic compartments, albeit within the normal range. Pathological estimates could not be found or may have escaped detection because the investigated persons were few, were healthy volunteers, and in a static hemostatic situation when the blood samples were taken. Moreover, investigators in general were more concerned with VTE factors than are risk factors for arterial disease, such as smoking and hypertension, and with measuring all kind of biochemical and hematology variables for safety reasons, required by the authorities than in true clinical outcomes. During at least the last decade the gold standard for examining the thrombogenic potential of (newly introduced) OC preparations is and was measuring the variables in the hemostatic system in young healthy volunteers. Epidemiology had to show us that clinical endpoints were of more relevance.

Inheritable Clotting Defects

A major leap ahead in the understanding of the clotting mechanism in OC users arose from an epidemiological study on an interaction between a newly discovered inheritable coagulation disorder and OC use (27). Factor V Leiden, a single point mutation in the Factor V (37) leading to the resistance to activated protein C, was studied in a population-based case-control study, the Leiden Thrombophilia Study (LETS) (38).

In the Leiden study, 474 consecutive patients with objectively confirmed first DVT occurring between 1988 and 1993 were recruited from three anticoagulation clinics which monitor all anticoagulant treatment in a well-defined geographical area. A healthy control subject of the same sex and approximately same age was drawn for each patient. Six to 19 months after the acute event, all patients and control subjects were thoroughly interviewed, and blood samples were taken. For the analysis of OC users, 155 patients and 169 controls aged between 15 and 49 years, who were premenopausal, non-pregnant and not in their puerperium, were included.

The carrying of Factor V Leiden (FVL) increases the risk of DVT almost eight-fold, use of oral contraceptives increases the risk four-fold; and in combination they should increase the risk to a maximum of 30-fold. However, the actual risk of DVT in OC using carriers of FVL was 35, which is higher than the summed effect of both factors. This implies that the simultaneous presence of both risk factors leads to an additional number of women experiencing thrombosis than would have been expected if the risks were independent. Thence, the two factors showed a

Table 1 Absolute risk of deep venous thromboembolism

FVL	OC use	Incidence per 100,000 women (years)
-	-	8
-	+	30
+	-	57
+	+	285

Table 2 Prevalence of heritable clotting defects in a healthy population and among VTE patients

	Healthy population	VTE patients	Ref.
Antithrombin	0.2	1.1	38,39
Protein C	0.2	2.7	38,40
Protein S	1.3	1.3	38
FVL	Caucasian, 3-5%	20% of consecutive, random VTE patients; 50% of unexplained VTE	38

synergistic effect. This means that in the presence of both factors, thrombosis will occur in a substantial number of women who would not have experienced thrombosis if they have only one of the risk factors.

The biological background might be that FVL and oral contraceptive use both lead to changes in the anticlotting cascade, for instance the activation of protein S and C, which enhance each other. Since FVL and OC use are common risk factors, this synergistic effect may affect many women. The incidence calculated from the LETS data are shown in Table 1, while prevalence data on the known inheritable clotting factors are shown in Table 2. The absolute risk of DVT for antithrombin, protein C, protein S deficiency in non OC and OC users are low (41).

Screening

The finding of a genetical cause for a disease is nearly always accompanied by a strong desire to screen for the trait. Screening recommendations for FVL in potential OC users were no exception. Such policy, however, might deny effective contraception to about 5% of white women, while preventing only a small number of deaths due to PE. Taking a personal and family history of DVT when prescribing OC will detect persons from families with a tendency to multiple VTE and might be worthwhile (42). A genetic defect in the coagulation system, such as factor V Leiden, is not an absolute contraindication for pill use, but should always be subjected to assessment of individual risk (43).

Third-Generation Progestins

Representatives of first-generation progestins, derivatives of nortestosterone, are norethisterone and lynestrenol. At the end of the 1960s the second-generation progestin, levonorgestrel (LNG), which is also a derivative of

nortestosterone, was introduced. The third-generation progestins, derivatives of LNG, were developed to reduce androgenic metabolic side-effects with a similar or even higher contraceptive efficacy. Representatives of this group are desogestrel (DSG) and gestodene (GSD). A third derivative, norgestimate (NGM), is difficult to classify because it is partially metabolized to LNG and partially to other intermediates.

Historically, the first-generation progestins were coupled to high doses of estrogens, that is 50 µg or more. Second-generation progestins have been coupled to lower doses of EE2, that is 30 µg in the monophasic pill, and were already called lower dose pills. The third-generation gestagens DSG, GSD and NGM contain also 30 µg EE2 or lower. In Europe the major brands contain DSG and GSD, in the USA NGM and in part DSG.

Four Studies: WHO

Most studies on VTE in OC users were undertaken in northern Europe and in the US in the 1960s and 1970s when higher doses of steroids were applied than today and when objective diagnosis of VTE was lacking. WHO, therefore, conducted an international multicentre, hospital-based, case-control study between 1989-1993 (44). Included were 1143 women (aged 22-44 years) with a history of idiopathic VTE and 2998 age-matched controls. OC use was associated with an increased risk of VTE both in Europe (RR 4.15; 95% CI 3.09-5.57) and in non-European countries (RR 3.25; 95% CI 2.59-4.08). These figures were unaffected by certainty of diagnosis (definite, probable, possible), the age of the user, a history of hypertension or by smoking, the last two being risk factors for arterial disease. A body mass index of more than 25 kg/m² was an independent weak risk factor for VTE, predominantly among users of DSG and GSD containing pills. Totally unexpected, the WHO study showed a further doubling or tripling of the risk of VTE among users of third-generation OCs. In a detailed analysis (29) comparing 769 cases with 1979 age-matched hospital controls and in one centre with 246 community controls matched for age and general practice, there was a three-fold elevated risk of VTE in women using LNG and a 9-fold risk in women using DSG or GSD containing pills compared with non-users. A direct comparison of DSG and GSD containing pills with LNG-OCs revealed risk estimates of 2.2 and 3.0, respectively (adjusted for body mass index).

Four Studies: GPRD

The scientists from WHO needed a second opinion and asked Professor Jick from Boston for an analysis of the database of the General Practice Research Database (GPRD), owned by the UK Health Departments, comprising 238,130 women (30). The RR of VTE associated with DSG and GSD containing OCs was twice that of LNG pills. The excess risk for VTE among women using DSG and GSD containing OCs compared with those containing LNG was 16 per 100,000 women years (Table 3).

Table 3 Absolute risk of non-fatal VTE (30)

Group	Non-fatal VTE cases per 100 women (years)
non-OC users	3.8
OC with LNG	16.1
OC with DSG	29.3
OC with GSD	28.3

Four Studies: LETS

From the original LETS data base (38), 126 women and 159 controls were selected with the following criteria: known type of pill used at the time of thrombosis (index data were obtained from an interview and checked with the hospital discharge letter), complete information available on the pill type, and that at least five cases and controls per type of pill were used. A positive family history was defined as one or more parents or siblings with VTE. The highest age-adjusted RR was found for the DSG containing pill of 8.7. All other OC types, including pills containing a second-generation progestin and 50 µg EE2, gave a risk ranging from 2.2 to 3.8. The RR for the DSG containing pill was similar among women with and without a family history, which means that preferential prescription because of family history cannot explain these findings. Nor could the excess risk be explained by previous pregnancy, and the risk was highest in the youngest age categories where one would expect most new users (31).

Four Studies: Transnational

At the request of, but not funded by, the German authorities, the Transnational case-control study was undertaken in response to concern that GSD might increase the risk of vascular events. In an interim report (45) on 471 cases and 1772 controls, the adjusted odds ratio for VTE in OC-users vs. non-users was 4 (95% CI 3.1–5.3); the odds ratio for DSG and GSD containing OCs vs. second-generation products was 1.5 (95% CI 1.1–2.1).

Biases

The publication of these four studies prompted a series of similar counter-arguments in letters to publishers and again in recent publications. Attention was drawn to biases such as starter/healthy user bias, prescribing bias, referral bias and diagnostic bias.

Starter and healthy user bias means that venous thrombosis occurs mainly at the start of OC use and that the starters generally had the new, third-generation OCs. Thus, among these first-time users, the women who are most at risk, are susceptible to the thrombogenic effects of OCs, use the new third-generation pills. In contrast, second-generation pill users in the studies consist mainly of healthy women who had already used the pill for a long time and who had never developed thrombosis, not even during pregnancy, and therefore stayed with their trusted brand. In short: the second-generation products users are a selection of healthy users, the third-generation users are susceptible for thrombosis.

Table 4 RR of VTE among women aged 25–44 years who used different OCs [see (46) by year of market introduction]

OC	Year of market introduction	RR of VTE
LNG	1972/74	1
POP	1971/74	1.1
DSG+30 µg EE2	1981	1.5
GSD	1986	2
NGM	1986/92	2.4
DSG+20 µg EE2	1992	2.8

Table 5 RR of VTE among women aged 16–24 years and 25–44 years (derived from Table 4) who used different OCs

OC	RR of VTE in women (years)	
	16–24	25–44
LNG	1	1
POP	1.9	1.1
DSG+30 µg EE2	2.6	1.5
GSD	1.4	2
NGM	1.7	2.4
DSG+20 µg EE2	0.4	2.8

This, in principle, is a worthwhile argument. The authors of the Transnational tried to support the healthy user effect by their finding that a successive increase of VTE risk among women aged 25–44 years was associated with the introduction of a new OC on the market, in comparison with LNG (46) (Table 4).

Reconstructing the data of the women aged 16–24 years, which comprise one-third of the cases and nearly 50% of the controls, we arrive at the data, shown in Table 5, indicating an overall higher VTE risk of third-generation products and almost an inverse relation with the year of OC introduction, which refutes the conclusion of the authors of the Transnational study (46).

Another argument that mitigates against this type of bias is that the difference in RR for VTE between third- and second-generation OCs did not disappear when the group of first-time users, who experienced VTE for the first time, was excluded (Table 6). All four studies actually dealt with first thrombosis events; in three of them the first-time users were explicitly described. The RR in the group of the first-time-users became slightly larger compared with the overall figures.

VTE occurs frequently in the first year of OC use, especially in first-time users. However, VTE among first-time-users is twice as frequently found in the group of third-generation OC users group, as in the second-generation OC users group (29).

There is thus no justification to explain the effect by starter/healthy-user bias.

Prescription bias means that third-generation products were preferentially prescribed to women at high risk so that the increased relative risk merely reflect a higher baseline risk. When examining this argument, we should ask ourselves how a prescribing physician would predict that a young woman who has never had a venous thrombosis, is

Table 6 RR of VTE concerning third- vs second-generation OCs

Study	RR		
	First-time user	Later	Overall
Transnational (45)	2.7	1.4	1.5
GPRD:			
DSG (30)	9.2	1.8	1.9
GSD	5.6	1.8	1.8
WHO (29)	5.4	2.4	2.2-3

at higher risk of developing VTE, so that he or she would prescribe a third-generation contraceptive. Smoking is not a risk factor for VTE but is for arterial disease. Obesity is not a risk factor; only gross obesity might be a weak risk factor. Superficial varicose veins as a result of an earlier thrombotic event can be a weak risk factor, but all four studies were restricted to first thrombosis events. The most interesting risk factor for VTE is family history, in particular when coupled to FVL. Yet, knowledge about FVL is too recent to have influence of the results of the four original studies.

A third objection is that all studies might have overestimated the risk of OCs because of a diagnostic bias towards a diagnosis of VTE in women who use the pill. In the WHO (29) and the GPRD study (30), a separate analysis was made for cases with definite and probable diagnosis to see whether the association would disappear in the more secure diagnosis. This was not the case.

Further, other potential biases have been put forwarded. One argues that the newer studies have shown only a lower frequency of thrombosis among second-generation users compared to the earlier studies (47), which suggests that the higher risk among third-generation users is not higher, but equal to, second-generation users. The best comparisons always remain those within studies than among studies because the same diagnostic criteria were used, as was the case in the four original studies.

With switching bias, one tries to indicate that headaches and dizziness are reasons for switching from second- to third-generation pills (48). There are no data to suggest that these symptoms are risk factors for VTE. Further, in some databases one sees a switching in the direction of third-generation pills, but in other databases the switch is the other way around (49).

Mortality Rate

Protection against myocardial infarction (MI) by third-generation vs. second-generation products was suggested by one study, and in view of the wide confidence intervals this has been overemphasized (50). While that finding has not been confirmed by preliminary data from a Danish study (51), one should also bear in mind that among women aged 15-49 years the mortality risk from VTE is higher than that risk from MI (52).

Lidegaard and Milgrom (53) argued that an increase in the overall incidence of VTE since the introduction of third-generation pills should be expected but has not been demon-

strated, can be rebutted by the finding of a recent increase in VTE mortality among young women both in the Netherlands and in the United Kingdom (52,54).

Conclusion

Apart from the social and financial consequences, deep venous thromboembolism may be followed by the serious condition of pulmonary embolism and by post-thrombotic syndrome. Despite adequate treatment, approximately 5% of patients with DVT treated with heparin have major bleeding. About 50% of patients with proximal vein thrombosis and one-third of patients with DVT will suffer from post-thrombotic syndrome, which is a chronic complication with symptoms of pain, swelling and occasionally ulceration of the skin of the limb (55). Vessel reflux, obstruction or both are observed in almost all patients with the syndrome (56).

Before each treatment a physician must balance the pros and cons based on a patient's history and the evidence available. That policy should also apply to the prescription of oral contraceptives. A personal or family history of VTE is reason for selective screening of inheritable coagulation factors such as the mutated factor V. Women with risk factors should not be bluntly barred from OCs but should always be subject to assessment of individual risk and benefit. The first choice of prescription for healthy, first-time users is a second-generation OC.

Drug regulatory authorities should be aware that intermediate end-points have thus far failed to adequately address the thrombogenic potential of OC preparations (57) and should adapt their operative regulations in asking for more up-to-date assay protocols when dealing with such products. The scientific community is assiduously engaged in elucidating which mechanism oral contraceptives interfere in the development of venous thromboembolism. Epidemiologists can concentrate, among others, on the relative risk for thrombosis for each OC product and on the likelihood of recurrence of VTE (58).

In combination such efforts can increase the safety of one of the safest and most widely used categories of drugs: oral contraceptives.

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Summary

Studies conducted in the first three decades after discovery of a link between venous thromboembolism and oral contraceptive users showed a relative risk of first thrombosis during oral contraceptive use of 2.9 (95% CI 0.5-17). In recent studies in which the sub-50 µg ethinyl estradiol containing pills were investigated comparing current users with non-users, the RR is 3.8 for non-fatal deep VTE and 2.7 for superficial VTE, deep VTE and pulmonary embolism (PE) together and 2.1 for fatal VT and PE together. The association is attributed to the estrogenic

component and not related to duration of pill use. The risk disappears once the pill has been stopped, and it is not elevated among past users. Smoking does not appear to be risk factor for VTE; obesity and varicose veins are, at the most, weak risk factors.

Since a causal relationship between OC use and VTE is tempting, clues for unraveling the mechanism were sought in the hemostatic system. Studies of the coagulation system found changes in the activation of coagulation and fibrinolytic compartments, but within the normal range. An epidemiologic study showed that the risk of VTE among women using OCs is 30-fold increased by the presence of a mutation of factor V, called Factor V Leiden (5% prevalence in the Caucasian population). Selective screening for the mutated factor V should be limited to women with a personal or family history of VTE.

Four epidemiologic studies showed a two-fold increase in risk of VTE with the use of OCs containing third-generation progestins (gestodene and desogestrel), relative to second-generation products (levonorgestrel). Biases cannot devalue the conclusion that the increased risk of VTE in especially first-time and younger users of third-generation OCs is highly likely. The clinical consequence is therefore that second-generation OCs are the first choice in prescription to first-time users.

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