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REVIEW ARTICLE

Hormone therapies and venous thromboembolism: where are we now?

A. VAN HYLCKAMA VLIEG* and S. MIDDELDORP†
**Leiden University Medical Center, Department of Clinical Epidemiology, Leiden; and †Academic Medical Center, Department of Vascular Medicine, Meibergdreef, the Netherlands*

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Deep vein thrombosis is a common disease, with an incidence of one to three per 1000 individuals per year [1]. Numerous risk factors are known, which can be divided into genetic and acquired [2]. One of the most well-known acquired risk factors is the use of female hormones, i.e. oral contraceptive use or the use of hormone replacement therapy. Apart from the use of hormones orally, other routes of administration are also available, e.g. intrauterine devices, injectables, subcutaneous implants, or skin patches. While most research regarding the risk of venous thrombosis has been conducted on oral hormone use, an increasing number of studies are focusing on the thrombotic effect of these alternative routes of administration. Here, we will review the current knowledge on the risk of venous thrombosis associated with premenopausal hormone use for contraception and with postmenopausal hormone replacement therapy. The impact of hormone use for women who have an increased risk for venous thrombosis will be discussed. These include carriers of thrombophilia, women with a positive family history of venous thrombosis, and women who have experienced venous thrombosis.

Oral contraceptives

Combined oral contraceptives (containing an estrogen and a progestagen) were first approved in the USA in 1960. It is estimated that more than 100 million women worldwide use an oral contraceptive [3].

Soon after their introduction, it became apparent that the use of these female hormones was associated with an increased risk of thrombosis. The first report of an increased risk of venous thrombosis associated with oral contraceptive use appeared in 1961 [4]. Subsequently, numerous reports have been published on the increase in thrombotic risk, indicating a two-fold to six-fold increased risk of deep vein thrombosis associated with current oral contraceptive use [5–11].

Correspondence: Astrid van Hylckama Vlieg, Department of Clinical Epidemiology, C7-P, Leiden University Medical Center, PO Box 9600, 3500 RC Leiden, the Netherlands.
Tel.: +31 71 5264037; fax: +31 71 5266994.
E-mail: A.van_Hylckama_Vlieg@lumc.nl

Most currently available oral contraceptives are combined preparations containing both an estrogen (i.e. ethinylestradiol [EE2]) and a progestagen. Numerous types of oral contraceptives are available, containing different doses of estrogen and different types of progestagen. The first available preparations contained a high dose of the estrogen EE2. However, after the reported increased thrombotic risk associated with combined oral contraceptive use was attributed to the amount of estrogen in the contraceptive pill, the dose of estrogen was reduced stepwise. The initial lowering of the estrogen dose from $>$ 50 μg to 30 μg was indeed shown to be associated with a clear decrease in the risk of venous thrombosis [12,13]. In two recently published studies, it was shown that a further decrease in the estrogen dose to 20 μg led to an additional lowering of the risk of venous thrombosis [10,11]. In the MEGA study, a large case–control study, we showed that, after adjustment for type of progestagen, oral contraceptives containing 20 μg of estrogen were associated with a slightly decreased risk of venous thrombosis as compared with oral contraceptives containing 30 μg of estrogen (odds ratio [OR] 0.8, 95% confidence interval [CI] 0.5–1.2) [10]. The study by Lidegaard *et al.* [11] also showed that a reduction in estrogen dose from 30 or 40 to 20 μg was associated with an 18% reduction in the risk of venous thrombosis [11].

The progestagens in combined oral contraceptives appear to counter the prothrombotic effect of the estrogens. Numerous different types of progestagens with different chemical compositions are available. The oldest types of progestagens, i.e. the first-generation progestogens, were lynestrenol and norethisterone. Nowadays, these first-generation progestagens are not used very often. Second-generation oral contraceptives, which are widely used, contain the progestagens levonorgestrel or norgestrel. Newer types of oral contraceptives, i.e. the third-generation oral contraceptives, contain the progestagens gestodene or desogestrel. Norgestimate is categorized as a third-generation progestagen. However, as it is, in part, converted to levonorgestrel, it may metabolically belong more to the second-generation progestagens. Preparations containing cyproterone acetate are used for the treatment of acne vulgaris, seborrhea, or mild hirsutism, and have an antiovulatory action similar to that of a progestagen. Preparations

containing drospirenone, which is an antimineralcorticoid, also inhibit ovulation.

There is evidence that the different progestagens counter the prothrombotic effect of estrogens differently, and are therefore associated with different venous thrombotic risks [14]. The risk of venous thrombosis was reported to be increased for users of the third-generation oral contraceptives as compared with users of the second-generation oral contraceptives [15]. However, this finding was not confirmed in all studies. The difference in thrombotic risk between third-generation and second-generation oral contraceptives has been the subject of a long ongoing debate, with non-believers explaining the difference in risk by bias and confounding. However, a large meta-analysis countered most of these arguments of bias and confounding, and demonstrated an increased risk of thrombosis for third-generation as compared with second-generation oral contraceptives; subsequently, several other studies confirmed this finding [16]. Furthermore, the results of studies on the effects of different types of oral contraceptives on the hemostatic system were in line with these findings, i.e. showing that there was a more prothrombotic risk profile, including more activated protein C (APC) resistance, associated with third-generation oral contraceptives than with second-generation oral contraceptives [17–21].

Oral contraceptives containing cyproterone acetate have been associated with a highly increased risk of venous thrombosis or fatal pulmonary emboli; however, this was not confirmed by all studies [22–24]. Recent studies have indicated that these oral contraceptives are associated with an elevated thrombotic risk as compared with oral contraceptives containing levonorgestrel [10,11].

EE2 with drospirenone has been approved as an oral contraceptive in all European Union countries since 2000. Shortly after their introduction, several case reports indicated a highly increased risk of venous thrombosis associated with these oral contraceptives [25–28]. This high risk of thrombosis was confirmed by our large case–control study and a large follow-up study, which both reported a higher risk of thrombosis as compared with oral contraceptives containing levonorgestrel or gestodene [10,11].

The so-called mini-pill is an oral progestagen-only preparation. Whereas oral progestagen-only preparations are associated with an increased risk of venous thrombosis when used for therapeutic reasons (containing different progestagens or higher doses of the progestagens used in oral contraceptives) [29,30], oral progestagen-only preparations used for contraceptive reasons appeared to be, at most, associated with a mildly increased risk of thrombosis [30,31]. More recently, Lidegaard *et al.* [11] have shown that oral progestagen-only oral contraceptives do not appear to be associated with an increased risk of venous thrombosis, regardless of the type of progestagen: desogestrel-containing progestagen-only preparations, rate ratio (RR) 1.1, 95% CI 0.4–3.4; norethisterone-containing or levonorgestrel-containing preparations, RR 0.6, 95% CI 0.3–1.0.

Effect of oral contraceptive use on the coagulation system

Oral contraceptive use is associated with changes in the levels of coagulation factors, leading to a predisposition to venous thrombosis. Oral contraceptive use is associated with increased resistance to the natural anticoagulant activity of APC [32]. In line with the increased thrombotic risk associated with oral contraceptives containing desogestrel as compared with levonorgestrel, these third-generation pills induce more pronounced APC resistance than the second-generation preparations [17,18,33]. The highest APC resistance, resulting in the most thrombotic tendency of the coagulation system, was found in women using oral contraceptives containing cyproterone acetate [33]. Similar differences between these types of oral contraceptive were observed in levels of anticoagulant proteins, such as protein S and tissue factor pathway inhibitor (TFPI); that is, oral contraceptives associated with a higher risk had lower levels of both free protein S and free TFPI [20,34]. Furthermore, the changes induced in coagulation factors and fibrinolytic parameters differ between second-generation and third-generation oral contraceptives [19,21].

From the results of these studies, it is clear that the use of oral contraceptives is associated with a procoagulant risk profile. Still, one might question whether these intermediate endpoints, e.g. markers of hemostasis that have been related to the risk of venous thrombosis, indicate a true increased risk of venous thrombosis associated with hormone use. However, in line with observed differences in the risk of venous thrombosis associated with different progestagens, all studies using these intermediate endpoints point in the same direction, with a more thrombotic risk profile in users of the third-generation oral contraceptives containing desogestrel or gestodene, and in users of oral contraceptives containing cyproterone acetate or drospirenone, than in users of oral contraceptives containing levonorgestrel.

Non-oral contraceptives

Oral contraceptives are the most frequently used hormonal contraceptives. However, other routes of administration of hormonal contraceptives are also available, e.g. intrauterine devices, injectables, subcutaneous implants, or skin patches. The risk of venous thrombosis associated with these non-oral contraceptive methods has been studied to a much lesser extent than that associated with oral contraceptives.

In the following paragraphs, we provide an overview of the available information on the risk of venous thrombosis associated with depot medroxyprogesterone (DMPA) injectable progestagen-only contraceptives, the hormone-releasing intrauterine device, the hormonal contraceptive ring, the hormonal contraceptive patch, and the hormonal contraceptive implant.

Injectable DMPA progestagen-only contraceptives

DMPA is a long-acting injectable progestagen-only contraceptive. In 1998, the World Health Organization reported a small increase in thrombotic risk associated with the use of injectable

progestagen (medroxiprogesterone)-only contraceptives (OR 2.2; 95% CI 0.7–7.3) [31]. Although, also in the MEGA study, a small number of women used DMPA-only contraceptives, we found a clearly increased risk of venous thrombosis associated with these contraceptives as compared with non-use (OR 3.6; 95% CI 1.8–7.1) [35]. Other studies mainly investigated intermediate endpoints, e.g. coagulation factors and APC resistance. In contrast to these clinical findings, Walsh *et al*. reported a decrease in sex hormone-binding globulin (SHBG) level, a probable marker of the risk of venous thrombosis [36,37]. Several studies that assessed the effect of DMPA-only contraceptives on coagulation or inflammation markers reported little or no effect [36,38,39].

Levonorgestrel-releasing intrauterine device

The levonorgestrel-releasing intrauterine device or system is a T-shaped plastic contraceptive that is inserted into the uterine cavity [40]. After insertion of a levonorgestrel-releasing intrauterine device, plasma levels of levonorgestrel are 150–200 pg mL^{-1} in the peripheral blood [41], as compared with a maximal level of 800 pg mL^{-1} during the use of a 30-μg levonorgestrel-only pill. The use of the levonorgestrel-releasing intrauterine device was not associated with an increased risk of venous thrombosis in a large follow-up study on venous thrombosis (RR 0.9; 95% CI 0.6–1.3) or in the MEGA case–control study (OR 0.3; 95% CI 0.1–1.1) [11,35]. Furthermore, with the use of the thrombin generation-based APC resistance assay, higher sensitivity to APC in women 3 months after the insertion of the levonorgestrel-releasing intrauterine device than before the insertion was observed, suggesting a low thrombosis risk, whereas there was no change after insertion of a copper intrauterine device [42]. The decrease in APC resistance appeared to be most pronounced in women who switched from a combined oral contraceptive to the levonorgestrel-releasing intrauterine device.

Transdermal patches and hormone-releasing vaginal ring

New types of combined contraceptive are the transdermal patch and the hormone-releasing vaginal ring. The contraceptive patch was designed to deliver 20 μg of EE2 and the contraceptive vaginal ring 15 μg EE2 per day. Both types of contraceptive contain a third-generation progestagen. The transdermal patch contains norelgestromin, the primary active metabolite of norgestimate, and the vaginal ring contains etonogestrel, a metabolite of desogestrel [43].

So far, little information is available regarding the thrombotic risk associated with these contraceptive methods. As compared with oral contraceptives containing norgestimate, for users of the transdermal patch, the reported risks of venous thrombosis varied between no increase (OR 1.0; 95% CI 0.7–1.5) to a more than two-fold increase (incidence rate ratio 2.2; 95% CI 1.3–3.8) [44–46].

Further studies assessing the effect of these contraceptive methods on the risk of venous thrombosis mainly used intermediate endpoints. Again, findings were contradictory. In a randomized crossover trial, similar adverse effects on vascular risk markers with an oral contraceptive containing norgestimate and with the contraceptive patch were observed [47]. Other studies, however, reported more prothrombotic effects associated with the use of the hormonal patch than with different types of oral contraceptives [48–50].

Even less information is available on the risk of venous thrombosis associated with the vaginal ring. As compared with combined oral contraceptive use (mainly third-generation oral contraceptives), a beneficial effect associated with the use of the vaginal ring was reported [49], whereas in a different study, the vaginal ring was associated with more resistance to APC and a higher level of SHBG than the use of levonorgestrel-containing contraceptives [50,51].

Hormonal implants

The etonogestrel implant is a progestagen-only contraceptive that is implanted under the skin. Etonogestrel is an active metabolite of the third-generation progestagen desogestrel. The delivery dose of progestagen varies over time, from 60–70 μg d^{-1} in the first weeks of use to 25–30 μg d^{-1} after 3 years. Very little is known about the thrombogenicity of the etonogestrel implant. Lindqvist *et al*. [52] reported in 2003 that etonogestrel implant use was not related to hypercoagulable changes in the anticoagulant system or the prothrombotic factors V, VII, and VIII. In a study by Vieira *et al*. [53], it was reported that the etonogestrel-releasing implant was associated with a reduction in APC resistance and the levels of several prothrombotic factors (prothrombin, FVII, FX, and F_{1+2}), whereas plasminogen activator inhibitor-1 and FXI levels were increased. However, all factors remained within the normal range, suggesting that the use of an etonogestrel implant is not associated with a prothrombotic risk profile.

An overview of recent estimates of the thrombotic risks associated with the use of different types of hormonal contraceptives is shown in Table 1.

Hormone replacement therapy

Until the late 1990s, hormone replacement therapy was considered to be an effective measure to improve cardiovascular risk factors, in particular lipid profiles [54], and protect women against the postmenopausal rise in the incidence of arterial cardiovascular disease [55,56]. However, large, randomized controlled trials showed that hormone replacement therapy does not prevent arterial cardiovascular disease, and even has a detrimental effect in the first year of use [57–59]. Nowadays, the indication for hormone replacement therapy is limited to improving quality of life by alleviating perimenopausal complaints, and it should be given at the lowest possible dose for the shortest possible duration [60].

Like contraceptive hormones, hormone replacement therapy is available in various forms. It generally provides a low dose of estrogen, most often together with progesterone or a progestin.

Table 1 Recent estimates of relative risks associated with use of contraceptives

	MEGA case–control study [10,35], odds ratio (95% CI)	Danish National cohort study [11], rate ratio (95% CI)	WHO [31], odds ratio (95% CI)	Jick *et al.* [44], odds ratio (95% CI) Cole *et al.* [45], incidence rate ratio (95% CI)
Combined oral contraceptives				
Estrogen 30 μg and noresthisterone	3.9 (1.4–10.6)			
Estrogen 30 μg and levonorgestrel	3.6 (2.9–4.6)	2.02 (1.75–2.34)*		
Estrogen 37.5 μg and lynestrenol	5.6 (3.0–10.2)			
Estrogen 30 μg and norgestimate	5.9 (1.7–21.0)			
Estrogen 30 μg and desogestrel	7.3 (5.3–10.0)	3.55 (3.30–3.83)*		
Estrogen 30 μg and gestodene	5.6 (3.7–8.4)			
Estrogen 30 μg and drospirenone	6.3 (2.9–13.7)	4.00 (3.26–4.91)*		
Estrogen 35 μg and cyproterone acetate	6.8 (4.7–10.0)			
Progestagen-only				
Pills				
Levonorgestrel 30 μg or norethisterone 350 μg		0.59 (0.33–1.04)		
Desogestrel 75 μg		1.10 (0.35–3.41)		
Progestagen-only injectable	3.6 (1.8–7.1)		2.2 (0.7–7.3)	
Levonorgestrel-releasing intrauterine device	0.3 (0.1–1.1)	0.89 (0.64–1.26)		
Transdermal Patches†				1.0 (0.7–1.5) [44] to 2.2 (1.3–3.8) [45]

CI, confidence interval; WHO, World Health Organization.
All compared with non-use unless stated otherwise: *with 20–40 μg of estrogen; †as compared with oral contraceptives containing norgestimate. No risk estimates are available for the vaginal ring or hormonal implants.

Conjugated equine estrogens are derived from the urine of pregnant mares, contain several biologically active estrogen compounds, and are the most widely used components of hormone replacement therapy. Esterified estrogens are synthetic and fabricated from soybean and yam. Unopposed estrogen is restricted to women who have had a hysterectomy, because of the increased risk of endometrial cancer. Hormone replacement therapy can be taken by mouth, or delivered via patches, creams, gels or, more rarely, injection. Dosage can be varied cyclically, with estrogens being taken daily and progesterone or progestins taken for about 2 weeks every 1 or 2 months (sequentially combined hormone replacement therapy), or a constant dosage being used, with both types of hormones taken daily (continuous combined hormone replacement therapy).

Both observational studies and randomized controlled trials have consistently shown an approximately two-fold to three-fold increased risk of venous thrombosis in users of hormone replacement therapy [58,61–63]. Most early studies of venous thromboembolism in users of hormone replacement therapy were performed among women using conjugated equine estrogens alone or with medroxyprogesterone acetate. Although, in the Women's Health Initiative study, estrogen-only hormone replacement therapy in women without a uterus was associated with only a small increase in the risk of venous thrombosis in the first 2 years of use, and the risk was less than with the combination of estrogen plus progestin (hazard ratio (HR) 1.47; 95% CI 1.06–2.06) [64], this was not confirmed in a recent meta-analysis of both observational studies and randomized controlled trials [65]. Furthermore, a case–control study suggested that esterified estrogen is not associated with an increased risk of venous thrombosis [66,67].

Only a limited number of observational studies have assessed the risk of venous thrombosis associated with transdermal estrogen use, with inconsistent results, ranging from no increased risk to a point estimate of an approximately two-fold increased risk [61,68–71]. After meta-analysis, the pooled risk estimate for a first episode of venous thrombosis associated with transdermal estrogen was 1.2 (95% CI 0.9–1.7) [65]. Since this meta-analysis, other studies finding no increased risk of venous thrombosis in users of transdermal estrogen have been published [71,72]. An analysis in the UK's General Practice Research Database found no increased risk for venous thrombosis in users of transdermal estrogen with or without progestin (adjusted rate ratio 1.01 [95% CI 0.89–1.16], and 0.96 [95% CI 0.77–1.20], respectively) [71]. A recent large French epidemiological study showed that, although the overall risk of idiopathic venous thrombosis was not increased in users of transdermal hormone replacement therapy (HR 1.1; 95% CI 0.8–1.8), transdermal estrogen combined with norpregnane derivatives, in particular, increased the risk of idiopathic venous thrombosis as compared with other progestins [72].

Tibolone is a synthetic steroid whose metabolites have estrogenic, progestagenic and androgenic activities, and is also used as hormone replacement therapy. Trials that primarily assessed the effect of tibolone on osteoporotic fractures and breast cancer did not show an increased risk for venous thrombosis (HR 0.57, 95% CI 0.19–1.69) [73,74]. Both trials, however, showed other harmful effects, i.e. a higher risk of stroke [73] or an increased risk of recurrent breast cancer [74], in women treated with tibolone. The absence of an increased risk of venous thrombosis was also

observed in the UK's General Practice Research Database [71].

Effect of hormone replacement therapy on the coagulation system

Oral hormonal replacement therapy has very similar effects on coagulation and fibrinolysis variables as the use of oral contraceptives, all pointing towards a prothrombotic effect. In particular, oral estrogen-containing hormone replacement therapy decreases the levels of the natural coagulation inhibitors antithrombin, protein C, and protein S, and increases resistence to APC [75–77]. On the other hand, a systematic review of trials comparing the effects of transdermal hormone replacement therapy with oral hormone replacement therapy on markers concluded that these effects are absent or at least lower with transdermal hormone replacement therapy use [78]. The effects of tibolone on markers of thrombosis risk are also less than with oral hormone replacement therapy or absent [75–77].

Implications for prescribing in clinical practice – hormonal contraceptives

Baseline risk of venous thrombosis for women of fertile age

The absolute risk of venous thrombosis increases sharply with age, in particular after the age of 45 years [79,80]. Considering fertile women, the incidence rate of first venous thrombosis in a large Norwegian cohort study ranged from 0.36 per 1000 person-years in women aged 20–24 years to 0.37 and 0.82 per 1000 person-years in women aged 40–44 and 45–49 years, respectively [1]. If no valid observations on the absolute risk are available, the reported relative risk increases caused by the use of oral contraceptives should be multiplied by this baseline risk, which varies considerably with age. Even a small increase in the risk of venous thrombosis is relevant, given the huge number of women who use oral contraceptives worldwide, but these risks need to be balanced against the beneficial effects in terms of avoidance of unintended pregnancies [81].

Women with hereditary thrombophilia

The presence of hereditary thrombophilia strongly increases the risk of venous thrombosis associated with the use of oral contraceptives. For instance, as compared with women who do not use oral contraceptives and do not carry the FV Leiden mutation, the risk was found to be increased 35-fold in heterozygous women using oral contraceptives [6]. This risk increase has led to questions regarding the need to screen young women for FV Leiden prior to oral contraceptive use. However, in the absence of a clear family history of venous thrombosis, i.e. in the general population, where approximately 5% of women carry the mutation, the number needed to be tested to withhold oral contraceptives in carriers and to prevent a single death from pulmonary embolism would exceed half a million [82].

The situation may be different for women who have a positive family history of venous thrombosis. In clinical practice, the question often arises of whether oral contraceptives are contraindicated, and whether testing for thrombophilia would influence this decision [83]. It is important to note that selection bias is apparent in the observed risks of venous thrombosis in thrombophilia, meaning that thrombophilic individuals who are selected from families with a tendency to venous thrombosis have a higher risk than individuals with the same defect who have been identified through population testing [84]. Thus, when assessing the risk of venous thrombosis in an individual woman, it is important to clearly define the population to which she belongs; that is, does she have a personal or family history of venous thrombosis, or was she identified because of routine screening or other health problems (e.g. because of recurrent miscarriage)? Absolute risk estimates for asymptomatic family members of patients with venous thrombosis and known hereditary thrombophilia were obtained in several family studies. Carriers have a two-fold to 10-fold increased risk of venous thrombosis as compared with their female relatives who do not carry the defect, depending on the type of thrombophilia [85–94]. These kinds of family study have yielded useful risk estimates in this particular group of women while they are using oral contraceptives. In Table 2, the absolute risks per year of use of oral contraceptives and per type of thrombophilia are shown. Estimates obtained in well-sized retrospective studies are useful and valid, as the observations were made in women who were still unaware of their thrombophilic status and thus reflect a real-life situation.

For asymptomatic women with antithrombin, protein C or protein S deficiency and at least one first-degree or second-degree relative with venous thrombosis, the risk was found to be 4.3% (95% CI 1.4–9.7) per year of oral contraceptive use. This means that, within symptomatic families with these defects, approximately 25 (95% CI 10–66) women with thrombophilia need to refrain from oral contraceptive use to prevent one venous thrombosis event per year (assuming a population baseline risk of one in 10 000 in women not carrying a thrombophilic defect, which may not be completely realistic), and thus 50 (95% CI 20–132) women need to be

Table 2 Absolute risk of venous thrombosis in asymptomatic carriers of thrombophilia, estimated in retrospective family studies

	Oral contraceptive use (% per year of use, 95% CI)	Overall* (% per year, 95% CI)
Hereditary deficiencies of antithrombin, protein C, or protein S	4.3 (1.4–9.7) [85]	1.5 (0.7–2.8) [85]
Factor V Leiden	0.5 (0.1–1.4) [85,86]	0.5 (0.1–1.3) [85,86]
Prothrombin 20210A	0.2 (0.0–0.9) [88]	0.4 (0.1–1.1) [88]
Elevated FVIII:c	0.6 (0.2–1.5) [89]	1.3 (0.5–2.7) [89]
Mild hyperhomocysteinemia	0.1 (0.0–0.7) [90]	0.2 (0.1–0.3) [90]

CI, confidence interval.
*All carriers, including men and women of all ages, provoked and unprovoked venous thrombosis.

tested. For the milder thrombophilias, in particular those caused by FV Leiden and the prothrombin 20210A mutation, the risk estimates are more precise, because of the much higher prevalence of these mutations. For these gain-of-function mutations, approximately 200 (95% CI 77–1000) women need to refrain from oral contraceptive use to prevent one venous thrombosis event per year, and 400 (95% CI 152–2000) need to tested. Whether these numbers justify testing patients with venous thrombosis for thrombophilia and subsequent family testing is a matter of opinion rather than science [83,95,96].

Women with a positive family history of venous thrombosis

A family history of venous thrombosis is a reason for concern, but the sensitivity or predictive value appears to be very low. In a small study of 50 women who had an objectively diagnosed episode of venous thrombosis, only 16% had a positive family history [97]. In the large MEGA case–control study, 31% of 1605 patients with venous thrombosis had at least one first-degree relative who also had had venous thrombosis. A positive first-degree family history increased the risk of venous thrombosis from 2.2-fold (any relative) to 3.9-fold (more than one relative) [98]. As expected, also among carriers of thrombophilia, a positive family history increased the risk by 2.7-fold to 4.9-fold, thus interacting with the effect of the genetic risk factor alone.

Women with a personal history of venous thrombosis

According to our opinion, oral contraceptives should not be prescribed to women with a history of venous thrombosis [81]. The evidence for an adverse effect is indirect: venous thrombosis that occurred during oral contraceptive use was less likely to recur when the oral contraceptives were stopped [99]. In a prospective study of 272 women after a first episode of venous thrombosis, the recurrence rate was 1.3% per person-year in women who did not use oral contraceptives, as compared with approximately 3% per year in those who used oral contraceptives at some point during follow-up [100]. There was no apparent difference between women who used oral contraceptives at the time of their first venous thrombosis event and those who did not.

It is noteworthy that there is no indication to immediately discontinue oral contraceptives in women who are diagnosed with venous thrombosis. Anticoagulants effectively prevent the extension and recurrence of venous thrombosis [101], whereas effective contraception is crucial while women are using vitamin K antagonists, because these agents may lead to warfarin embryopathy [102]. Thus, oral contraceptives may be continued until shortly before discontinuation of anticoagulant therapy.

As effective contraception is vital for many women of fertile age, and hormonal methods are more effective than barrier methods and female tubal ligation, hormone-releasing intrauterine devices are often advised for women who have a history of venous thrombosis and have discontinued anticoagulant therapy. The results from the MEGA study and the large Danish cohort study suggest that this is, indeed, a safe contraceptive method with regard to the risk of venous thrombosis, although this study was limited to first thrombotic events, and the safety has not been tested in women with a history of venous thrombosis. Similarly, the risk for a first venous thrombosis is not clearly increased for progestagen-only pills, although the upper limit of the CI, particularly for the desogestrel-containing progestagen-only pill, does not exclude a significant 3.41-fold increase in risk.

Implications for prescribing in clinical practice – hormone replacement therapy

Given the much higher baseline risk of women who are exposed to hormone replacement therapy, because of their higher age, the impact of a relative risk increase on the absolute risk of venous thrombosis is markedly higher than in oral contraceptive users. In women aged 50–54 years, the incidence rate for a first venous thrombosis was 1.17 per 1000 person-years [1]. In the HERS trial, in which postmenopausal women younger than 80 years with confirmed coronary artery disease were included, the incidence rate for a first venous thrombosis was 6.3 per 1000 person-years in women on hormone replacement therapy, as compared with 2.2 per 1000 person-years in women using placebo (HR 2.89, 95% CI 1.50–5.58) [57]. In the WHI study, these rates were 3.4 and 1.6, respectively (HR 2.11, 95% CI 1.58–2.82) [59].

Women with hereditary thrombophilia or a positive family history

Risk estimates for thrombophilic women using hormone replacement therapy are less precise, because of the relatively small numbers of European women who used to take hormone replacement therapy and were included in the types of retrospective study that are informative for this situation. Thus, the known relative risks for the various thrombophilias should be multiplied by the baseline risk in the relevant age category. In general, women known to be carriers of thrombophilia, or with a positive first-degree family history of venous thrombosis, should be advised not to take hormone replacement therapy to relieve perimenopausal symptoms [65].

Guidelines recommend that hormone replacement therapy should be given at the lowest dose and for the shortest duration possible. On the basis of the current evidence, transdermal estrogen or tibolone should be preferred over combined hormone replacement therapy.

Women with a personal history of venous thrombosis

Hormone replacement therapy is contraindicated in women with a history of venous thrombosis. A randomized controlled trial of combined hormone replacement therapy in women with prior venous thrombosis was terminated early because of a marked difference in risk of recurrence between the women

who were given combined hormone replacement therapy and those given placebo (10.7% vs. 2.3%) [103]. To our knowledge, the effects of other routes of hormone replacement therapy have not been formerly tested in women who have a history of venous thrombosis.

Conclusions

All oral estrogen-containing hormonal regimens, used either for contraception or for hormone replacement postmenopausally, increase the risk of venous thrombosis. Therapeutic doses of progestagen-only preparations have a similar effect. Increases in venous thrombosis risk are modulated by dose of estrogen and type of progestagen. Although data are not abundant, current knowledge indicates that the risk of venous thrombosis is not clearly increased for the levonorgestrel-containing intrauterine device, transdermal estrogen, and tibolone. Hemostatic and fibrinolysis markers, most notably assays that measure resistance to APC, have shown effects of hormones that are in the same direction as epidemiologic data obtained with venous thrombosis as a clinical endpoint.

In order to minimize the risk of venous thrombosis associated with oral contraceptives, prudent prescribing in women who have an increased risk is the only option. However, solely having a risk factor may not be an absolute contraindication, but offers the possibility for women to make an informed decision about the use of this contraceptive method.

In our opinion, a personal history of venous thrombosis should be considered a contraindication for combined oral contraceptive use. Carriership of thrombophilia, in particular a deficiency of antithrombin, protein C or protein S, and, to a much lesser extent, FV Leiden or the prothrombin 20210A mutation, warrants counseling and balancing of benefits and risks, in which the family history of venous thrombosis should be taken into account. A strong family history in the absence of a known inherited thrombophilic defect warrants caution as well. A levonorgestrel-releasing intrauterine device does not increase the risk of a first venous thrombosis, an observation that may be extrapolated in clinical practice to offer women with a history of venous thrombosis a very effective contraceptive method. Similarly, progestagen-only pills could be considered, although risk estimates are less solid, particularly for desogestrel-containing progestagen-only pills. Hormone replacement therapy is contraindicated in women with a personal history of venous thrombosis, and should be discouraged in asymptomatic women with thrombophilia. If it is considered in exceptional cases, transdermal administration of estrogen or tibolone is preferred over oral hormone replacement preparations containing estrogen and progestin.

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Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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