

Estrogens, progestogens and thrombosis

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Summary. Hundreds of millions of women worldwide use either oral contraceptives or postmenopausal hormone replacement. The use of oral contraceptives leads to an increased risk of venous thrombosis, of myocardial infarction, of stroke and of peripheral artery disease, the risks of which are highest during the first year of use. Women with coagulation abnormalities have a higher risk of venous thrombosis when they use oral contraceptives (or postmenopausal hormones) than women without these abnormalities. The risk of venous thrombosis is also higher for preparations containing desogestrel or gestodene (third-generation progestogens) than for those containing levonorgestrel (second-generation progestogens). A previous thrombosis as well as obesity also increase the risk of oral contraceptive-related thrombosis. Hormone replacement therapy increases the risk of venous thrombosis, and has no beneficial, and possibly even a detrimental, effect on the risk of arterial disease. The risk of arterial disease in oral contraceptive users and users of hormone replacement therapy is at most weakly affected by the presence of prothrombotic abnormalities.

Keywords: venous thrombosis, myocardial infarction, stroke, estrogens, progestogens, oral contraceptives, hormone replacement therapy.

Introduction

Widespread use of female hormones began in the 1960s with the availability of oral contraceptives. It is estimated that worldwide 100 million women use an oral contraceptive [1]. Hormone replacement therapy gained popularity from the 1970s onward, and recent estimates show that 30–40% of postmenopausal women in the USA, and 33% of women in the UK, are users of postmenopausal hormone substitution [2–4]. With such a large number of people taking a drug, even the smallest increase in risk of side-effects will affect the lives of many. Therefore, knowledge of these risks and efforts to reduce them are of crucial importance. Female hormones have a variety of

side-effects, of which thrombosis is the most frequent and most important. Side-effects include venous thrombosis, myocardial infarction, peripheral artery disease and ischemic stroke.

The first thrombotic side-effect of oral contraceptives was reported in 1961, when a nurse developed pulmonary embolism shortly after starting an oral contraceptive containing 100 µg estrogen (mestranol) and norethynodrel as progestogen for complaints of endometriosis [5]. Ischemic stroke in an oral contraceptive user was first reported in 1962 [6], and the first case of myocardial infarction (MI) in 1963 [7]. For a long time it was believed that estrogens in postmenopausal hormone replacement had no effect on thrombosis, or would even lower the risk. Early studies in men, when estrogens were tried for the treatment of coronary disease, showed an increased risk of thrombosis [8], as was observed in the administration of estrogens to transsexuals [9]. Recently, it has been shown that estrogens in hormone replacement therapy also increase the risk of venous thrombosis [10–12], as well as of MI [13].

Although venous and arterial thrombosis both have occlusive clot formation as the final event leading to disease, risk factors for both disorders only partially overlap. As Virchow first pointed out in the mid-nineteenth century, causes of thrombosis can be divided into those that affect blood flow (i.e. stasis), those that affect blood composition (i.e. hypercoagulability) and those that affect the vessel wall (e.g. atherosclerosis) [14]. The two latter categories nowadays are often also classified as either of genetic or environmental origin. In the low pressure venous vascular bed, stasis plays a major role as a risk factor for venous thrombosis, as does hypercoagulability. Previous venous thrombosis is the strongest predictor of a subsequent venous thrombosis, due to damage to the venous valves, which leads to stasis. The occurrence of arterial thrombosis is mainly determined by the development of atherosclerotic changes in the arterial vessel wall, while stasis plays no role. The relevance of a hypercoagulable state in the etiology of arterial disease is controversial. For some determinants it is not obvious how to classify them, i.e. age is related to both venous and arterial thrombosis, and older age may be accompanied by more stasis, vessel wall changes as well as an increased prothrombotic state. Pregnancy increases venous thrombotic risk due both to the effect of an altered hormonal state, and to stasis because of vein compression. Hyperhomocysteinemia increases the risk of venous and arterial

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Table 1 Risk factors for thrombosis

Stasis	Vessel wall changes	Hypercoagulability
Venous thrombosis		
age	age	antithrombin deficiency
previous thrombosis	previous thrombosis	protein C deficiency
surgery		protein S deficiency
pregnancy		FV Leiden
puerperium		prothrombin 20210A
plaster casts		antiphospholipid syndrome
prolonged travel		dysfibrinogenemia
immobilization		high levels of prothrombin
		high levels of FVIII
		high levels of FIX
		high levels of FXI
		high levels of TAFI
		pregnancy
		malignant disease
		estrogens
Arterial thrombosis		
–	age	estrogens
	smoking	antiphospholipid syndrome
	hypertension	hyperhomocysteinemia
	hypercholesterolemia	FV Leiden (?)
	diabetes mellitus	prothrombin 20210A (?)
	lack of exercise	high levels of FVIII (?)
		high levels of FIX (?)

disease, but the mechanism remains obscure. Table 1 lists the major determinants of arterial and venous thrombosis.

The large number of determinants of thrombosis known today has led to the concept of thrombosis as a multigenic and multicausal disease, i.e. disease will only develop in the presence of several interacting determinants [15,16]. Therefore, in reviewing female hormones as risk factors of thrombotic disease, we will also review their effect in the presence of other risk factors.

Oral contraceptives

Composition and mechanism of contraception

Most oral contraceptives contain an estrogen and a progestogen (indicated as 'combination preparation') and the same combination is taken every day for at least 21 days each cycle (indicated as 'monophasic preparation'). In biphasic and triphasic preparations the dose of both compounds varies over the cycle of administration. There are single preparations that only contain a progestogen, which can also be used for parenteral depot, subcutaneous, intrauterine and intravaginal administration. In addition to this, transdermal combined contraceptives have recently become available.

The contraceptive action is brought about by the progestogen, which acts by suppressing luteinizing hormone (LH). Nowadays the estrogen is added to prevent blood loss during the cycle ('breakthrough bleeding'), which often occurs in progestogen-only preparations or combination preparations with a very low estrogen content. The failure rate with good compliance is very low.

Combination preparations are by far the most used. Since oral contraceptives first became licensed in 1959, the estrogen dose has been reduced. Early preparations contained 150 µg mestranol or ethinylestradiol, the latter of which is the estrogen in virtually all combination preparations currently used. Ethinylestradiol is a synthetic, slightly altered version of the naturally occurring estradiol, which is inactive when taken orally. The dose of ethinylestradiol has been stepwise reduced over the years, and nowadays most preparations contain either 50 µg or 30 µg ethinylestradiol, while some recently introduced brands contain even less, i.e. 20 µg or 15 µg ethinylestradiol.

The progestogen content has also changed over time, but in this case the concern was over the chemical composition of the progestogen rather than the dose [17]. Early preparations contained lynestrenol or norethynodrel, derivatives of norethindrone or nethisterone that are also known as first-generation progestogens or estranes, and are not used much in oral contraceptives anymore. The estrane steroids, derivatives of testosterone, are constructed out of the basic steroid skeleton of 17 carbons (three 6-carbon rings and one 5-carbon ring, also called the gonane structure) and an extra carbon on the 13-position. Second-generation progestogens are gonanes, and include norgestrel and levonorgestrel, of which levonorgestrel is widely used. Third-generation progestogens, which have the same basic steroid molecule as the gonanes, are desogestrel and gestodene. These are both also widely used, despite their increased thrombogenicity. Finally, some progestogens are difficult to classify: norgestimate is categorized as a third-generation gonane, but because after uptake it is in part rapidly converted to levonorgestrel, it may metabolically belong more among the second-generation progestogens.

Two substances used in oral contraceptives in combination with an estrogen need to be treated separately. First, the anti-androgen cyproteronacetate (a pregnane progestogen derived from progesterone), which is used for treatment of acne vulgaris, seborrhea or mild hirsutism, and which has a similar anti-ovulatory action as a progestogen [18–20]. Secondly, drospironone, which is an antimineralocorticoid, with anti-aldosterone and anti-androgenic effects, which also inhibits ovulation [21,22].

Oral contraceptives and venous thrombosis

The first controlled study showing that oral contraceptives increase the risk of venous thrombosis was performed by the Royal College of General Practitioners in the UK [23]. From this case-control study, a 3-fold increased risk was reported for oral contraceptive users vs. non-users. Subsequent case-control studies confirmed the elevated risk, with estimates for the relative risk of users vs. non-users between four and 11 [24–27], as did large prospective follow-up studies in the 1970s [28–30]. Overall, all studies performed until 1990 showed a 3-fold increased risk [31]. An important finding from these studies was that the risk was not cumulative with longer use, i.e. the risk brought about by oral contraceptives was immediate and only lasted as long as oral contraceptives were taken.

The most recent studies, including a large multinational study by the World Health Organization, still show similar risks of venous thrombosis caused by oral contraceptives [32–35]. Even though the risk is clearly increased, at 2- to 6-fold, it is the absolute risk that is most relevant to women using oral contraceptives. Since oral contraceptives, in contrast to postmenopausal hormonal replacement therapy, are used by young women, the baseline risk (among non-users) is low, and the risk in oral contraceptive users, although increased, remains small in absolute terms. The absolute risk of venous thrombosis in women of reproductive age is less than one per 10 000 per year [32]. In oral contraceptive users, it becomes two to three per 10 000 per year [32,36]. For most women, these risks are so low that they accept them, and consider them less important than the benefits of oral contraceptives, i.e. a highly reliable method of contraception. Still, because of the very large number of women who use oral contraceptives thrombotic events do occur, often followed by a post-thrombotic syndrome [37], and are sometimes fatal. Therefore, the search for the safest oral contraceptive remains highly relevant.

The risk of venous thrombosis is highest during the first year of use, reaching an absolute risk of 12 per 10 000 women per year (for second-generation progestogen containing oral contraceptives) [38,39]. However, there is no 'duration of use' effect, in the sense that risk accumulates with prolonged use. On the contrary, the effect is immediate and reversible, i.e. it returns to baseline shortly after discontinuation.

Nowadays, the most commonly used brands contain 30 µg ethinylestradiol or less. The use of very low doses of ethinylestradiol of 20 or even 15 µg is accompanied by poor cycle control in some women, i.e. spotting and breakthrough bleeding [40]. There is not much evidence supporting a reduced risk of venous thrombosis with these ultra-low dose formulations, and there are no clear time-trends of the risk going down: there was a 4- to 6-fold increased risk in the earliest, and in the newest reports. Head-to-head comparison showed lower risk for 30 µg vs. 50 µg ethinylestradiol containing oral contraceptives in one study [41], but not in another study [42]. In the most recent comparison, in our ongoing Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (MEGA) study, including 612 women with a venous thrombosis before age 50, 75% of whom were taking oral contraceptives at the time of the event, we observed a clearly, about 2-fold, lower risk for oral contraceptives containing 30 µg ethinylestradiol than for those with 50 µg ethinylestradiol.

Following the first three reports in 1995 which showed a higher risk of venous thrombosis in oral contraceptives containing the third-generation progestogens desogestrel or gestodene [42–44], a series of studies have confirmed a 2-fold higher risk for these progestogens compared with oral contraceptives containing the second-generation progestogen levonorgestrel [1,45]. The risk appeared especially high in starters, who had a risk of over 30 per 10 000 per year when using an oral contraceptive with a third-generation progestogen [39].

Recently, it has been shown that oral contraceptives that contain cyproteronacetate confer a substantially increased risk

of venous thrombosis, with an even higher risk than for third-generation oral contraceptives. In a small group of women with idiopathic venous thrombosis, oral contraceptives containing cyproteronacetate conferred a 4-fold higher risk than those containing levonorgestrel [46]. In the MEGA study, the risk was increased 18-fold compared with non-users.

As yet, no data are available on oral contraceptives containing drospirenone. However, a series of reported cases of venous thrombosis after the introduction of an oral contraceptive containing this anti-ovulatory antimineralocorticoid has led Dutch general practitioners to caution against its use in the absence of sufficiently proven safety [47].

Whilst there are differences between brands of oral contraceptives with regard to thrombotic risk, there are also differences between women. While obesity increases the risk of thrombosis about 2-fold for body mass index (BMI) > 30 kg m⁻² [48,49], overweight (BMI > 25 kg m⁻²) and obese (BMI > 30 kg m⁻²) women have a 10-fold increased risk of thrombosis when they use oral contraceptives [49]. In familial thrombophilia caused by deficiencies of protein C, protein S or antithrombin, oral contraceptives greatly enhance the risk of thrombosis in carriers of one of these defects [50,51]. While these deficiencies are rare in the general population (0.02–0.2%), factor V (FV) Leiden and prothrombin 20210A are common (2–6%), although they are slightly weaker risk factors (relative risk 3–8). Heterozygous FV Leiden carriers have a 20–30-fold increased risk of thrombosis when they use oral contraceptives [32], and in homozygous carriers oral contraceptives confer an even higher risk [52,53] (Table 2). Prothrombin 20210A carriers who use oral contraceptives were reported to have a 16-fold increased risk compared with non-users with the wild-type genotype [54]. High levels of several procoagulant factors (FII, FVIII, FIX, FXI, FX) confer a 2- to 3-fold increased risk when levels exceed the 90th percentile of the distribution in the population [55–59]. When data of women of reproductive age were re-analyzed in the Leiden Thrombophilia Study, the combination of oral contraceptive use and high levels (compared with non-users with normal levels of the clotting factor), showed a 10-fold increased risk for high levels of FII and FXI, while for the other procoagulant factors the combined risk did not appear to exceed the separate risk of oral contraceptives and high levels [60].

Oral contraceptives and the risk of arterial disease

Many studies have confirmed the initial case reports on an association between oral contraceptive use and the occurrence of MI [7,61–68]. The most recent data are from the World Health Organization, reporting a 5-fold increased risk of MI, as well as a 3-fold increased risk of ischemic stroke [69,70]. In the recent RATIO (Risk of Arterial Thrombosis In relation to Oral contraceptives) study, it was shown that oral contraceptive users have a 4-fold increased risk of peripheral artery disease (PAD) [71].

There is little evidence that the lowering of the dose of the estrogen in oral contraceptives has led to a lower risk of arterial thrombosis. In a large population-based study on arterial disease in young women (including 248 women with MI, 203 women

with ischemic stroke, 152 women with PAD and 925 controls, all aged less than 50), little or no difference was observed for oral contraceptives containing 50 µg or 30 µg ethinylestradiol [71–73]. Third-generation progestogens (desogestrel and gestodene) have a favorable effect on the lipid profile [74]. It was therefore hoped that they would confer a lower risk of arterial thrombosis than oral contraceptives containing a second-generation progestogen, e.g. levonorgestrel. Some initial small studies showed a reduced risk, while others did not [69,75,76]. Two recent large studies, the MICA study from the UK [77] and the RATIO study from the Netherlands [73], also yielded different results, with one showing a 2-fold increased risk for oral contraceptives containing a third-generation progestogen relative to second-generation progestogens [77], and the other showing the opposite [73]. Although both studies were large, neither could exclude the absence of a difference. Since there were no obvious biases in either study that could explain this difference, it is most likely that the difference in risk of myocardial infarction between oral contraceptives with a third- or a second-generation progestogen, if any, is small. In the RATIO study, there was no difference between oral contraceptives with a second- or a third-generation progestogen with regard to the risk of ischemic stroke, or the risk of peripheral artery disease [71,72].

The risk of myocardial infarction is much higher in oral contraceptive users who smoke or have hypertension than in those without such conventional risk factors [1,63]. In the World Health Organization study, no increased risk was found in women who had had a blood pressure screening before prescription [69], which corroborates a pooled analysis of two studies on the west coast of the USA that reported no increased risk [78]. In the RATIO study, the overall risk of MI for oral contraceptive users was increased 2-fold. However, it was much higher for women who also smoked (14-fold), had hypertension (6-fold), had hypercholesterolemia (25-fold), had diabetes (17-fold) or were obese (5-fold) [73]. For ischemic stroke, with an overall 2-fold increased risk, these interactive effects with conventional risk factors were also seen, although they were less striking: women who also had hypertension had an 8-fold increased risk, those who also smoked a 4-fold increased risk, and those with hypercholesterolemia a 11-fold increased risk [72]. Almost all young women with PAD are smokers [71], and the combination of smoking and oral contraceptive use led to a 36-fold increased risk in the RATIO study [71]. Similarly, very high relative risks were found for the combination of oral contraceptive use with hypercholesterolemia (50-fold increased risk) and with diabetes (40-fold increased risk).

Contrary to the case of venous thrombosis, coagulation abnormalities play a minor role in arterial disease [79–82]. Women with FV Leiden or prothrombin 20210A do not have an increased risk of myocardial infarction when they start using oral contraceptives, beyond the risk in women without these mutations [73]. While in the RATIO study an increased risk of MI was observed for women with elevated levels of FVIII or FIX (2- to 3-fold increased risk for levels exceeding the 90th percentile of the distribution in the population), this risk was not

enhanced more than expected by oral contraceptive use (B.C. Tanis, unpublished data).

Hormone replacement therapy

Content and routes of administration

Hormonal replacement therapy has been prescribed to postmenopausal women for three reasons: relief from menopausal complaints, reduction of the progression of osteoporosis, and lowering of the risk of cardiovascular disease. Unopposed estrogens increase the risk of endometrial cancer, and therefore, except in women who have had a hysterectomy, most preparations contain an estrogen and a progestogen. The estrogens in oral preparations are usually conjugated estrogens retrieved from pregnant mare urine, or micronized estradiol. The progestogen mostly used in combination preparations is medroxyprogesterone acetate, a pregnane progestogen. Besides oral administration, the hormones can also be administered transdermally (by patches) and subcutaneously.

There is no doubt that estrogens relieve symptoms of the menopause, predominantly by reducing hot flashes, which, however, are also reduced by 50% with placebo [83]. It also is established that prolonged use of estrogens reduces the progression of osteoporosis and may increase bone density [84–86]. It is less clear whether this leads to a reduced incidence of fractures, although observational studies showed clear effects [87,88]. Two recent randomized trials, however, yielded conflicting results. In the Women's Health Initiative (WHI), over 16 000 women received either estrogens and progestogens or placebo for over 5 years, and the risk of hip fractures was reduced by one-third [13]. In over 2000 women followed for more than 8 years, half of whom received placebo, in the Heart and Estrogen/progestin Replacement Study (HERS), no effect on fractures was observed [89]. The main reason to prescribe postmenopausal hormone replacement therapy has been to reduce risk of cardiovascular disease, after several observational studies showed a strong favorable effect [87,88,90–94]. These studies have been criticized because women who chose to use hormones had a better cardiovascular risk profile than those who did not, e.g. they smoked less and exercised more [95–97]. Therefore, randomized placebo-controlled trials were initiated.

Hormone replacement therapy and risk of venous thrombosis

Because of an almost mythical belief in estrogens as a panacea for the postmenopausal woman, it took until 1996 before serious studies into thrombotic evidence were undertaken. Then, several studies in rapid succession established a clearly increased risk of venous thrombosis for users of hormonal replacement therapy, with a 2- to 4-fold increased risk compared with non-users [10–12,98–103] (Fig. 1).

It has been postulated that the absence of a first-pass effect through the liver with transdermal administration might lead to less risk, but an increased risk has been shown for patches

HRT and venous thrombosis

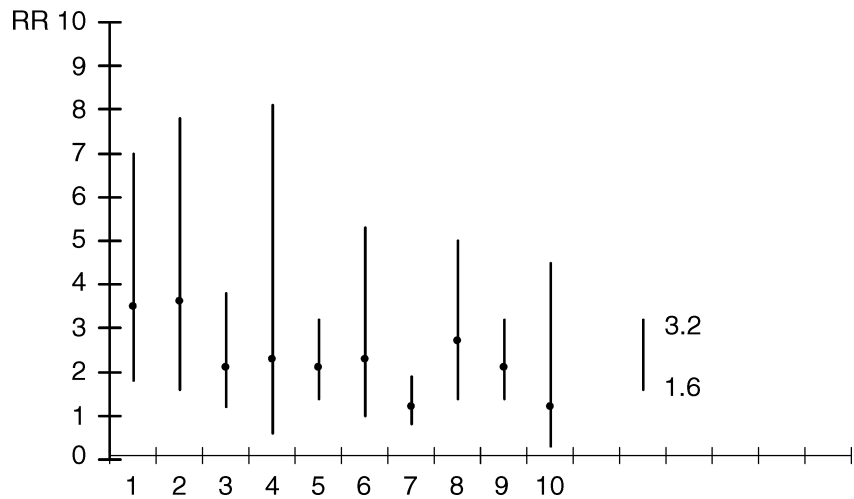


Fig. 1. Risk of venous thrombosis in studies of hormonal replacement therapy. The figure shows the relative risk of a first venous thrombosis in 10 studies [10–13,98–101,103,109] of users of hormonal replacement therapy compared with non-users. When events and risks were reported separately for deep-vein thrombosis and pulmonary embolism, a composite relative risk and confidence interval was recalculated from the data in the paper. The pooled confidence interval was calculated with the 'odd-man-out' graphical method [131].

[99,100], and also for the various types of estrogens, i.e. conjugated estrogens and estradiol [99,103]. As is the case for oral contraceptives, the risk of venous thrombosis is higher shortly after therapy has started [10,11,99,100,103]. This is likely to be caused by the presence of prothrombotic abnormalities in these women, as has been shown for oral contraceptive users who developed thrombosis early after they had started taking them [38]. In the Oxford study, a high risk was observed for users of hormone replacement therapy who had coagulation abnormalities, such as APC-resistance, increased levels of D-Dimer or high FIX levels [104]. In this study, women who carried the FV Leiden mutation had a 15-fold increased risk of venous thrombosis, a synergistic effect analogous to what has been observed for oral contraceptives and FV Leiden [32] (Table 2). No such synergy was present for carriers of

prothrombin 20210A who used hormone replacement therapy. Very similar results for FV Leiden and hormonal replacement therapy were reported from the HERS study [105] (Table 2). In women with a previous venous thrombosis, the risk of a recurrence becomes very high during use of postmenopausal hormones, as was shown in a randomized trial [106].

Hormone replacement therapy and arterial thrombosis

Three randomized placebo-controlled trials have not confirmed the beneficial effect with regard to arterial disease. In the HERS study, in women with prior coronary disease, no effect of hormones was found during 4 years of follow-up [107]. While the initial analysis suggested an increased risk during the first 2 years of the trial, and a lower risk among hormone users in

Table 2 FV Leiden, exogenous hormones and the risk of venous thrombosis

FV Leiden		Relative risk	95% confidence interval
Vandenbrouke <i>et al.</i> [32]			
	Oral contraceptives		
-	-	1	
-	+	3.7	2.2–6.3
+	-	6.9	1.8–28.3
+	+	34.7	7.4–224
Rosendaal <i>et al.</i> [130]			
	Hormone replacement		
-	-	1	
-	+	3.2	1.7–6.0
+	-	3.9	1.3–11.2
+	+	15.5	3.1–76.7
Herrington <i>et al.</i> [105]			
	Hormone replacement		
-	-	1	
-	+	3.7	1.4–9.4
+	-	3.3	1.1–9.8
+	+	14.1	2.7–72.4

Synergistic effects on the risk of venous thrombosis for carriers of FV Leiden who use either oral contraceptives or postmenopausal hormones, shown as the risk of each factor (hormones, FV Leiden) and combined, relative to non-carrier non-users [32,105,130].

subsequent years, an extension of the follow-up in unblinded fashion for 2.7 years did not substantiate protection with prolonged use; the relative risk (RR) was 1.0, with a narrow 95% confidence interval of 0.8–1.2 [108]. In the WHI, a primary prevention trial of hormones vs. placebo, an increased risk of coronary heart disease (RR = 1.29, 95% CI 1.0–1.6) was observed after 5 years of follow-up [13]. In both HERS and WHI conjugated estrogens were combined with progestogens, which formulation has been put forward as an explanation for the absence of a positive effect. However, in the Estrogen in the Prevention of Reinfarction Trial (ESPRIT), a randomized placebo-controlled trial among survivors of a first myocardial infarction, unopposed estradiol was administered for 2 years, and no effect was observed (RR = 1.0, 95% CI 0.7–1.4) [109].

Both the WHI and ESPRIT trials, with relative risks of 1.4 and 1.6, confirmed previous observations of an increased risk of ischemic stroke with the use of postmenopausal hormones, whereas no difference was observed in the HERS trial [2,13,109,110]. In one study, this increased risk appeared confined to the first 6 months of use [2]. In analogy to what is known for venous thrombosis, several studies have been aimed at assessing genetic risk factors that would identify high-risk women, in whom one would expect events to occur early after initiation. For FV Leiden and prothrombin 20210A, no excess risk of myocardial infarction was observed for FV Leiden carriers who used hormone replacement therapy, while hypertensive women who carried prothrombin 20210A and used hormones had an 11-fold increased risk compared with wild-type hypertensive non-users [110]. For ischemic stroke, risk appeared higher (2-fold increase) for hormone users who carried either FV Leiden or prothrombin 20210A [111]. Finally, women with polymorphisms in the FXIII gene (val34leu and his95arg) appeared to have substantially lower (70% reduction) risks of myocardial infarction when they used hormones than women without these variants [112]. Although these analyses may point to important gene–environment interactions by which high- or low-risk women may at some time be identified, they were all too small to yield definitive answers and need to be confirmed.

Although it is still not entirely clear why observational studies and randomized trials gave the same findings for the side-effect of venous thrombosis, but conflicting results on the intended effect of reduction of arterial disease, the results of a large series of studies including randomized trials leave no room for doubt that postmenopausal hormones do harm.

Biological mechanisms

Use of estrogens in oral contraceptives and hormone replacement therapy leads to many changes in the coagulation system, as well as on inflammatory markers and lipids [113–120]. The most important effects are an increased level of procoagulant FVII, FIX, FX, FXII and FXIII, and a reduced level of the anticoagulant factors protein S and antithrombin. Together, these changes lead to a tilted ‘hemostatic balance’ [121] towards a prothrombotic state. Such a prothrombotic state

has become evident from studies that showed changes in global tests of hemostasis, i.e. APC-resistance and thrombin generation tests [117,122–125]. Many of these effects are more pronounced for oral contraceptives containing desogestrel or gestodene (third-generation progestogens) than for those containing levonorgestrel (second-generation progestogens), leading to a more pronounced prothrombotic state as evidenced by global assays [123–127]. In a crossover study in which women were exposed to a combination oral contraceptive with either levonorgestrel or desogestrel, and subsequently to only levonorgestrel or desogestrel, it appeared that the progestogens themselves did not affect the coagulation factor levels, but that the estrogenic effects were less compensated by desogestrel than by levonorgestrel in the combination preparation, leading to the prothrombotic changes of third-generation contraceptives [128].

Clinical implications

The major issue in coming to clinical guidelines is to translate the relative risk from the researcher to the absolute risk for the patient. A risk factor with a high relative risk, which acts on a very low baseline risk, may be less relevant to the patient than a factor with a moderate relative risk acting on a high baseline risk: the likelihood of an event, and the increase in the likelihood of an event, may be larger for the latter factor. This is the case when we contrast oral contraceptive use and hormone replacement therapy: the latter is used by an age-group that has an at least 10-fold higher baseline risk of thrombotic disease than among the younger users of oral contraceptives. A second major consideration is whether equally effective safer drugs are available. However low the absolute risk, there is never an excuse for not choosing the safest drug. A third important guideline should be that drugs should only be used when their efficacy has been clearly proven. In general, these considerations will lead us to sooner take additional risk factors that may modulate risk into account in older than in younger women, and to avoid the use of hormones in women with a personal, and possibly also in those with a family history of thrombosis, as well as in women with gross obesity or hypertension. Oral contraceptives that contain the third-generation progestogens desogestrel and gestodene should be avoided. Hormone replacement therapy has not been shown to be effective for a reduction of cardiovascular disease, and therefore prolonged use will not offer cardiovascular benefits [129].

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