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Female Hormones and Thrombosis

F.R. Rosendaal, F.M. Helmerhorst, J.P. Vandenbroucke

Abstract—Exogenous hormones are used by more than a hundred million women worldwide as oral contraceptives or for postmenopausal hormone replacement. Oral contraceptives increase the risk of venous thrombosis, of myocardial infarction, and of stroke. The risk is highest during the first year of use. The venous thrombotic risk of oral contraceptives is high among women with coagulation abnormalities and with so-called third-generation contraceptives (containing desogestrel or gestodene). The risk of myocardial infarction does not appear to depend on coagulation abnormalities or the type of oral contraceptive. Hormone replacement therapy increases the risk of venous thrombosis. This risk is also highest in the first year of use and among women with coagulation abnormalities. The risk becomes very high in women with a previous venous thrombosis. Randomized trials have not confirmed a beneficial effect of postmenopausal hormones on the occurrence of myocardial infarction. (*Arterioscler Thromb Vasc Biol.* 2002;22:201-210.)

Key Words: venous thrombosis ■ myocardial infarction ■ stroke ■ oral contraceptives
■ hormone replacement therapy

Oral contraceptive use was first associated with thrombosis in 1961, with a report of pulmonary embolism in a nurse, who had just begun taking an oral contraceptive containing 100 μg mestranol for the treatment of endometriosis.¹ In 1963, the first case of myocardial infarction in an oral contraceptive user was reported.² Estrogens increase the risk of venous thrombosis when used as oral contraceptives or as postmenopausal hormone replacement.³⁻⁵ A similar effect was observed in men when estrogens were used as a treatment of coronary disease⁶ or in sex-change treatment.⁷ Recently, it has been demonstrated that the progestins in combination oral contraceptives also affect the risk of thrombosis.⁸⁻¹⁰

Thrombosis is a serious disorder. Venous thrombosis, although rarely fatal, often leads to a disabling postthrombotic syndrome.¹¹ Arterial thrombosis may be fatal, as myocardial infarction, or lead to disabling sequelae in stroke.

The risk factors for thrombosis (Table 1) can be divided into 3 groups of causes, according to Virchow¹²: reduced blood flow, changes in the vessel wall, and changes in the composition of the blood. In venous thrombosis, causes related to stasis and blood coagulability are most important, whereas in arterial disease, vessel wall changes stand out. Genetic risk factors for venous thrombosis lead to hypercoagulability, whereas the acquired causes are either associated with decreased flow (as found in immobilization, paralysis, surgery, and plaster casts) or related to blood coagulation (associated with the lupus anticoagulant, pregnancy, oral contraception, and malignancies).

Oral Contraceptives

Content and Mode of Action

Oral contraceptives first became licensed for birth control in 1959. Most oral contraceptives contain an estrogen and a progestogen, with both contained in each pill (monophasic preparations). Over the years, the estrogen dose and the progestogen compound have changed. The first oral contraceptive in the United States contained 150 μg mestranol. Since then, the estrogen dose has been reduced, first to 50 μg and then to 30 and to 35 μg , and some currently available brands contain only 20 or 15 μg ethinyl estradiol. The change in progestogen concerned the chemical composition of the progestogen rather than the dose because the progestogen component prevents ovulation. Early oral contraceptives contained a first-generation progestogen, in the 1970s, the second generation was used, and third generation progestogens were used from the early 1980s in Europe and the 1990s in the United States.

Oral contraceptives act by preventing ovulation through the action of the progestogen, which suppresses luteinizing hormone. Estrogens are mainly needed to prevent breakthrough bleedings. With complete compliance, the failure rate is <1%.

Ethinyl estradiol is a synthetic slightly altered version of the naturally occurring estradiol, which is inactive when taken orally. In the absence of a formal classification system of progestogens, these are usually grouped into "generations" that are based on when they were first produced. First

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TABLE 1. Risk Factors for Venous Thrombosis

Risk Factors		
Acquired	Inherited	Mixed/Unknown
Age	Antithrombin deficiency	Hyperhomocysteinemia
Previous thrombosis	Protein C deficiency	High levels of factor VIII
Immobilization	Protein S deficiency	APC resistance in the absence of FVL
Major surgery	FVL	High levels of factor IX
Orthopedic surgery	Prothrombin 20210A	High levels of factor XI
Malignancy	Dysfibrinogenemia	High levels of TAFI
Oral contraceptive use		
Hormonal replacement therapy		
Antiphospholipid syndrome		
Myeloproliferative disorders		
Polycythemia vera		

FVL indicates factor V Leiden; TAFI, thrombin-activatable fibrinolysis inhibitor.

generation progestogens include norethisterone, norethynodrel, lynestrenol, and ethynodiol acetate. The second generation includes norgestrel, levonorgestrel, and norgestriene. The third generation includes desogestrel, gestodene, and norgestimate. Norgestimate is often grouped among second-generation progestogens, because after uptake, it is partly converted to levonorgestrel. Cyproterone acetate (not available in the United States) and drospirenone are not yet categorized.

Oral Contraceptives and Venous Thrombosis

An early comparative study was based on information gathered by the Royal College of General Practitioners.¹³ From a comparison of patients and healthy controls (case-control study), it was reported in 1967 that oral contraceptive users had a 3-fold increased risk of venous thrombosis compared with nonusers. This was confirmed by other studies from the United Kingdom and the United States, with relative risk estimates ranging between 4 and 11.^{14–17} In the 1970s, large prospective follow-up studies again confirmed these findings.^{18–20} When we combine all studies performed until the 1990s, a 3-fold increased risk results.²¹ These studies also showed that oral contraceptives conferred an immediate effect: the risk did not become larger with longer duration of use and disappeared when oral contraceptives were discontinued.

These early studies were performed when objective testing for venous thrombosis was not widely used. We now know that the clinical diagnosis of venous thrombosis suffers from a high rate of false positives^{22,23}; therefore, these studies probably had substantial misclassification. This is supported by studies that compared the risk by level of certainty of diagnosis and that usually found higher risk estimates.^{14–16,19,20,24} Therefore, the risk of oral contraceptives may have been underestimated in the older studies.

In recent studies, performed in the 1990s, a 2- to 6-fold increased risk for venous thrombosis was found in oral contraceptive users.^{25–28} In a Dutch study, the absolute risk was estimated at 0.8 per 10 000 per year among nonusers and 3.0 per 10 000 per year among oral contraceptive users.²⁵ In

a study in the United Kingdom, a similar annual risk, 2.0 per 10 000 users, was found.²⁹ These numbers indicate a low absolute risk; ie, several thousands of women would need to abstain from oral contraceptives to prevent 1 case of thrombosis per year (numbers needed to treat). Because oral contraceptives are the most reliable form of reversible contraception, it has even been argued that such a policy might lead to an increase in venous thrombotic events through an increase in unintended pregnancies.²¹ Nevertheless, because oral contraceptives are so widely used, they are responsible for a large share, if not the majority, of all venous thromboses in young women.

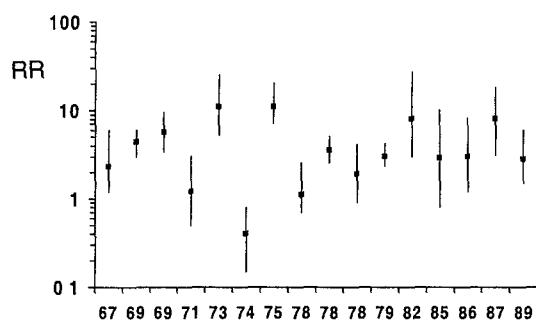
Diagnostic Suspicion and Referral Bias

The so-called referral or diagnostic suspicion bias is the hypothesis that has been brought forward to explain the absence of a reduction of the risk of thrombosis associated with the use of oral contraceptives since the 1960s. This bias involved women presenting with leg complaints being referred for thrombosis especially if they used oral contraceptives, because doctors were aware of this association. If, subsequently, women with thrombosis were compared with healthy women, there would be an excess of oral contraceptive users among patients, spuriously suggesting an increased risk.

Two studies compared women who were referred for diagnostic tests that were positive for thrombosis with women who were referred for the same tests, which proved negative for thrombosis.^{30,31} In this setting, referral bias would have acted similarly for both groups. The relative risks for thrombosis associated with oral contraceptive use found in these 2 studies were 6.4³⁰ and 3.9³¹; ie, they were similar to those found in studies with population controls. This demonstrates that the risk of venous thrombosis is still present and cannot be explained by referral bias.

Effect of Lowering of the Estrogen Dose

The first oral contraceptives contained doses of 100 to 150 μg mestranol or ethinyl estradiol, which over time has been reduced to 50 μg and, subsequently, to 30 μg and, even in



Relative risk (RR) for venous thrombosis in oral contraceptive use. The RRs (users vs nonusers) are shown from studies published between 1967 and 1989, with 95% CIs. A relative risk of 1 indicates equal risks, and a relative risk >1 indicates a higher risk for users than for nonusers. The studies include case-control studies,^{13 15-17 158-162} follow-up studies,^{18-20 163-165} and 1 randomized controlled trial.¹⁶⁶ Some figures were estimated from data in the original articles (reprinted with permission from *Thrombosis and Hemostasis*).

some of the newest brands, to 20 μg ethinyl estradiol. One of the aims of this dose reduction was to lower the risk of thrombosis. However, when we look at the risk estimates from studies published from the 1960s to the 1990s, such a risk reduction appears not to be present (Figure). In several direct comparisons, a lower risk with a lower estrogen dose has been found.^{20 24 32} In the most recent of these studies, a 10-fold increased risk compared with that for nonusers was found for users of oral contraceptives containing >50 μg ethinyl estradiol, and there was a 4-fold increased risk for contraceptives containing <50 μg ethinyl estradiol.³² Several other studies have not confirmed a lowering of risk with lower estrogen doses. In the Leiden Thrombophilia Study, a direct comparison of oral contraceptives that contained either 50 μg or 30 μg ethinyl estradiol and the same progestin (levonorgestrel) found no difference.⁸ There are no data involving oral contraceptives containing 20 μg ethinyl estradiol.

Effect of Changes in the Progestogen Content

Although estrogens have been known to be associated with the risk of thrombosis for many decades, it has always been considered that the progestogens in these combination preparations did not affect risk at all. However, in 1995, 3 studies published simultaneously reported an increase of thrombosis in women using oral contraceptives containing the newest progestins, i.e., desogestrel and gestodene (also known as third-generation progestins).⁸⁻¹⁰ Most subsequent studies confirmed this finding,^{29 31 33-37} but some did not.^{38 41} A recent meta-analysis combining the evidence from all studies found an overall 1.7-fold increased risk for users of third-generation oral contraceptives compared with second-generation users.⁴² Interestingly, the relative risk was >2-fold increased in studies funded through public agencies but only 1.3-fold in studies sponsored by pharmaceutical companies producing third-generation contraceptives.⁴² The risk for third-generation users was higher during the early phases of use but remained 2-fold increased compared with the risk for second-generation users of oral contraceptives during long-term use.

In the debate after the publication of the original studies, potential biases have been put forward as alternative explanations.^{39 40 43-52} Careful consideration, reanalyses of the original studies, new studies, and an extensive comprehensive look in the meta-analysis led to the conclusion that bias could not explain the observations of an increased risk.^{42 53-56} An independent expert committee convened by the World Health Organization concluded that third-generation contraceptives carried an increased risk of venous thrombosis.⁵⁷

Strong support for the epidemiological findings came from a biochemical study in 1997 showing that the plasma of women using third-generation contraceptives was tilted toward a prothrombotic state, as measured with a newly developed assay.⁵⁸ This assay measures sensitivity to activated protein C (APC), but unlike the standard APC-resistance test, which is based on the activated partial thromboplastin time, it is based on clotting activation through the extrinsic pathway by tissue factor.⁵⁸⁻⁶⁰ In this assay, the endogenous thrombin potential (ETP) is quantified, ETP is defined as the time integral of free thrombin concentration, usually derived from residual levels of amidolytic activity, determined in the presence and absence of added APC, yielding an APC-sensitivity ratio.⁵⁸ This APC-resistance test proved sensitive in detecting factor V Leiden but was far more sensitive to exogenous factors than was the activated partial thromboplastin time-based APC-resistance test.^{61 62} In the ETP-based APC-resistance test, use of third-generation oral contraceptives led to prothrombotic abnormalities comparable to those found in heterozygous factor V Leiden.⁵⁸ This result was confirmed by a randomized crossover trial of second- and third-generation oral contraceptives.⁶³ Differential effects were observed on procoagulant, anticoagulant, and fibrinolytic factors.⁶³⁻⁶⁶ The main effects were a more pronounced APC resistance in the ETP-APC test as shown before,⁶³ a large increase in factor VII levels,⁶⁴ and sharp decreases in free and total protein S,⁶⁶ which was subsequently confirmed in another study.⁶⁷ These are all changes that would be expected to lead to an increased risk of thrombosis.

Other Risk Factors and Oral Contraceptive Use

For clinical purposes, it is important to consider whether some women have a higher risk of thrombosis when using oral contraceptives than do others. For venous thrombosis, risk factors to be considered include a personal or family history of venous thrombosis and prothrombotic abnormalities, i.e., factor V Leiden, prothrombin 20210A, and deficiencies of protein C, protein S, or antithrombin.

A previous thrombosis is, by far, the strongest predictor for venous thrombotic events. In most studies, the recurrence rate after 3 months of anticoagulation is between 2% and 5% per year.⁶⁸⁻⁷³ It is currently unclear whether the recurrence rate is higher for individuals with coagulation abnormalities.^{71 74-82} Oral contraceptives are often withheld after a first episode of thrombosis, therefore, there are no firm data on the recurrence risk with continued use.

In families with deficiencies of protein C, protein S, and antithrombin, the risk of first thrombosis appears to be increased in women who have 1 of these abnormalities and

who use oral contraceptives, with a very high risk in anti-thrombin deficiency⁸³. Among relatives of unselected patients with 1 of these deficiencies, oral contraceptive use further increased thrombotic risk 6- to 8-fold⁸³. Although deficiencies of natural anticoagulants are rare (1/5000 to 1/250), factor V Leiden and prothrombin 20210A are found in 2% to 7% percent of most Caucasian populations⁸⁴⁻⁸⁶. Carriers of factor V Leiden who use oral contraceptives have a 20- to 30-fold increased risk of developing venous thrombosis,^{17,38} and there is an even much higher risk for homozygous factor V Leiden carriers using oral contraceptives.^{87,88} Prothrombin 20210A is a mild risk factor for thrombosis, increasing risk 2- to 3 fold. However, in combination with oral contraceptives, the risk appears to be higher, with a 16-fold increased risk compared with that for noncarrier nonusers.³⁸

High levels of factor VIII are a common, moderately strong risk factor for venous thrombosis.^{89,91} In combination with oral contraceptives, no synergistic effect has been observed, ie, the combination of high levels of factor VIII and oral contraceptive use led to no higher risk than did the sum of the separate effects.⁹²

The risk of thrombosis in users of oral contraceptives is highest during the first year of use.^{37,93} This is particularly the case among women with prothrombotic defects,⁹³ which are indicative of a high thrombosis potential⁹⁴ in these women, in whom a small further increase in risk is sufficient to bring about thrombosis. However, the risk is also higher in the first year than during prolonged use in women without known prothrombotic defects, suggesting the presence of as-yet-undefined risk factors.⁹³

Oral Contraceptives and the Risk of Arterial Disease

The first report of an association between oral contraceptive use and myocardial infarction was published in 1963,² an association with ischemic stroke was first published in 1968,⁹⁵ and an association with hemorrhagic stroke was published in 1973.⁹⁶ The association with arterial disease was confirmed in a series of studies.^{97,104} Recently, the multicenter study by the World Health Organization (WHO) showed a 5-fold increased risk of myocardial infarction with currently used oral contraceptives,¹⁰⁵ as well as a 3-fold increased risk of ischemic stroke¹⁰⁶ and a 1.5- to 2-fold increased risk of hemorrhagic stroke.¹⁰⁷ It has repeatedly been shown that the risk of myocardial infarction is particularly high among users of oral contraceptives who also smoke or have hypertension.^{57,99} Among women without major cardiovascular risk factors, the risk of myocardial infarction seems very low,⁵⁵ and in some studies, no excess risk was observed at all.¹⁰⁸

Over the years, the dose of estrogen has been lowered, and the progestogen has been modified, mainly in an effort to reduce the risk of arterial disease among users of oral contraceptives. It is unclear whether the lower risk of myocardial infarction associated with the use of oral contraceptives in several of the newer studies is the result of the lowering of the estrogen dose or of selective prescription to

women without cardiovascular risk factors. The WHO study, which showed a large effect of blood pressure screening, suggests that the latter played a major role.¹⁰⁵

Contraceptives containing third-generation progestins desogestrel and gestodene have a favorable effect on the lipid profile, with a slight increase in HDL. Several small studies had conflicting results regarding whether the risk of myocardial infarction would be lower with these contraceptives.^{105,109,110} Two recent large studies on myocardial infarction in young women and the use of oral contraceptives failed to demonstrate a benefit for third-generation preparations.^{111,112} Prothrombotic abnormalities, which play a major role in the etiology of venous thrombosis, at most mildly increase the risk of myocardial infarction,¹¹³⁻¹¹⁵ and this risk is only in women with major cardiovascular risk factors, in particular, smoking. There does not seem to be an enhanced risk of myocardial infarction with contraceptive use in women with these mutations.¹¹²

Hormone Replacement Therapy

The use of postmenopausal hormone substitution has become widespread in recent decades.¹¹⁶ Besides relief from menopausal complaints, hormone replacement is prescribed to reduce the progression of osteoporosis and the development of cardiovascular disease. Several observational studies showed impressive cardiovascular benefits, ie, a halving of the risk of cardiovascular events and deaths.¹¹⁷⁻¹²³ Because women who used hormone replacement usually had a better cardiovascular risk profile than did nonusers, selection bias offered an alternative explanation for the apparent benefits.^{124,126} Therefore, several randomized trials have been performed or are in progress.

Content and Types of Hormone Replacement Therapy

Most preparations nowadays contain an estrogen and a progestin, this combination was introduced after it was shown that unopposed estrogen therapy increases the risk of endometrial cancer (reviewed in Grady et al¹¹⁶). Estrogen-only hormone replacement is still used in women without a uterus. Conjugated estrogens in oral preparations are extracted from pregnant mare urine, the progestin compound is usually medroxyprogesterone acetate. Micronized estradiol is available in tablets or can be delivered transdermally (patches), percutaneously by gels, or subcutaneously by pellets.¹²⁷

Hormone Replacement Therapy and Risk of Venous Thrombosis

In an early study of adverse effects of estrogen replacement therapy, a slight risk increase of venous thrombosis was observed.¹²⁸ This was not confirmed in subsequent studies,¹²⁹⁻¹³¹ and the idea that estrogen replacement could cause venous thrombosis was dismissed as "medical superstition."¹³² However, from 1996 onward, a series of studies has demonstrated that hormone replacement users have a 2- to 4-fold increased risk of venous thrombosis.^{3-5,133-138}

TABLE 2. Factor V Leiden, Exogenous Hormones, and the Risk of Venous Thrombosis

Factor V Leiden	Oral Contraceptives	Relative Risk	95% CI
-	-	1	
-	+	3.7	2.2 to 6.3
+	-	6.9	1.8 to 28.3
+	+	34.7	7.4 to 224

Factor V Leiden	Hormone Replacement	Relative Risk	95% CI
-	-	1	
-	+	3.2	1.7 to 6.0
+	-	3.9	1.3 to 11.2
+	+	15.5	3.1 to 76.7

Risks of venous thrombosis are shown for carriers of factor V Leiden, users of either oral contraceptives or hormone replacement therapy, or both relative to noncarriers nonusers^{25,142}

Risk of thrombosis is highest in the first year of use,^{3,4,134,135,138} and in some studies,^{134,135,138} but not in all,^{3,137} the risk was limited to the first year. Oral use and transdermal patches increase the risk of thrombosis,^{134,135} and an association with thrombosis has been found for conjugated estrogens as well as for estradiol.^{134,138}

Why did the early studies not detect the thrombosis risk associated with thrombosis? This may have been caused by less reliable diagnostic methods in the past, which may have been adequate to detect the risk of the then high-dosed oral contraceptives but not of the lower estrogen dose in hormonal replacement therapy. The less widespread use of hormone replacement may also have been a factor.

Hormone Replacement Therapy and Arterial Thrombosis

The beneficial effects of postmenopausal hormones noted in observational studies have not been confirmed in the 2 randomized trials conducted to date. One study, including women with prior coronary disease, found no benefit of hormone substitution over placebo during 5 years of follow-up,¹³⁹ whereas an increase in venous thrombosis was reported from this trial.^{136,137} Post hoc analyses showed that the arterial events were clustered in the first year, with lower risks in the active group than in the placebo group in years 4 and 5.¹³⁹ The other placebo-controlled trial is an ongoing study of nearly 30 000 women without prior disease.¹⁴⁰ In the first 2 years of follow-up in that study, an excess of myocardial infarction and venous thrombosis occurred in the treatment group.

Effect of Other Risk Factors

One randomized trial of hormone replacement therapy has been conducted among women with a previous deep vein thrombosis.¹²⁷ The study was terminated prematurely and showed a high rate of recurrence of 8.5% per year in the treatment group versus only 1.1% in the placebo group.¹²⁷

The higher risk of venous thrombosis in the first year suggests that for hormone replacement therapy, as for oral

contraceptives, some women are at higher risk, probably because of prothrombotic abnormalities. In the Oxford case-control study, a high risk was observed in women who were APC resistant and used hormone replacement therapy.^{3,141} In a subsequent genetic analysis, it was confirmed that the APC resistance in these women was based on carrying factor V Leiden. Whereas factor V Leiden alone increased the risk 4-fold and hormone replacement increased the risk only 3-fold, the combination led to a 15-fold increased risk.¹⁴² Table 2 shows the effect of factor V Leiden in combination with either oral contraceptives or hormone replacement therapy on the risk of venous thrombosis.

For the arterial side, the increased risk in the first year in the randomized trials suggests a similar genetic predisposition in some women. Further evidence has come from a study reporting that in women with prothrombin 20210A, the use of hormones increases the risk of myocardial infarction, in particular among hypertensive women, with an 11-fold increased risk.¹⁴³

Biological Mechanism of the Effect of Hormones on Thrombotic Risk

Estrogens have many different effects on the coagulation system.^{62,144,147} These include increases in the levels of procoagulant factors VII, X, XII, and XIII and reductions in the anticoagulant factors protein S and antithrombin. These changes predict a change toward a more procoagulant state (which is confirmed in studies examining global tests, such as APC resistance or thrombin generation),^{61-64,66} which is not counterbalanced by an increased fibrinolytic activity.⁶⁵ The estrogens in hormonal replacement therapy have hemostatic effects similar to those in oral contraceptives.^{148,149}

It is currently unclear how these effects are brought about at the molecular level of the estrogen receptor. It is likely that these effects at the cellular level are also under genetic control, because the hemostatic system of some women appears to be more sensitive to the effect of estrogens than that of other women.¹⁵⁰ It is also unclear how estrogens and progestins interact in their effect on thrombosis, for instance, in the higher risk of oral contraceptives containing a third-generation progestin. It appears that estrogens are prothrombotic rather than proatherogenic, which explains the absence of an increased risk in former users.

Other Hormones

Selective estrogen receptor modulators, such as tamoxifen and raloxifene, have antiestrogenic effects on breast and endometrial tissue and are used in the treatment and prevention of breast cancer. However, these drugs have estrogenic effects on blood clotting. A placebo-controlled trial of tamoxifen in nearly 14 000 women with an increased risk of breast cancer showed increased risks of ischemic stroke (relative risk 1.6), of pulmonary embolism (relative risk 3.0), and of deep vein thrombosis (relative risk 1.6).¹⁵¹ Another placebo-controlled trial with tamoxifen in hysterectomized women also showed an increased risk of venous thrombosis, including superficial thrombophlebitis.¹⁵² In a randomized trial of breast cancer prevention, raloxifene increased the risk of venous thrombosis 3-fold.¹⁵³ In a case-control study

of tamoxifen use for breast cancer treatment, it was shown to increase venous thrombotic risk 7-fold¹⁵⁴ These studies convincingly show that currently used selective estrogen receptor modulators increase the risk of thrombosis

Clinical Implications

Although many aspects of the thrombotic risks associated with female hormones are only just emerging, some clinical implications seem evident First, in the choice of contraception, a personal history of thrombosis needs to be taken into account The risk of thrombotic disease can be limited by considering other types of contraception in women with a personal history of thrombosis, a family history of thrombosis, gross obesity, and major cardiovascular risk factors A contraceptive with 30 µg ethinyl estradiol should be the first choice, but there is little information that would favor the use of oral contraceptives with a lower dose of estrogen Oral contraceptives containing third-generation progestogens, ie, desogestrel or gestodene, should be avoided because of the increased risk of venous thrombosis Especially in smokers, oral contraceptives should not be continued beyond the 35th year of age because of the increased risk of arterial disease Indiscriminate screening for prothrombotic mutations before the prescription of oral contraceptives is unlikely to be cost effective or even to have a positive risk-benefit balance^{155 156} It is currently unclear whether screening in the presence of a positive family history should be preferred over alternative contraception in all those women.

The best currently available data for postmenopausal hormone replacement do not support a cardiovascular benefit. The route of administration (oral or transdermal) does not materially affect the risk of side effects Therefore, hormonal replacement therapy should not be prescribed for the prevention of cardiovascular disease, and short-term prescription for relief of menopausal symptoms should be the main indication A recent statement from the American Heart Association also urges caution in the prescription of postmenopausal hormones¹⁵⁷ Hormone replacement should be avoided in women with a personal or family history of venous thrombosis

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