

Oral Contraceptives, Hormone Replacement Therapy and Thrombosis

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Summary

Oral contraceptives and hormone replacement therapy are used by hundreds of millions of women worldwide. Since the early 1960s it is known that female hormones increase the risk of venous thrombosis, myocardial infarction and stroke. This risk is still present with current low-dose oral contraceptives and, even though in absolute terms the risk is small, oral contraceptives form the major cause of thrombotic disease in young women. The risk is higher during the first year of use (up to 1 per 1000 per year), with the use of desogestrel- or gestodene-containing oral contraceptives ("third generation progestogens") and among women with a prothrombotic predispositon. Hormone replacement therapy increases the risk of venous thrombosis, while results of randomised trials so far do not substantiate the expectation of a beneficial effect on the risk of arterial cardiovascular disease. First results are emerging that specific subgroups of women, with prothrombotic or other abnormalities, may be at risk, especially during the first years of use of hormone substitution.

Introduction

Symptomatology and Epidemiology

Venous thrombosis has an annual incidence of 1-3 per 1000 individuals per year (1, 2). It is uncommon in young individuals and becomes more frequent with advancing age (1). It mostly manifests in the deep veins of the leg, but may occur in other sites, such as the upper extremities, cerebral sinus, liver and portal veins or retinal veins. Embolisation occurs when parts of the clot dislodge and are transported by the blood flow, usually through the heart to the vasculature of the lungs (3).

Thrombosis is a serious disorder; it can result in fatal pulmonary embolism. Estimates of the case fatality rate of venous thrombosis vary widely. Two large natural history studies (2, 4) found that 12-25 percent of all events of venous thrombosis were fatal, while recent trials found much lower figures, around 1-3 percent (5-10 percent for pulmonary embolism) (5-7). This wide range may be caused by the inclusion of thrombosis as secondary cause of death in the studies with a high estimate, and the selection of patients with a good prognosis in clinical trials. The Worcester study also showed that the case fatality rate was highly dependent on age, with a low mortality among those aged forty or less at the time of thrombosis (2). The postthrombotic syndrome leads to chronic morbidity in a substantial number of patients (8).

Risk factors for thrombosis are usually divided into genetic and acquired factors. Mechanistically, they fall into three groups of causes according to Virchow: reduced blood flow, changes in the vessel wall and changes in the composition of the blood (9). For venous thrombosis, the first (stasis) and third group (changes in blood coagulability) appear most prominent, while for arterial disease, factors that affect the vessel wall, i.e. promote atherosclerosis, are most relevant. The genetic risk factors for venous thrombosis are all associated with changes in the blood composition, while acquired causes are either associated with decreased flow, i.e., immobilisation, paralysis, surgery, plaster casts, or related to blood coagulation, such as the lupus anticoagulant, pregnancy, oral contraception, malignancies. Table 1 lists the main risk factors for venous thrombosis.

Hormones and Venous Thrombosis

The first report of venous thrombosis related to the use of oral contraceptives was in 1961, when Jordan wrote about a nurse who had developed pulmonary embolism, shortly after starting a course of a combined oral contraceptive containing 100 μg mestranol for the treatment of endometriosis (10). It has subsequently been shown that oestrogens increase the risk of thrombosis in women, when used as oral contraceptive or as hormone replacement therapy in postmenopausal women (11-13). Oestrogens also increase the risk of thrombosis in men, which became apparent when they were tried in the treatment of coronary disease (14) as well as in the course of sex change treatment (15). More recently, it has been demonstrated that not only oestrogens but also progestogens in combination oral contraceptives may increase the risk of thrombosis (16-18), while progestin-only preparations may also increase the risk of thrombosis (19, 20).

Oral Contraceptives

Composition

Most oral contraceptive drug preparations supply an oestrogen and a progestogen. In the majority of oral contraceptives used, these are both contained in each pill (monophasic preparations), and a woman takes the same combination for three weeks, followed by a pill-free week during which a withdrawal bleeding takes place. The mode of action is the suppression of the ovulation process through the combined actions of the progestogen and to a lesser extent the oestrogen compound the progestogen compound suppresses luteinizing hormone (LH) and the LH-surge, while the oestrogens suppress follicle stimulating hormone (FSH). Since the amount of oestrogen has been minimised, ovarian follicle development can be detected during pill use. The major role

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Risk factors for venous thrombosis

acquired	inherited	mixed/unknown
age	antithrombin deficiency	hyperhomocysteinaemia
previous thrombosis	protein C deficiency	high levels of factor VIII
immobilisation	protein S deficiency	APC-resistance in the absence of FVL
major surgery	factor V Leiden (FVL)	high levels of factor IX
orthopaedic surgery	prothrombin 20210A	high levels of factor XI
malignancy	dysfibrinogenaemia	high levels of TAFI
oral contraceptives		
hormonal replacement therapy		
antiphospholipid syndrome		
myeloproliferative disorders		
polycythaemia vera		

the oestrogen component in the pill is to prevent spotting and breakthrough bleedings by organizing the endometrium. In biphasic and triphasic combinations, the content of the pills taken during one cycle varies, with more oestrogens in the early phase of the cycle, and more progestogens in the later phase of the cycle. Some preparations only contain a progestogen, and are mainly used when oestrogens are considered contra-indicated; they cause a higher frequency of spotting and breakthrough bleedings leading to a lower compliance. Most oral contraceptives have a 1% failure rate with complete compliance. Since progestogens also affect the viscosity of cervical mucus, even ovulations that do occur (escape ovulation) during perfect use seldomly lead to pregnancy. Reliability of progestogen-only oral contraceptives is probably similar to those for combined oral contraceptives (21).

Naturally occurring sex steroids are inactive when taken orally. Hence, early research in the 1930s focussed on manufacturing slightly altered hormones that could be taken orally. Adding an ethinyl group at the 17-position of oestradiol led to the potent oral oestrogen ethinyloestradiol, which was subsequently used in oral contraceptives. Mestranol is the 3-methylether of ethinyloestradiol, which is rapidly metabolised into ethinyloestradiol, and has also been used in oral contraceptives.

Orally active progestogens are predominantly based on the synthetic testosteron derivative ethisterone. The progestogens in this class, which are all those currently used in oral contraceptives, are called 19-nortesterones There is no formal classification system of progestogens and they are usually grouped into "generations" based on when they were first produced. First generation progestogens include norethisterone, norethynodrel, lynestrenol and ethynodiolacetate. The second generation includes norgestrel, levonorgestrel and norgestrione. The third generation includes desogestrel, gestodene and norgestimate. Although, temporally, norgestimate should be included in the third generation group, it is also often classified among second-generation progestogens, since after uptake it is partly converted to levonorgestrel.

The first human trial with oral contraceptives was performed in 1956, and the first licensed use for birth control was in 1959, the culmination of nearly 40 years of research that began with animal experiments of ovarian transplantation in 1921 in Innsbruck (22). Since the first use, changes in the composition of oral contraceptives have concerned the oestrogen dose and the progestogen compound. Enovid, the first oral contraceptive in the USA, contained 150 μg mestranol. Over the years, the oestrogen dose has been reduced from 100-150 μg first to 50 μg, then to 30-35 μg, while some oral contraceptives that are currently available contain only 20 μg ethinyloestradiol. For the progestogen compound in combined oral contraceptives, change over time concerned the chemical composition of the progestogen rather than the dose. While the first oral contraceptives contained a first generation progestogen, the second generation was used throughout the seventies, and the third generation progestogens became widely used from the mid-1980s onward (new oral contraceptives were introduced in different countries at various times, e.g., oral contraceptives with a third generation progestogen had a majority market share in Southern Europe in the beginning of the 1990s, when they were only just entering the market in the USA).

Currently, over a 100 million women worldwide use oral contraceptives (23). This widespread use by young and usually healthy women indicates that even a rare deleterious effect could affect many women, at an age when serious disease is infrequent. Serious cardiovascular side effects of oral contraceptives are thrombotic events, including venous thrombosis, myocardial infarction and stroke. In this review we will mainly focus on venous thrombosis.

Older Studies on Risk of Venous Thrombosis and OCs

After the first report in 1961, more case reports followed rapidly. A hallmark study, comparing women with thombosis to control women without thrombosis (case-control study) was based on data recorded by the Royal College of General Practioners (24). In this study, published in 1967, it was found that oral contraceptives increased the risk of thrombosis nearly 3-fold. Another British study found a relative risk of 6 (25, 26), and two US studies yielded relative risks of 4 and 11 (27, 28). In the 1970s, large prospective follow-up studies were conducted which confirmed the results of the case-control studies (29-31). The risk estimates from studies published before 1990 are shown in Fig. 1. Overall, the studies pointed to a 3-fold increased risk of venous thrombosis in users of oral contraceptives (32). Several important attributes of the risk emerged from these studies: the risk does not increase with longer duration of use, and disappears immediately when oral contraceptives are discontinued, i.e., past-users do not have an increased risk. Higher relative risks were found for idiopathic than for secondary thrombosis (25-27, 33).

Most of these studies were performed before objective testing for venous thrombosis was possible or in widespread use. We know that a substantial proportion of all clinical diagnoses of deep-vein thrombosis are false-positives (34, 35), so it is likely that these early studies suffer-

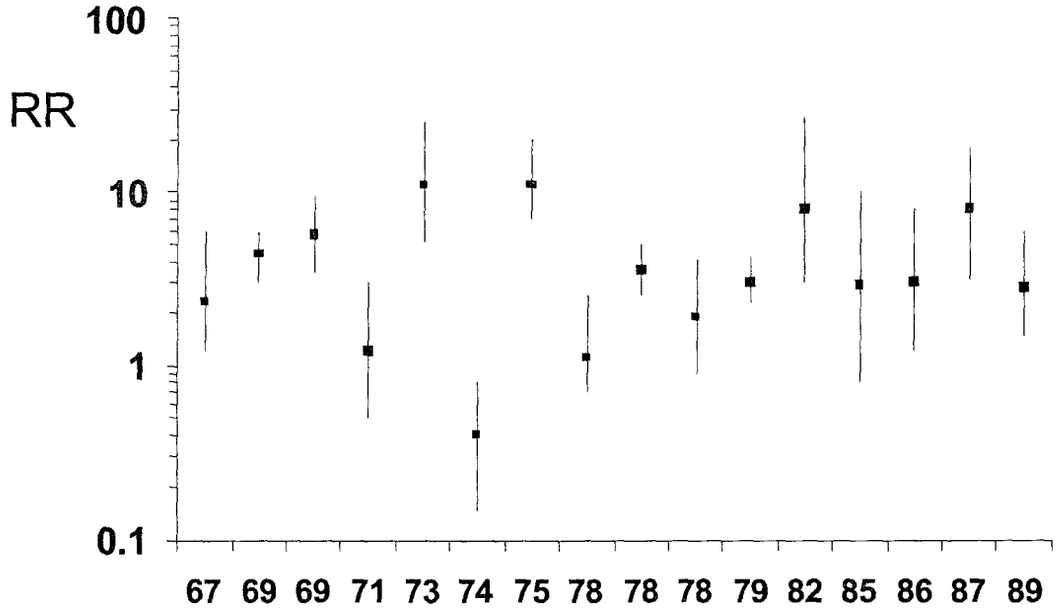


Fig. 1 The relative risk for venous thrombosis in oral contraceptive use. The relative risks (users vs. non-users) are shown from studies published between 1967 and 1989, with 95%-confidence intervals. A relative risk of 1 indicates equal risks, a relative risk exceeding one indicates a higher risk for users than for non-users. The studies include case-control studies (24, 26-28, 46, 160-163), follow-up studies (29-31, 165-167) and one randomized controlled trial (168). Some figures were estimated from data in the original papers

ed from substantial misclassification with regard to venous thrombosis. Studies that divided diagnoses by level of certainty (e. g. "definite" vs. "probable" vs. "possible") thrombosis, or those that focussed on the more severe events, usually reported higher relative risk (25-27, 30, 31, 36), which supports the existence of misclassification. This suggests that the risk of oral contraceptives is underestimated in the older studies.

Recent Studies on Risk of Venous Thrombosis and OCs

Studies in the 1990s showed similar relative risk estimates to the earlier studies with a two- to six-fold increased risk of venous thrombosis (37-40), while several studies published after 1995 showed a risk differential by progestogen content (see below). The absolute risk of venous thrombosis in women of reproductive age is estimated at 1-2 per 10,000 per year (1, 2, 41). Data of Dutch national registries showed incidence rates of all venous thrombotic events among young individuals of 2 per 10,000 per year in those aged 15-24 years, and 4 per 10,000 per year in those aged 25-39 (42). In another Dutch study, an annual incidence for deep-vein thrombosis was reported of 0.8 per 10,000 among women not using oral contraceptives, and 3.0 per 10,000 per year in oral contraceptive users (37). A similar rate of 2.0 per 10,000 among users of oral contraceptives was reported for women in the United Kingdom (43). In absolute terms, these risks do not seem large. On the other hand, since oral contraceptives are used by large numbers of women, their use is responsible for the majority of all venous thrombotic events in young women (44).

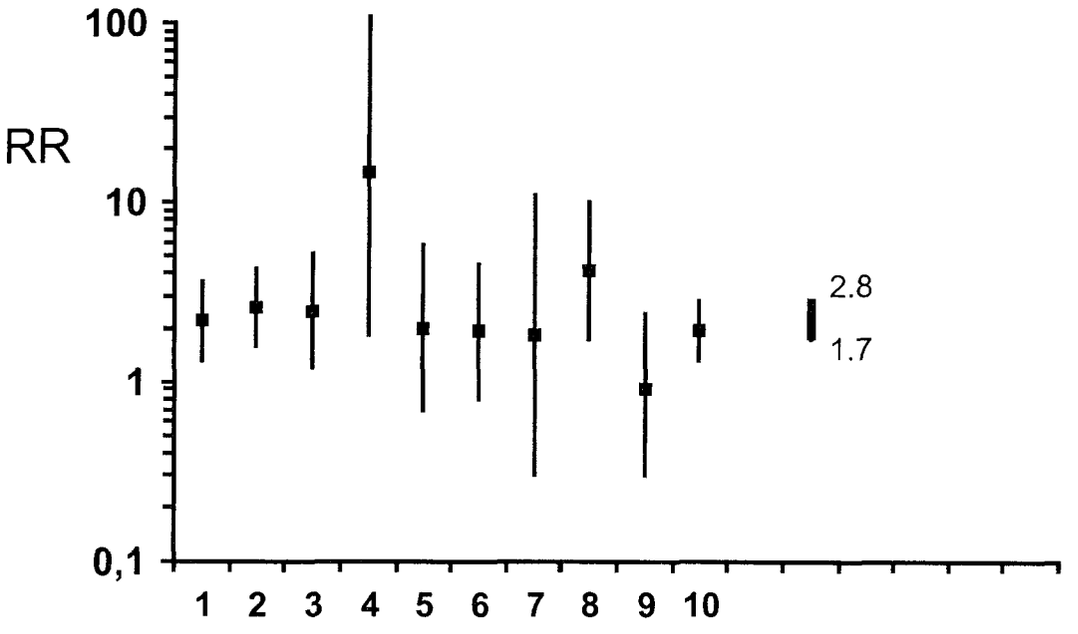
Referral Bias

Some have sought to explain the absence of a reduction of the risk of thrombosis associated with the use of oral contraceptives since the 1960s by so-called referral or diagnostic suspicion bias. The idea is that physicians would, when consulted by a woman with complaints that could point to thrombosis, preferentially refer those who used oral contraceptives for further diagnostic tests. This would lead to an overestimate of the frequency of oral contraceptive use among thrombosis patients, and subsequently an overestimate of the risk when these patients were compared to a randomly selected control group of women without thrombosis. Two studies have demonstrated that this bias does not explain the currently observed risk estimates (45, 46). In these studies, women referred for diagnostic tests for thrombosis and who subsequently tested positive, were compared to women referred for the same reason but who tested negative. Because patients and controls were referred under the same suspicion of thrombosis, referral and diagnostic suspicion bias were eliminated. Relative risks associated with oral contraceptive use were 6.4 (45) and 3.9 (46), i. e., very similar to recent studies with population controls.

Effect of Oestrogen Dose

Since the early use of oral contraceptives the oestrogen dose has gradually been decreased, from 100-150 μg ethinyloestradiol or mestranol in the first brands, to 50 and 30 μg, and recently even to 20 μg ethinyloestradiol. The expected result of this change was a reduction in the incidence of cardiovascular side effects. Such a trend is not obvious when the risk estimates found in studies published from the 1960s to the 1990s are evaluated, as Fig. 1 shows: the risks do not appear to have decreased over time. However, such a time-trend, or the absence of it, may be deceiving because of other changes that occurred over time, such as improvements in diagnostic methods. In several studies, a lower risk for oral contraceptives with a lower oestrogen content was found (31, 36, 47). In the most recent of these, the risk of venous thrombosis was increased over 10-fold (compared to non-users) for oral contraceptives containing more than 50 μg ethinyloestradiol, and 4-fold for those containing less than 50 μg ethinyloestradiol (47). Reports from several other studies, however, did not identify a difference between oral contraceptives by oestrogen dose (16, 30, 39, 48). In the Leiden Thrombophilia Study, a direct comparison of oral contraceptives containing either 30 μg or 50 μg ethinyloestradiol, and the same second generation progestogen (levonorgestrel), showed 3- to 4-fold increased risks for both oestrogen dosages compared to non-users (16).

It seems plausible from the available literature that the earliest contraceptives containing 100 μg or more ethinyloestradiol conferred a higher risk of venous thrombosis than current formulations containing 50 μg or less. It remains highly questionable whether the further reduc-



... Risk of venous ... with third gen... contraceptives ... desogestrel ver... second generation con... studies spon... public funding. ... publication year. ... 2 ... 3 (16). ... 5 (51) 6 (46). ... 8 (53), 9 (54). ... The summary ... confidence interval of ... relative risk was esti... a graphical, "odd... method (169)

... 30 µg ethinyloestradiol led to a further lowering of risk, while there are no data at all suggesting a lower risk of the newest oral contraceptives containing only 20 µg ethinyloestradiol.

Effect of Progestogen Content

At the end of 1995, three studies simultaneously reported an increased risk of venous thrombosis in women who used oral contraceptives with the progestogens desogestrel or gestodene ("third generation contraceptives") (16-18). Subsequently, more than 10 studies have reported on this issue, most of which confirmed that oral contraceptives containing desogestrel or gestodene had an increased risk of thrombosis (43, 46, 49-53), while some did not (54-57). Fig. 2 shows the estimates of non-commercially-sponsored studies (to reduce heterogeneity of estimates [58, 59]), with a summary 95%-confidence interval of 1.7- to 2.8-fold increased risk of third-generation versus second-generation oral contraceptives. The risks are considerably higher during the first year of use (60) and then might become as high as 3 per 1000 per year for users of oral contraceptives containing a third generation progestogen (53).

These findings have led to considerable controversy and several inherent biases were claimed to be present (61-66). These were said to include preferential prescription, diagnostic bias, attrition of susceptibles, starter or healthy-user effects, effects of switching types of oral contraceptives, and effects of different age distributions of the users of various oral contraceptive types. From reanalyses of previously published data, and new studies, it was claimed that such biases were present (20, 55, 56, 67-69). Thus controversy has fuelled the debates (43, 70-73). It has been pointed out that commercial interests may have affected the debate (58, 59, 74, 75) and that "considerable sums of money have been spent in denigrating well conducted studies with both clear hypotheses at the outset and clear analyses, studies which unexpectedly found that newer pills containing desogestrel and gestodene were associated with higher risks of venous thrombosis than older preparations with other progestogens. Often highly personalised attacks have been made to discredit the work of well-respected researchers, regulatory authorities, and the World Health Organisation" (76).

The various possible biases that have been proposed have been carefully reviewed, and it was concluded that they could not explain the observation of a higher thrombotic risk with oral contraceptives containing the third generation progestogens desogestrel and gestodene (77-79). An independent expert committee convened by the World Health Organisation came to the same conclusion (80).

One of the original aims in developing contraceptives with a third generation progestogen was to reduce the risk of myocardial infarction. An early study suggested such a beneficial effect (81), while other studies did not (82, 83). Since each of these included fewer than 30 women with a myocardial infarction who used oral contraceptives (and fewer than 10 who used third generation contraceptives), no conclusions could be drawn. A large study in the United Kingdom of more than 400 women with a myocardial infarction at a young age, including 40 patients who used oral contraceptives (20 with a third generation brand) yielded no evidence for a reduced risk (relative risk 1.8, 95% confidence interval 0.7-4.8 for third versus second generation oral contraceptives) (84). It has been known for many years that oral contraceptives have a variety of metabolic effects, including effects on the procoagulant, anticoagulant and fibrinolytic system (85, 86). These changes were within the normal range and therefore considered of little relevance, while it was also suggested that the pro- and antithrombotic effects might keep each other in balance (85, 86). In 1997, it was first reported that third generation oral contraceptives had a different and stronger procoagulant effect than second generation contraceptives, in a test that quantified the response of plasma to activated protein C (APC) on thrombin generation (87). In this test, the endogenous thrombin potential (ETP), which is defined as the time-integral of free thrombin concentration, usually derived from residual levels of amilodytic activity (α2M-IIa), is determined in the presence and absence of added activated protein C, yielding an APC-sensitivy ratio (87). The major difference of this EPT-APC-sensitivity ratio to the standard APC-resistance test (88, 89) is that initiation of coagulation takes place via the extrinsic pathway by tissue factor, while the original test is based on the APTT (87-89). The ETP-APC-sensitivity test proved effective in detecting factor V Leiden, as was the APTT-based APC-sensitivity test, but showed much greater sensitivity to hormonal effects, which only

led to mild changes in the APTT-based APC-sensitivity test (90, 91). With this test, a clear difference was found between users of second and third generation contraceptives (87). From the results in individuals with various factor V genotypes (Leiden or wildtype) and non-users and users of various types of oral contraceptives, it was apparent that in the ETP-APC-sensitivity test, third generation oral contraceptives induced a coagulation abnormality of about the same magnitude as that seen in carriers of factor V Leiden. This coincides with the approximately equal clinical effects, ie, a 7- to 8-fold increased risk of venous thrombosis for carriers of factor V Leiden, and a 6- to 10-fold increased risk of venous thrombosis in users of third generation oral contraceptives compared to women not using an oral contraceptive (77, 87). This study was criticised on design issues which led to a randomised cross-over study, in which women volunteers used an oral contraceptive with levonorgestrel (second generation progestogen) for a fixed period of two cycles, and an oral contraceptive with desogestrel (third generation progestogen) for two cycles, in a randomised order with a two-cycle wash-out period in-between (92). In this study contraceptives were compared on a large number of effects on procoagulant, anticoagulant and fibrinolytic factors (92-95). First of all, the pronounced effect of oral contraceptives containing desogestrel in inducing APC-resistance was confirmed (92). Secondly, while levonorgestrel-containing contraceptive increased factor VII, as had been reported earlier (reviewed in [85, 86, 96, 97]), the increase was much larger with desogestrel-containing contraceptive (12% vs. 32% increase) (93). Thirdly, desogestrel-containing oral contraceptive led to a decrease in both total and free protein S, while no effect of the levonorgestrel-containing oral contraceptive was observed (95). Finally, in an analysis of fibrinolytic parameters, increased endogenous fibrinolytic parameters were observed for both types of oral contraceptives, which was, however, not accompanied by a change in clot lysis time, suggesting that the increased fibrinolytic activity during oral contraceptive use was counterbalanced by TAFI-mediated down-regulation of fibrinolysis (94). This down-regulation of fibrinolysis, which is factor XI–independent, was more pronounced with the desogestrel-than with the levonorgestrel-containing contraceptive (94). The overall picture from these studies is that oral contraceptives with a third generation progestogen affect the haemostatic system in a more pronounced way than contraceptives with a second generation progestogen, in a direction that is prothrombotic. It has been been demonstrated in the Leiden Thrombophilia Study that APC-resistance as established by the enogenous thrombin potential (ETP-APC-sr) is a strong predictor of venous thrombosis, which clinically validates the results of the laboratory studies with this test (98).

Effect of Other Risk Factors

In women with deficiencies of natural anticoagulant proteins, i.e., protein C, protein S or antithrombin, high risks of venous thrombosis have been found among oral contraceptive users. In selected families with familial thrombophilia due to these deficiencies, annual risks among oral contraceptive users ranged from 6-27 percent, with the highest risk in antithrombin deficient women (99). In female relatives of unselected patients with these deficiencies, oral contraceptive use also increased the risk of thrombosis, by 6- to 8-fold (100) over above the thrombotic risk brought about by the thrombophilic defect.

Several studies have shown that APC-resistance is common (10-37 percent) among women who developed thrombosis during oral contraceptive use (50, 101, 102). In two population-based studies a high risk was found for factor V Leiden carriers who used oral contraceptives, indicating 20- to 30-fold increased risks compared to women without factor V Leiden who did not use oral contraceptives (37, 54). In a comparison of unselected relatives with various thrombophilic defects, the synergistic effect with oral contraceptives appeared even higher for deficiencies of natural anticoagulants than for factor V Leiden (100). The interaction of oral contraceptives with factor V Leiden was most striking for those using a third-generation progestagen (16). Homozygosity for factor V Leiden leads to a 50- to 100-fold increased risk of venous thrombosis (103). In a series of homozygous patients, 80 percent of the women with thrombosis had been using oral contraceptives, which suggests a very high risk of oral contraceptives in these women (104).

The prothrombin 20210 G to A variant, which by itself increases the risk of thrombosis 2- to 4-fold (105) also interacts synergistically with oral contraceptives, with a 16-fold increased risk of thrombosis in carriers who used oral contraceptives compared to non-carrier non-users (54).

High levels of factor VIII are, like factor V Leiden and prothrombin 20210A, common in the general population and may therefore affect many individuals (106, 107). The combination of high levels of factor VIII and use of oral contraceptives was associated with a 10-fold increase in risk compared to individuals with lower levels (<150 IU/dl) who did not use oral contraceptives. This estimate did not exceed the sum of the separate effects of the two risk factors (108).

The synergistic effects with oral contraceptives on the occurrence of deep vein thrombosis of factor V Leiden and prothrombin 20210A, and deficiencies of protein C, protein S and antithrombin, are also present for thrombosis at unusual sites. The risk of cerebral vein thrombosis was highly increased in women with either factor V Leiden or prothrombin 20210A who used oral contraceptives (109, 110).

Screening for other Risk Factors

When other factors enhance the risk of oral contraceptives, consideration could be given to screening for abnormalities prior to prescription. Theoretically, screening may offer benefit if the joint effect of the two risk factors exceeds the sum of the separate effects, in which case withholding oral contraceptives from the high-risk group would lead to a larger reduction of thromboses than random withholding (111). For deficiencies of protein C, protein S and antithrombin, it is obvious that the population prevalence is too low to render screening for these abnormalities worthwhile. This may be different for factor V Leiden and prothrombin 20210A, each of which has a population prevalence of several percent. Some have argued that the risks of thrombosis, even in the presence of such a genetic defect and oral contraceptive use, are still small in absolute terms (less than 3 per 1000 per year), and that therefore the number of women needed to screen to prevent one fatal thromboembolism is very high (112, 113). Others have taken a more proactive view towards screening, citing as a reason the severe morbidity that may follow non-fatal thrombotic events, e.g. the postthrombotic syndrome (114). It is important to realise that the issue of screening involves other issues than thrombosis morbidity and mortality, but also psychological effects, social effects (e.g. insurance problems), and, finally, cost. Data balancing all these various aspects are currently lacking, and in the absence of convincing data screening cannot be recommended.

Biological Mechanism

Over the last few years major advances have been made in understanding why oral contraceptives cause thrombosis. Numerous publica-

...have demonstrated effects of oral contraceptives on the haemostatic system (91, 115-118). Effects include increases in procoagulant factor VII, factor X, factor XII and factor XIII, reductions in the anticoagulants protein S and antithrombin, and an increase in the fibrinolytic factor plasminogen (reviewed in [85, 86, 96]). The net effect is an acquired APC-resistance with coagulation activation and thrombin formation (90-93, 95), which is not counterbalanced by the increased fibrinolytic activity (94). It is not clear how oral contraceptives exert these various biochemical effects on the molecular level, i.e., what role is played by the hormone receptors, or how the oestrogen and progestogen compounds interact in bringing about these effects. Since venous thrombosis is a multicausal disease, the development of thrombosis in an oral contraceptive user will be the result of interactions with other risk factors, such as the genetic make-up of the woman (16, 119). It has been shown that the haemostatic system of some women, the so-called hyper-responders, is more sensitive to exposure to oral contraceptives than that of others, and it is plausible that these women are at highest risk of developing thombosis (120).

Risk of Arterial Disease

Oral contraceptives also increase the risk of myocardial infarction, first reported in 1963 (121), of ischaemic stroke, first reported in 1968 (33), and of haemorrhagic stroke, first reported in 1973 (122). A recent study by the World Health Organisation showed a 5-fold increased risk for myocardial infarction (83). This, and other studies reviewed in the 1998 WHO Report on cardiovascular disease and oral contraception (80) confirmed a high risk in women with major cardiovascular risk factors, in particular smoking and hypertension. The recent study by the World Health Organisation on ischaemic stroke showed a 3-fold increased risk associated with the use of oral contraceptives (123), and a 1.5- to 2-fold increased risk of haemorrhagic stroke (124).

Hormone Replacement Therapy

Expectations and Early Results

Postmenopausal hormone substitution has been used for several decades (125, 126). While in the 1970s only a few percent of postmenopausal women used hormone replacement therapy, it became widespread in the 1990s (11-13, 125). The early indication was relief of menopausal symptoms, but more recently it was suggested that hormone replacement therapy could confer other benefits, affecting major diseases. This was based on the observation of the more rapid progression of osteoporosis and development of cardiovascular disease in women after menopause. It was hypothesised that hormone replacement therapy would reduce the development of osteoporosis and the incidence of fractures, and lower the incidence of cardiovascular disease, in particular myocardial infarction. Observational studies in the early 1980s confirmed these effects (127-133). For cardiovascular disease, impressive risk reductions were reported, with a halving of the risk of cardiovascular events and cardiovascular death (129, 130), and even a similar risk reduction for all-cause mortality (131). It was also shown, however, that women who used hormone replacement therapy often had a different cardiovascular risk profile than non-users, and that selection bias offered an alternative explanation for the apparent benefits (134-136). To resolve this matter, several randomised, controlled, trials have been performed or are in progress.

Composition and Types of HRT

Early hormone replacement therapy consisted of an oestrogen only (oestrogen replacement therapy, ERT, also referred to as unopposed hormone replacement therapy). Because of the strong evidence that unopposed oestrogen therapy increased the risk of endometrial cancer (reviewed in [126]), nowadays oestrogen-only hormone replacement therapy is restricted to women after hysterectomy, while, for women with an intact uterus, a progestogen compound, e.g. medroxyprogesterone acetate, is added. Conjugated oestrogens used in oral preparations are distilled from urine of pregnant mares. Micronised oestradiol and oestradiol-valerate that is hydrolised to oestradiol is also available in tablets (137). Alternatively, oestradiol may be delivered transdermally (patches), percutaneously by gels, subcutaneously by pellets every six months and rarely, nasally. It is generally thought that the oestrogen dose in hormone replacement therapy is lower than in oral contraceptives. It should be noted, however, that comparing the effective doses of different compounds from very different origins with different clinical assays, is problematic.

Risk of Venous Thrombosis

In the first systematic study of adverse effects of hormone replacement therapy, in 1974, a slight excess of oestrogen users was reported among patients with venous thrombosis compared to healthy controls (14% versus 8%). Subsequent studies failed to find an association (138-140) and in commentaries it was authoritatively stated that the notion that oestrogen replacement therapy could cause venous thrombosis was based on "medical superstition" (141). In 1996, a number of studies showed that the risk of venous thrombosis was increased in users of hormone replacement therapy (11-13, 142). These four observational studies reported relative risks for current users between 2.1 and 3.6 compared to non-users. These, and subsequent studies that confirmed the association between hormone replacement therapy and venous thrombosis (143-147) included case-control studies and prospective follow-up studies, concerned deep vein thrombosis as well as pulmonary embolism, and dealt with idiopathic and secondary thrombosis. In most studies, the risks were highest in the first year of use (11, 12, 143, 144, 147), with a complete restriction to the first year in some studies (143, 144, 147), while in other studies the risk also remained elevated after several years of use (11, 146). Elevated thrombotic risks were found for users of oral as well as users of transdermal hormone substitution (143, 144) and for conjugated oestrogens as well as for oestradiol (143, 147).

One may wonder why the early studies did not detect a risk, while in recent studies hormone replacement therapy was shown to increase venous thrombotic risk, which even was of the same magnitude as the relative risk brought about by oral contraceptives. One explanation is the lack of objective diagnostic testing for venous thrombosis in the older studies. A misclassification that would result in the inclusion of many individuals in the case-group who are actually not suffering from thrombosis, thereby diluting the effect. It is not implausible that the high oestrogen doses in oral contraceptives led to a high risk of thrombosis which was detectable in studies performed with unreliable diagnostic methodology, which lacked the accuracy to detect the risk brought about by hormone replacement therapy. A second explanation is the low prevalence of use of hormone replacement therapy at the time of the early studies, which led to a low power to detect differences in risk. In the Boston Collaborative Drug Surveillance Program, the

frequency of hormone substitution was 8% in the control population and 14% (age-standardised) among the patients, which would yield a relative risk estimate of nearly two, with wide confidence intervals since the prevalences were based on only 18 women with venous thrombosis (125). Interestingly, the only recent study that did not find an association between hormone replacement therapy and the risk of venous thrombosis, also had a low frequency of use among the healthy population, of 5 to 6 % (139). In contrast, in most of the other studies well over 25% of control women used hormone substitution (11-13, 147), up to 50% in the randomised trial (146).

Of special interest is a randomised trial among women with prior venous thrombosis (137). This study was terminated when other studies pointed to an increased thrombotic risk with hormone replacement therapy (11-13, 145) and showed a high rate of recurrence of 8.5 percent per year in the treatment group (versus 1.1 percent per year in the placebo group) (137).

Risk of Arterial Thrombosis

While observational studies have suggested a clear benefit of hormone replacement therapy for the development of arterial disease, this has not been borne out by a randomised trial, rendering further credibility to the self-selection of women with a better cardiovascular risk profile amongst users of hormone replacement therapy. The Heart and Estrogen/progestin Replacement Study (HERS) was a secondary prevention trial, in which over 2500 women with prior coronary disease were randomised to receive either hormone substitution or placebo (148). Over the five year duration of this trial, in which an excess of venous thrombosis was observed (145, 146), no benefit with regard to arterial disease could be demonstrated (RR = 1.0, CI 95 0.8-1.2). Post-hoc analyses suggested a pattern of early harm and late benefit, with rate ratios of 1.5 in the first year, and 0.75 in the fourth and fifth year of use (148). The Women's Health Initiative (149) is a large on-going placebo-controlled primary prevention trial in which nearly 30000 women have been enrolled. In the first two years of this large study, an excess of both myocardial infarction and venous thrombosis was observed in the treatment group (150).

Effect of other Risk Factors

The high risk of venous thrombosus during early phases of use suggests, as for oral contraceptives (151), that there is a subgroup of women with a genetic predisposition to thrombosis who are at particular risk when exposed to hormone replacement therapy. The results of HERS indicate that this is also likely to be the case for arterial disease (148). In the study of hormone replacement after prior venous thrombosis, the majority of women who experienced a recurrence had genetic (factor V Leiden) or acquired (anti-cardiolipin antibodies) predisposition (137). In a re-analysis of the Oxford case-control study (11), a high risk of thrombosis was observed in women who were resistant to APC (152). In a subsequent genetic analysis, we found that, while the presence of a prothrombotic mutation (either factor V Leiden or prothrombin 20210A) increased the risk of thrombosis 4.5-fold, and the use of hormone replacement therapy increased the risk 3.6-fold, the combination of these two risk factors led to an 11-fold increased risk. This suggests a synergistic effect (Rosendaal, unpublished data). Recently, it was reported that in women with a prothrombotic gene defect (prothrombin 20210A), hormone replacement therapy increased the risk of myocardial infarction. The effect of this therapy was most pronounced among hypertensive women (11-fold increase), while women without the prothrombotic variant had no increased risk of myocardial infarction when using hormone substitution (153). A study has been started to investigate women who develop thrombotic events during the first year of the primary prevention trial (WHI) for susceptible subgroups due to genetic abnormalities.

Biologic Effects

Hormone replacement therapy affects many biological parameters. In a randomised trial (Postmenopausal Estrogen/Progestin Interventions Trial, PEPI) it was shown to improve lipoprotein profile and decrease plasma fibrinogen (154). In the same study a decrease of soluble E-selectin was seen (155), which was in line with the decrease of another soluble marker of inflammation, ICAM, in another study (156). However, results from the PEPI trial also showed an increase in C-reactive protein, which renders the effects of hormone substitution on inflammation difficult to interpret (155). Effects on coagulation are similar to those of oral contraceptives, with evidence for coagulation activation, increased APC-resistance, increased factor VII, decreased antithrombin, and increased fibrinolytic activity by a decrease in PAI-1 (157) (reviewed in [158]), although the effects are not consistent among studies (159). The effects on inflammation markers, as well as on several coagulation parameters (factor IX, APC-ratio, PAI-1, t-PA) were only seen with oral hormone replacement therapy and not with transdermal patches (156, 160).

Conclusion

Oral contraceptives increase the risk of venous thrombosis at all oestrogen dosage formulations. This risk does not seem to have been lowered much, if at all, by dose reductions below 50 μg ethinyloestradiol, and is also influenced by the type of progestogen, i. e., so-called third generation progestogens (desogestrel and gestodene) increase the risk further. Oral contraceptives also increase the risk of myocardial infarction and stroke. In absolute terms, except for first-time users in the first year of use, these increases in risk are small. Therefore, the probability of complications need not outweigh the benefits of oral contraceptives, or compare unfavourably to the complication rates of other methods of birth control. Obviously, once an oral contraception is prescribed, the safest one should be used, especially since all monophasic combined oral contraceptives have equal efficacy and minor side-effect frequencies. Therefore, there is no place for third generation contraceptives, unless other contraceptives are poorly tolerated and provided the woman is informed about the increased thrombotic risks.

Even though there is little doubt that the risk of thrombosis is greatly enhanced in the concomittant presence of prothrombotic abnormalities, such as the frequently occurring factor V Leiden and prothrombin 20210A, no case can yet be made in favour of indiscriminate screening for these abnormalities prior to prescription. While obtaining information on a family history of venous thrombosis seems useful, it is also unclear whether a positive family history should lead to screening with selective withholding of oral contraceptives, or other policies (such as withholding oral contraceptives in all women with a positive family history). A personal history of thrombosis is a contra-indication for oral contraceptive use.

Hormone replacement therapy has been shown to ameliorate symptoms of menopause, and to reduce the progression of osteoporosis, but has not produced the expected reduction in cardiovascular disease. It increases the risk of venous thrombosis, and has, in the only randomised trial so far of women with prior coronary disease, not

...own an overall benefit. It is yet to be determined if subgroups of susceptible women can be identified, so that in future the therapy can be withheld from women whom it might harm, and be prescribed to women whom it would benefit.

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