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42

Venous and Arterial Thromboembolism in Users of Oral Contraceptives and Hormone Replacement Therapy

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Oral Contraceptives and Risk of Venous Thromboembolism 712
Risk of Venous Thrombosis with Postmenopausal Hormone Replacement Therapy 713
Risk of Venous Thromboembolism in Women with Inherited Thrombophilia Taking Exogenous Hormones 713
Oral Contraceptives and Risk of Stroke and Myocardial Infarction 714
Postmenopausal Hormone Replacement Therapy and Cardiovascular Risk Reduction 716
Conclusion 716

The association between the use of oral contraceptives with an increased thromboembolic risk has first been described in the early 1960s when case reports were published on pulmonary embolism (1) and ischemic stroke (2) in women using these drugs. The magnitude of the thromboembolic risk was thought to be related to the estrogen content; however, recent reports have shown relative risks of 4 to 6 for deep vein thrombosis with recent low-estrogen-containing anti-contraceptives, which is not substantially different from older reports. Furthermore, hormonal replacement therapy, which has an extremely low estrogen content compared to anticonceptives, still increases the risk for venous thromboembolism by 2.1- to 3.6-fold. Several recent studies have shown that it is not just the estrogen component of anticonceptives that is responsible for the risk of venous thrombosis since preparations containing a third-generation progestin (desogestrel, gestodene) lead to a twofold higher risk than products containing a second-generation progestin (mostly levonergestrel).

Studies published in the 1970s showed an increased risk of thrombotic stroke and an increased risk of acute myocardial infarction in current users of oral contraceptive agents. Recently published case-control studies no longer find an increased risk of ischemic stroke with the current use of low-dose anticonceptives (<50 μg estrogen), with the exception of hypertensive or smoking women. Current users of postmenopausal hormone substitution have a relative risk of 0.50 of coronary heart disease as compared to nonusers. The association of progestin to estrogen does not seem to attenuate the cardioprotective effects of postmenopausal estrogen therapy.

ORAL CONTRACEPTIVES AND RISK OF VENOUS THROMBOEMBOLISM

The association of the use of oral contraceptives and an increased risk of venous thromboembolic disease has been well established in a series of epidemiologic studies (3–5). Several studies have suggested a dose-response relation between the estrogen component of oral contraceptives and the magnitude of the thrombotic risk (6–8), which extends from 50 to 30 μg of estrogen (9). In the latter study the relative risk of venous thromboembolism in users of oral contraceptives containing >50 μg of estrogen as compared to those taking <50 μg of estrogen was 1.7. In the WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception (10), the odds ratios for venous thromboembolic disease tended to be lower when first- and second-generation progestagens were used in combination with low (<50 μg estrogen) rather than higher estrogen doses; in the Leiden thrombophilia study (11) the risk conferred by oral contraceptives containing 30 or 50 μg ethinylestradiol was the same. The risk reduction that has occurred by lowering the estrogen content of oral contraceptives, if any, has certainly not been a dramatic one. The early case-control studies in the 1960s reported relative risks for idiopathic deep vein thrombosis ranging from 4 to 8 (12–14), whereas in the most recent studies oral contraceptives still are found to be associated with a four- to sixfold increased risk (10,15,16). No other lifestyle or environmental risk factor influenced in a consistent way the risk for venous thromboembolism with the exception of body mass index, which was a weak independent risk factor; the odds ratios associated with venous thromboembolism were higher among those with a body mass index (BMI) above 25 kg/m^2 than among those with smaller BMIs (10).

Several studies published in 1995–1996 came with an unexpected result: The risk for venous thromboembolism is not only influenced by estrogen content but also by type of progestagen used. So-called third-generation oral contraceptives, containing desogestrel c gestodene as a progestagen, were associate with a twofold higher risk for venous thron boembolism than those containing a secon generation progestagen such as le onorgestrel. The published studies were subanalysis of women exposed to third-gene ation oral contraceptive pills of the WH Collaborative Study of Cardiovascular Di ease and Steroid Hormone Contraceptio (17); a case-control study of current users c the oral contraceptive pill from the Britis general practice research database (18); a re analysis of the Leiden thrombophilia stud (11); and a multinational case-control stud (15). All studies indicated a doubling of th adjusted odds ratio for venous thromboem bolism in patients taking third- rather tha second- generation oral contraceptive pills.

Venous thromboembolism is quite rare i the age group of women taking oral contra ceptives. Most recent studies report inc dences of around 1 per 10 000 women year this figure increases to 4 per 10,000 wome years in women using second-generation con traceptives and around 6 to 10 per 10,00 with the use of third-generation contracep tives.

Low-dose oral contraceptives containin third-generation progestagens seem to be les androgenic and have less impact on carbohy drate and lipoprotein metabolism than othe low-dose preparations (19); recent review have concluded that these third-generatio preparations do not differ from earlier low dose contraceptives in their impact on hemo static variables. The changes in hemostati parameters, at least for those that can be mea sured, in women using oral contraceptives ar minor and generally remain within the norma range. Furthermore, it has been suggested tha the use of oral contraceptives induces change in the procoagulant and anticoagulant path ways that may counterbalance each othe (19–21). Recently it was shown, using a method measuring endogenous thrombin po-tential of plasma, that the sensitivity to acti-vated protein C (APC) was decreased ir women using oral contraceptives, indepen-

dent of the kind of contraceptive used. Women who used third-generation oral contraceptives were less sensitive to APC than women using second-generation oral contraceptives and became comparable to female carriers of the factor V Leiden mutation which causes inherited APC resistance and is the most common cause of inherited thrombophilia (22). Joining their data on impaired APC sensitivity with epidemiologic data, these authors suggest that the increased incidence of venous thrombosis in women using oral contraceptives, especially in those using third-generation contraceptives, might be explained by acquired APC resistance. The exact molecular mechanism behind the thrombogenic potential of oral contraceptives remains to be elucidated (23).

The increased risk of venous thromboembolism appears to be related to current use of anticonceptives. In the WHO study (10) the increased odds ratios were fully realized within 4 months of starting oral contraceptives and had resolved within 3 months of stopping. These findings are in keeping with previous publications (4,24,25) and suggest that disturbance of coagulation balances induced by the anticonceptive are involved.

RISK OF VENOUS THROMBOSIS WITH POSTMENOPAUSAL HORMONE REPLACEMENT THERAPY

Until recently the risk of venous thromboembolism associated with postmenopausal hormone replacement therapy was thought to be probably nonexistent or at most very small; however, few epidemiologic studies had assessed the relation between postmenopausal hormones and thrombotic disease and most of them were too small to provide reliable estimates (26–28). The risk of venous thromboembolism associated with oral anticonceptives is to a large extent attributable to its estrogen content and the hemostatic alterations induced by postmenopausal replacement therapy on hemostatic parameters have been shown to be similar though less pronounced than with oral contraceptives; the paradoxical absence of increased venous thromboembolic risk was explained by the significantly lower estrogen content of postmenopausal hormones and different type of estrogen used. The results of three large studies studying the effect of postmenopausal hormone replacement therapy on venous thromboembolism (29,30) or pulmonary embolism (31) resolved the apparent paradox. In each of these studies a twofold to fourfold increased risk of venous thromboembolism was shown with estrogen-only as well as with combined estrogen-progestagen hormone replacement therapy. The risk seems to be higher shortly after the start of therapy (29,30). In these studies, women suffering from thromboembolic disease who had other risk factors for thrombosis, such as recent trauma or surgery, previous thromboembolism, cardiac disease, diabetes, or cancer, were excluded. Further research will be needed to establish the safety of postmenopausal hormone therapy when other risk factors for venous thromboembolism, including obesity, recent surgery, immobilization, or thrombophilic conditions, are present.

RISK OF VENOUS THROMBOEMBOLISM IN WOMEN WITH INHERITED THROMBOPHILIA TAKING EXOGENOUS HORMONES

Hereditary defects in the natural anticoagulant pathways, the antithrombin pathway (including antithrombin deficiency), and the protein C pathway (including deficiencies of protein C and protein S and resistance to activated protein C) predispose patients to the development of venous thromboembolism. Data on the thrombotic risk of women with antithrombin (AT), protein C (PC), and protein S (PS) deficiencies taking oral contraceptives are anecdotal due to the low prevalence of these defects. In a retrospective study of 96 women with proven deficiencies of either AT, PC, or PS, Pabinger et al. (32) found that the probability for thrombosis was significantly higher in AT deficient patients taking oral contraceptives as compared

to AT deficient patients not taking contraceptives. In patients with protein C or protein S deficiency there was no clear difference between users or non-users of oral contraceptives. Due to the higher prevalence of resistance to activated protein C, generally explained by the factor V Leiden mutation, more data are available concerning the risk of venous thrombosis associated with the use of oral contraceptives in this group. Data from the Leiden Thrombophilia Study (16) showed a fourfold increased risk for thrombosis among users of oral contraceptives, an eightfold increased risk of thrombosis among carriers of the factor V Leiden mutation compared with noncarriers, and a >30-fold increased risk for women who both were carriers of the mutation and used oral contraceptives. In this study the incidence of first venous thrombosis in women aged 15 to 49 years not using oral contraceptives was 0.8 per 10,000 person-years in noncarriers of factor V Leiden and 5.7 per 10,000 person-years in carriers of the mutation; in users of contraceptives the incidences rose to 3.0 per 10,000 person-years and 28.5 per 10,000 person-years, respectively. The absolute increase in thrombosis risk due to oral contraceptives is much larger in women who carry the factor V Leiden mutation than in women who do not. In a study of 29 patients homozygous for the factor V Leiden mutation oral contraceptives were found to enhance the risk of clinical manifestation of venous thrombosis at a young age (33). The factor V Leiden mutation was also shown to enhance the risk of deep vein thrombosis associated with oral contraceptives containing a third-generation progestagen (11). The risk of factor V Leiden carriers using a desogestrel containing anticonceptive is almost 50-fold increased as compared with noncarrier nonusers.

Although an enhancement of the risk of venous thromboembolism associated with the use of postmenopausal hormone replacement therapy by these hereditary thrombophilic conditions might be anticipated no data on this subject are currently available.

ORAL CONTRACEPTIVES AND RISK OF STROKE AND MYOCARDIAL INFARCTION

The issue of an increased risk of stroke associated with the use of oral contraceptives has been addressed in several, mostly retrospective studies (34,35). Relative risks among users of contraceptives in these studies were found between 3.7 and 4.8. Since most of these studies were conducted during a period when pills with a high estrogen and progestagen content were widely used, several recent studies were undertaken to address the question of whether recent contraceptives with low hormone contents still carry an increased risk of stroke. In a Danish retrospective case-control study of women aged 15 to 44 years who had suffered a thromboembolic attack without known predisposing factor, a crude odds ratio of 3 was found (36). After correcting for confounders such as age, smoking, and years of schooling, pills containing 50 μg estrogen were associated with an odds ratio for cerebral thromboembolic attack of 2.9 and those containing 30 to 40 μg estrogen with an odds ratio of 1.8. Progesterone-only pills did not increase the risk of a cerebral thromboembolic attack. Cigarette smoking increased the risk of cerebral thromboembolic attacks by 50% independent of oral contraceptive use or age. In the report of the WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception (37) the overall odds ratio of ischemic stroke in women aged 20 to 44 taking combined oral contraceptives was 2.99 in Europe and 2.93 in non-European countries. Odds ratios associated with contraceptives containing <50 μg of estrogen were 1.53 and substantially higher (5.30) for preparations containing >50 μg of estrogen. In this study odds ratios were lower in younger women and those who did not smoke, but among current users of oral contraceptives with a history of hypertension the odds ratio was 10.7.

The same study group (38) reported no increased risk of hemorrhagic stroke associated with contraceptives in women younger than

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35 years Odds ratios were >2 for women older than 35 years and >3 for those who also smoked cigarettes Current users of oral contraceptives with a history of hypertension (with the exception of pregnancy-related hypertension) had a 10- to 15-fold increased risk of hemorrhagic stroke as compared with nonusers without history of hypertension

Another recent study of the risk of stroke in users of low-dose oral contraceptives (containing <50 μg of estrogen) did not show an increased risk for ischemic stroke or for hemorrhagic stroke (39) A positive interaction between the current use of oral contraceptives and smoking was found with respect to the risk of hemorrhagic stroke Considering the width of their confidence interval and the results of the Danish study (36), Pettiti and colleagues conclude that the true relative risk of stroke among users of oral contraceptives, as compared with nonusers, is <2 5 Since the absolute incidence of ischemic stroke in young healthy women is small (5 4/100,000 women-years according to Pettiti), the absolute increase in incidence of stroke in current users of oral contraceptives will also be small

Shortly after their introduction oral contraceptives were associated with acute myocardial infarction in a case report (40) This association was thereafter confirmed in several case-control and cohort studies (41–44) More recent studies conducted in the 1990s and dealing mainly with newer contraceptives, which have low estrogen content and are used by younger women who do not have other risk factors for cardiovascular disease, could no longer demonstrate increases in risk of acute myocardial infarction associated with oral contraceptives (45–47) In the WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception, 368 women aged 20 to 44 with a definite or possible acute myocardial infarction who were admitted to hospital were studied (48) Women from Africa, Asia, Europe, and Latin America were included The overall odds ratio for acute myocardial infarction was 5 0 in Europe and 4 8 in the developing countries However, odds ratios associated with the use of oral contraceptives were not increased in women without other cardiovascular risk factors such as smoking or hypertension The estimated excess risk in such women in the European centers was about 3 per 106 Among oral contraceptive users who smoke 10 or more cigarettes per day, the odds ratios were >20 and the degree of excess risk associated with oral contraceptives is substantial only in older women who smoke (about 400 per 106 women-years) Whereas a risk reduction for cardiovascular events associated with third-generation as compared with second-generation progestagens has been anticipated based on less androgenic activity with an advantageous effect on lipid profile and possibly carbohydrate mechanism (49), it has yet to be clarified as to whether the risk of arterial diseases during treatment with the newer formulations differs from that of the older preparations (50) Two studies have failed to show a difference in the risk of ischemic stroke for users of third-generation contraceptives compared to second-generation contraceptives (37,51) Initial results of an international case-control study suggest a reduced risk of myocardial infarction associated with third-generation oral contraceptives as compared with second-generation preparations, but are based on a small number of cases (n = 6) and controls (n = 34) (odds ratio of 0 45 with wide confidence intervals) (52) This study confirms that the greatest risk for health comes from smoking while taking the pill, rather than from the type of pill being used, young women smokers who use the pill are 10 times more likely to suffer myocardial infarction than users who don't smoke (53)

While consistent reports show an increased risk of venous thrombotic disease with third-generation oral contraceptives, it is not yet clear if and how they differ from second-generation contraceptives in their risk on myocardial infarction If the latter will prove to be the case, decision analysis models will have to be set up that take into account the differences in age-dependent baseline risks for venous and arterial thrombotic disease Such model may

lead to preferential use of second-generation contraceptives in younger women and third-generation contraceptives in older women (54).

As for the risk of venous thromboembolism, the increased risk for myocardial infarction is associated with current use of anticonceptives. No increase in odds ratio was apparent with increasing duration of use among current users, and odds ratios were not increased in women who had stopped using oral contraceptives, even after long exposure (48). This again suggests that the effects are due to disturbances in coagulation rather than to, for instance, an atherogenic effect.

POSTMENOPAUSAL HORMONE REPLACEMENT THERAPY AND CARDIOVASCULAR RISK REDUCTION

In a meta-analysis of many observational studies (55) an overall risk reduction of approximately 36% was found when estrogen users were compared with those who had never used estrogen. Furthermore, the data suggest that most of this apparent protection is among the current hormone users who had a relative risk of 0.49. An even greater benefit was found in women with coronary heart disease: A summary relative risk from angiographic studies comparing women with occlusion to those without was 0.39. In several studies a reduction of all-cause mortality was documented (56,57). In a recent study of mortality associated with long-term postmenopausal hormone therapy (58), the age-adjusted relative risk of death from any cause was 0.54 in estrogen users and was largely due to reductions in coronary heart disease. However, currently much debate is ongoing whether the protective effect seen in these studies may be due, at least in part, to selection bias. Different authors observed that women who use estrogen replacement therapy are healthier and have a better cardiovascular risk profile prior to estrogen replacement therapy than women who do not take hormones (59–61). However, adjustment for known cardiac risk factors in many o large studies did not have a major impa the results (56,57,62).

The proposed mechanisms of cardiov lar protection are a reduction of low-de lipoprotein, an increase of high-de lipoprotein, and an increase of triglyce that results in an overall improvement c lipid profile (63). Estrogen replacement apy has been found to reduce lipoprote levels toward premenopausal values (64 to impede the oxidation of low-de lipoprotein (LDL) cholesterol (65). Th fects of estrogen replacement therapy o coagulation system are inconsistent: it l fibrinogen and plasminogen activato hibitor but it also lowers antithrombin protein C, which have an anticoagulant tion (66). Estrogen replacement therapy favorably influences endothelium fun and vascular tone (67,68).

Currently, to avoid abnormal endom proliferation and endometrial cancer, a estin is associated with the estrogen. ever, progestins tend to raise LDL and HDL levels (69) and to oppose the effe estrogen on vascular tone (70). In three r studies an almost identical reduction ir diovascular risk was found when wome ceiving estrogens plus progestin were pared with women receiving estrogen (71–73). In addition, the decrease of minogen activator inhibitor I induced b trogen or estrogen combined with me yprogesterone acetate was not different recent randomized crossover study (74).

CONCLUSION

Currently used combined oral antico tives with low estrogen content still ho increased risk of venous thromboembo The risk of thromboembolism is not con to the estrogen component but is also d dent on the type of progesterone.

Postmenopausal hormone replac therapy carries a two- to fourfold risk nous thromboembolism.

Inherited thrombophilia and oral contraceptives have a synergistic effect on the risk of venous thromboembolism

The risk of stroke and myocardial infarction associated with the use of oral contraceptives is very small in young women without other cardiovascular risk factors When other risk factors such as smoking or hypertension are present, the risk increases substantially

Postmenopausal hormone replacement therapy reduces cardiovascular risk regardless whether estrogen only or combined estrogen-progestin treatment are used However the magnitude of this reduction still is matter of debate, many authors argue that selection towards healthier women with less preexisting cardiovascular risk factors for treatment with estrogen replacement may bias the results

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