Medical Progress

**Oral Contraceptives and the Risk of Venous Thrombosis**

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In the early 1960s, shortly after the introduction of oral contraceptives, the first case reports appeared describing venous thrombosis and pulmonary emboli in women using this method of birth control. Later, myocardial infarction and stroke were also found to be associated with the use of oral contraceptives. These observations led to numerous epidemiologic and clinical studies of oral-contraceptive pills and thrombosis and subsequently to the development of new oral contraceptives with a lower estrogen content. These lower-estrogen contraceptives were considered safer: changes in hemostatic factors remained small, inconsistent in direction, and mostly within the normal range.1-4

Recent studies have challenged the concept that reducing the dose of estrogen in oral contraceptives eliminates the risk of venous thrombosis. These studies have included epidemiologic data suggesting that certain progestins may increase the risk of thrombosis associated with low-estrogen preparations, new findings regarding individual genetic susceptibilities to the thrombogenic effect of oral contraceptives, and new insights into the hemostatic changes that predispose women to thrombosis. These advances have consequences with respect to the development of new contraceptives and tailoring of the prescription of currently available preparations.

Arterial thrombosis is also a complication of oral-contraceptive therapy, but the risk factors for this condition differ from those for venous thrombosis. For example, smoking increases the risk of myocardial infarction associated with the use of oral contraceptives,5,6 but it has no material effect on the risk of venous thrombosis in users of oral contraceptives.7,8 In contrast, several prothrombotic genetic defects are strong risk factors for venous thrombosis and increase the risk associated with the use of oral contraceptives, but most are likely to be only weak risk factors for myocardial infarction or stroke. This review will focus on recent developments in our understanding of venous thrombosis as a side effect of oral-contraceptive use.

**Risks Associated with Low-Dose Oral Contraceptives**

In 1981, Stadel estimated that the risk of venous thrombosis was increased by a factor of four in users of oral contraceptives.9 This estimate reflected the use of the oral contraceptives available in the 1970s, which were predominantly “high-dose” (estrogen content, 50 µg or more of ethinylestradiol). At that time, little was known about the effect of lowering the dose of ethinylestradiol below 50 µg.

Primarily on the basis of studies involving the use of “low-dose” oral contraceptives (30 to 40 µg of ethinylestradiol), an expert committee of the World Health Organization concluded in 1998 that current users of oral contraceptives have a risk of venous thrombosis that is three to six times that of non-users.10 The highest risk occurred during the first year of use, and an increased risk persisted until, but not beyond, the discontinuation of the contraceptives.

A recent review of studies involving healthy young women without risk factors11 also reported that the risk of venous thrombosis increased by a factor of 3 to 6; one study estimated an increase in risk by a factor of 11 (Table 1).12,16 The absolute risk, however, remains low. A base-line risk of less than 1 per 10,000 person-years is increased to 3 to 4 per 10,000 person-years during the time when oral contraceptives are being used.6,8,11

One issue of concern regarding the methods used in studies of the risk of venous thrombosis with oral contraceptives is the possibility of diagnostic-suspiion and referral bias. In other words, the awareness by the physician that a patient with calf pain or swelling is taking oral contraceptives might increase the likelihood that the patient will be evaluated for deep-vein thrombosis17 and might lead to an overestimation of the risk posed by oral contraceptives. The finding in early studies that the risks associated with oral con-
oral contraceptives were similar regardless of whether the diagnosis of venous thrombosis was certain or uncertain suggested that such a bias was not the explanation for the observed risks.18,19

More recently, two studies addressed this issue by focusing on women who were referred to testing facilities for clinically suspected deep-vein thrombosis.20,21 A case was defined as an objectively confirmed diagnosis of venous thrombosis, and controls were women with similar cause for clinical suspicion who proved not to have venous thrombosis. Information about the use of oral contraceptives was obtained before diagnostic testing was conducted. The relative risk of confirmed venous thrombosis associated with oral contraceptives was 6.4 (95 percent confidence interval, 1.2 to 34.3) in the smaller study20 and 3.9 (95 percent confidence interval, 2.6 to 5.7) in the larger study.21 These results confirm the existence of an increased risk associated with the use of modern oral contraceptives that cannot be explained by surveillance bias.

**THE EFFECT OF PROGESTINS IN COMBINED PREPARATIONS**

Before 1995, the progestin component of oral contraceptives was not generally thought to contribute to the risk of thrombosis. However, more recent data showing a higher risk of venous thrombosis with third-generation progestins (desogestrel and gestodene) than with second-generation progestins (e.g., levonorgestrel and norgestrel) have challenged this view.15,22-24 Whereas the beneficial effects of third-generation progestins on the levels of high-density lipoprotein cholesterol had suggested that they might lower the risk of arterial thrombosis, studies demonstrated a relative risk of venous thrombosis in users of these oral contraceptives that was six to nine times that in nonusers.22-24

Of 16 original studies addressing the risk of third-generation as compared with second-generation oral contraceptives, 3 found no difference between the two types of contraceptives25-27 and all the others found higher risks associated with the use of third-generation preparations, with estimates of risk ranging from 1.4 to 4 times as high as that associated with second-generation preparations.15,21,24,28-35 In a prospective study involving a pharmacy data base in the Netherlands, the absolute risk associated with third-generation contraceptives approached 1 per 1000 new users per year during the first year of use.32 This finding is consistent with those of earlier studies that also found higher risks among first-time users.15,22,23,36

Findings of an increased risk with third-generation contraceptives led to a protracted debate about possible bias and confounding.6,16,37-47 Some suggested that oral contraceptives were being differentially prescribed on the basis of the patient’s underlying risk factors,41 but the appropriate stratification for risk factors such as obesity and age did not eliminate the difference in risk between third-generation and second-generation contraceptives.6,46 The possibility that the findings were due to selective “attrition of susceptibles”16,41 was addressed by the confirmation of the findings in a separate analysis of the first year of use.6,36,46 Reanalyses according to the duration of use were suggested,41,42 but they failed to reverse the findings convincingly.6,40,46 Taking into account these and other methodologic considerations, independent ex-

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**Table 1. Current Best Evidence of the Risk of Venous Thrombosis Among Apparently Healthy Users of Available Low-Dose Combined Oral Contraceptives.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Years Included</th>
<th>Age Range</th>
<th>Study Design</th>
<th>Events</th>
<th>No. in Whom Venous Thrombosis Developed</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Helmrich et al.12</td>
<td>1976–1983</td>
<td>18–49</td>
<td>Case–control Cohort</td>
<td>Nonfatal deep venous thromboembolism and pulmonary embolism</td>
<td>5</td>
<td>11.0 (3.7–32.0)</td>
</tr>
<tr>
<td>Vessey et al.13</td>
<td>1968–1985</td>
<td>25–56</td>
<td>Case–control Cohort</td>
<td>Fatal and nonfatal superficial venous thrombophlebitis, deep venous thromboembolism, and pulmonary embolism</td>
<td>3</td>
<td>3.3 (0.9–11.4)</td>
</tr>
<tr>
<td>World Health Organization14</td>
<td>1989–1993</td>
<td>15–49</td>
<td>Case–control Cohort</td>
<td>Nonfatal deep venous thromboembolism and pulmonary embolism</td>
<td>132 from Europe, &lt;35 yr old</td>
<td>4.3 (2.9–6.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>42 from Europe, ≥35 yr old</td>
<td>3.9 (2.3–6.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>93 from developing country, &lt;35 yr old</td>
<td>3.2 (2.3–4.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>28 from developing country, ≥35 yr old</td>
<td>2.5 (1.5–4.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>75</td>
<td>6.1 (2.5–15.1)</td>
</tr>
<tr>
<td>Jick et al.15</td>
<td>1991–1994</td>
<td>&lt;40</td>
<td>Cohort</td>
<td>Nonfatal deep venous thromboembolism and pulmonary embolism</td>
<td>5</td>
<td>4.3 (2.9–6.5)</td>
</tr>
<tr>
<td>Lewis et al.16</td>
<td>1993–1995</td>
<td>16–44</td>
<td>Case–control Cohort</td>
<td>Fatal and nonfatal deep venous thromboembolism and pulmonary embolism</td>
<td>334</td>
<td>4.4 (3.4–5.8)</td>
</tr>
</tbody>
</table>

*Adapted from Hannaford and Owen-Smith.31 CI denotes confidence interval.
perts who were not involved in the original studies concluded that bias and confounding could not explain the consistent epidemiologic findings of an increased risk.\textsuperscript{10,44–48} Recent package inserts for third-generation oral contraceptives used in the United States and the United Kingdom explain that they are associated with a higher risk of venous thrombosis than are other oral contraceptives.

The epidemiologic evidence that some oral contraceptives are more thrombogenic than others led to the elucidation of the hemostatic mechanisms that may underlie the association between oral contraceptives and venous thrombosis.

**SUSCEPTIBILITY TO PROTHROMBOTIC STATES**

**Hereditary Resistance to Activated Protein C and the Factor V Leiden Mutation**

In 1993, Dahlbäck et al. described a newly recognized hereditary prothrombotic condition\textsuperscript{49}: the diminished anticoagulant response, or resistance, to activated protein C. The activated protein C system is one of the hemostatic checks and balances that inhibit coagulation. Dahlbäck et al. described persons from families with multiple episodes of venous thrombosis who had normal levels of protein C, but in whom activated protein C did not have its expected anticoagulant effect. One year later, the molecular basis was identified as a mutation in coagulation factor V (the substitution of adenine for guanine at nucleotide 1691) at one of the sites where activated protein C exerts its inactivating effect by cleaving factor V.\textsuperscript{50} The mutant factor is commonly referred to as factor V Leiden. Its prevalence is about 5 percent in white persons, with some geographic variation, but it is virtually absent in Asian and African populations.\textsuperscript{51,52} The presence of factor V Leiden increases the risk of venous thrombosis by a factor of 4 to 10 in heterozygotes and by a factor of 50 to 100 in homozygotes.\textsuperscript{53}

It is now recognized that factor V Leiden greatly increases the risk of venous thrombosis associated with oral-contraceptive use (Fig. 1).\textsuperscript{8} As compared with the baseline risk for women who do not use oral contraceptives and do not carry factor V Leiden, the risk is increased by a factor of 4 in those who use oral contraceptives but do not carry factor V Leiden, by a factor of 7 in carriers of the factor V mutation who do not use oral contraceptives, and by a factor of 35 in women who carry the mutation and also use oral contraceptives. This susceptibility has been confirmed in other studies\textsuperscript{29,54} and is even higher in the few women who are homozygous for this mutation.\textsuperscript{53}

**Other Hereditary Prothrombotic Defects**

The prevalence of previously recognized prothrombotic defects — deficiencies of protein C, protein S, and antithrombin — is much lower than that of factor V Leiden; their combined prevalence is less than 1 to 2 percent.\textsuperscript{55,56} Their rarity makes it difficult to conduct extensive studies of the interaction between these defects and the use of oral contraceptives. Nevertheless, multiple case reports and studies in large families indicate that the risk is particularly high in young women with these defects who begin to use oral contraceptives.\textsuperscript{57–59} Another recently identified genetic defect, a mutation in the prothrombin gene (the substitution of adenine for guanine at nucleotide 20210), is a moderate risk factor for thrombosis; its prevalence among white persons is approximately 2 to 4 percent,\textsuperscript{60,61} and it has also been shown to increase the risk of venous thrombosis associated with the use of oral contraceptives.\textsuperscript{27}

Women who have a prothrombotic defect have oral-contraceptive–associated venous thrombosis not only more often, but also sooner: their risk of venous thrombosis in the first year of use is more than 10 times that in later years.\textsuperscript{62} Thus, the development of venous thrombosis in the first year of use may be a warning that a woman has a hereditary risk factor for venous thrombosis.\textsuperscript{62}

**Prothrombotic Conditions of Uncertain Heredity**

High levels of factor VIII are linked to blood groups other than O,\textsuperscript{63,64} which accounts in part for the observation that having a blood group other than O increases the risk of venous thrombosis by a factor of about 1.6 in general, and by a factor of 3.3 among users of oral contraceptives.\textsuperscript{65} However, some data have suggested that the effects of high levels of factor VIII and the use of oral contraceptives are merely additive.\textsuperscript{66}

A recent study of carriers of factor V Leiden demonstrated that women with blood groups other than O were four times as likely to have venous thrombosis than those with blood group O. This increased risk was greater than previous general estimates derived from studies in unselected patients and points to a possible interaction.\textsuperscript{67}

**MECHANISMS OF VENOUS THROMBOSIS INDUCED BY ORAL CONTRACEPTIVES**

Until recently, it was uncertain whether the use of low-dose oral contraceptives disturbed the hemostatic balance.\textsuperscript{1,4} Potential prothrombotic effects included increases in the levels of coagulant factors and decreases in the levels of the anticoagulant proteins antithrombin and protein S. However, these changes were believed to be at least partially counterbalanced by such antithrombotic effects as increases in the levels of other anticoagulant proteins and increased fibrinolysis. Furthermore, the levels of coagulation factors typically remained within the normal range during oral-contraceptive use.\textsuperscript{1,4}

New studies of the effects of second-generation and third-generation oral contraceptives on the pro-
coagulant, anticoagulant, and fibrinolytic pathways, in contrast, indicate that oral contraceptives have a net prothrombotic effect. Quantitatively, the effect is greater with preparations that confer a higher risk of thrombosis. The hemostatic factors involved in this process are shown in Figure 2.68

Procoagulant Effects

A recent randomized, crossover study69 confirmed that there are increases in the levels of prothrombin, factor VII, factor VIII, factor X, fibrinogen, and prothrombin fragment 1+2 and decreases in the levels of factor V during the use of oral contraceptives. The increase in prothrombin and factor VII and the decrease in factor V were significantly more pronounced with the use of third-generation oral contraceptives than with second-generation oral contraceptives (those containing desogestrel) than with oral contraceptives containing levonorgestrel. It is now recognized that modulated levels of resistance reported among users of oral contraceptives, carriers of factor V Leiden, and heterozygous carriers of factor V Leiden who use oral contraceptives correlate with the relative risks of venous thrombosis that have been found in epidemiologic studies to be associated with these conditions.76-79 Since resistance to activated protein C, even in the absence of factor V Leiden, is an independent risk factor for venous thrombosis,80,81 these observations support the theory that acquired resistance to activated protein C contributes to the increased risk of thrombosis in users of oral contraceptives. The molecular basis of acquired resistance to activated protein C during the use of oral contraceptives is unknown. Decreased levels of plasma protein S, the cofactor of activated protein C (the levels of which were significantly lower in users of desogestrel82), only partially explain the resistance to activated protein C found in users of oral contraceptives.

Fibrinolytic Effects

Changes in fibrinolytic variables (plasminogen, tissue plasminogen activator, plasminogen-activator inhibitor type 1, and plasmin—antiplasmin complexes) with the use of oral contraceptives suggest that fibrinolytic activity is increased.1-4,83 It is not known whether enhanced fibrinolytic activity during oral contraceptive use has clinical implications, since changes in the fibrinolytic system have not been demonstrated to affect the risk of venous thrombosis. One antifibrinolytic mechanism involves thrombin-activatable fibrinolysis inhibitor (TAFI), which, when activated, inhibits fibrinolysis by removing from fibrin the lysine residues that are essential for the binding and activation of plasminogen.84,85 Elevated levels of TAFI are a risk factor for venous thrombosis.86 An assay for clot lysis that probes the activity of both the fibrinolytic system and the TAFI-dependent antifibrinolytic pathway demonstrated that the overall clot-lysis time remained unchanged during oral-contraceptive use.83 This finding suggests that in the users of oral contraceptives an enhanced down-regulation of fibrinolysis by the TAFI system compensates for the increased fibrinolytic potential. Levels of TAFI are higher in women taking contraceptives containing desogestrel than in those taking contraceptives containing levonorgestrel, indicating a stronger down-regulation of fibrinolytic activity.
The increased TAFI-dependent inhibition of fibrinolysis most likely results from both elevated levels of TAFI and enhanced formation of thrombin (the activator of TAFI).

**Overall Hemostatic Effect**

The increase in procoagulant effects, the decrease in anticoagulant effects, and the equivocal effects on fibrinolysis (with increases in the activity of the antifibrinolytic system) indicate that oral contraceptives have a net prothrombotic effect. Significant differences between users of oral contraceptives that contain levonorgestrel and users of those that contain desogestrel in the plasma levels of prothrombin, factor V, factor VII, and protein S and in susceptibility to the anticoagulant action of activated protein C may explain the higher risk of venous thrombosis observed in users of third-generation oral contraceptives. The more pronounced hemostatic changes associated with third-generation oral contraceptives might be related to their increased estrogenic profile, which might also cause the moderate increase in the level of high-density lipoprotein cholesterol that has been observed in women using these contraceptives.

**CONCLUSIONS**

Hormonal contraception is used by more than 100 million women worldwide. The number of excess deaths from cardiovascular disease (venous and
arrest of or oral contraceptive, thrombosis, but is unknown whether it increases

200 per million per year.88

use oral contraceptives, the number of excess deaths

important at older ages. Among older smokers who

users, the risk of arterial thrombosis becomes more

of venous thrombosis is more important for younger

screening for risk factors that is performed before

studies in industrialized countries.5,6,88 The beneficial

ts of arterial thrombosis reported in recent

tives by such women may underlie the reduction in

contraceptives were stopped.92 Contraceptives con-

thrombotic disease that occurred during the use of

contraceptives from women with known risk factors

is limited by the absence, in the majority of cases, of

clinically recognizable risk factors for venous throm-

An investigation in New Zealand of a series of
deaths due to pulmonary emboli suggested that in

most cases physicians could not have foreseen the

The reduction of the dose of estrogen has had a

limited effect on reducing the risk of venous throm-

bosis. Third-generation progestins in combination

preparations increase the extent of adverse hemostatic

changes and the associated risk of thrombosis and thus

should not be the first choice for new users.34,39,40,47

The ability to prescribe prudently by withholding oral

contraceptives from women with known risk factors

is limited by the absence, in the majority of cases, of

clinically recognizable risk factors for venous throm-

bosis. An investigation in New Zealand of a series of
deaths due to pulmonary emboli suggested that in

most cases physicians could not have foreseen the

risk.89

In contrast, prudent prescribing can help prevent

arterial thrombosis; almost all women who have a

myocardial infarction during the use of oral contracep-
tives are older and either smoke or have other risk

factors for arterial disease — in particular, hyperten-
sion.5 The avoidance of the use of oral contracep-
tives by such women may underlie the reduction in

the rates of arterial thrombosis reported in recent

studies in industrialized countries.5,8,88 The beneficial

effect that third-generation contraceptives theoreti-
cally have on the lipid profile has not translated into

a lower incidence of stroke or myocardial infarction

in large case-control studies.90,91

To prevent venous thrombosis when prescribing

oral contraceptives, physicians generally consider a per-

sonal history of venous thrombosis to be an absolute

contraindication, although little is known about the

risk of recurrence during the use of oral contracep-
tives. The only existing evidence is indirect; venous

thrombotic disease that occurred during the use of

oral contraceptives was less likely to recur when the

contraceptives were stopped.92 Contraceptives con-
taining low doses of progestin alone (first-generation

or second-generation) are associated with a lower risk

of venous thrombosis than are combined prepara-
tions83,93; however, the risk among women with a his-
tory of thrombosis is unknown.

Gross obesity is a recognized risk factor for venous

thrombosis, but it is unknown whether it increases

the risk associated with the use of oral contraceptives,
and thrombosis is rare even among obese users. Obes-
sity is therefore not considered a contraindication to

the use of oral contraceptives. Superficial varicose veins

that are not the consequence of a previous venous thrombosis are not, by themselves, risk factors for
deep venous thrombosis.94 A family history of venous

thrombosis may cause concern, although the sensi-
tivity of a family history as a marker for identifying
persons at high risk remains unclear. A personal his-
tory of superficial thrombophlebitis might also sug-
gest a hereditary risk factor, especially if it is coupled

with a family history of the disorder.

The susceptibility to venous thrombosis conferred

by factor V Leiden and other prothrombotic muta-
tions has led to questions about the value of screening

for these mutations before oral contraceptives are

prescribed. In the absence of a clear family history

of venous thrombosis, there is little justification to

screen for prothrombotic mutations. More than half

a million women would need to be screened for fac-
tor V Leiden to avoid a single death from pulmonary

embolus, since only 5 percent of women are carriers

and the mortality associated with venous thrombosis

in young women is low.95 If all the costs associated

with the treatment of all occurrences of venous throm-

bosis — including the post-thrombotic syndrome that

occurs in up to one third of patients96 — were con-

sidered, and if the cost of screening became very low

(less than about $9), screening might be rationalized

on economic grounds.97 Such cost–benefit calcula-
tions, however, might be too general to be of use,

since the risk of carrying the factor V Leiden muta-
tion varies according to the presence or absence of a

family history of thrombosis — presumably because

of concomitant genetic or environmental risk factors.98

Also, denying oral contraceptives to women who test

positive for factor V Leiden would leave at least 5 per-
cent of young women without access to the most
efficacious form of contraception. Moreover, the im-

plications of a prothrombotic genetic defect in a wom-

an without a history of thrombosis are unclear, and

awareness of the presence of the defect has daunt-
ing psychosocial, medical, and legal consequences (in
terms of insurance, in particular). Finally, the absence

of a recognized biochemical or genetic defect does

not eliminate the possibility of thrombosis. Even in
the absence of one of the defects that are currently
known to be relevant, a strong family history of venous

thrombosis warrants caution about the use of oral

contraceptives, purely on clinical grounds. In the ab-
sence of decisive data regarding the risks and benefits

of genetic screening before prescribing oral contra-
ceptives, either in the general population or in high-

risk families, decisions regarding screening and pre-
scribing should be based on clinical judgment that
takes into account each woman’s family history and

risk factors.95

The past five years have yielded key advances in
understanding the epidemiology and the hemostatic
mechanisms of the risk of venous thrombosis associated with the use of oral contraceptives. An increased understanding of individual susceptibility to the hemostatic changes induced by oral contraceptives and of markers of the risk of thrombosis should lead to the development of preparations that are even safer.

We are indebted to the following persons for their previous collaboration and their extensive personal contributions to several of the studies described in this review: Dr. J. Curvers, Dr. G. Nicloues, Dr. G. Taux, and Mrs. M.C.I.G.D. Thomassen of the Department of Biochemistry, Cardiovascular Research Institute, Maastricht; Professor H.R. Büller, Dr. J.C.M. Meijers, and Dr. M.H. Prins of the Department of Vascular Medicine, Academic Medical Center, Amsterdam; and Professor R.M. Bertina of the Thrombosis and Hemostasis Research Center, Leiden University Medical Center, Leiden—all in the Netherlands.

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