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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-suspicion 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-
tracetives were similar regardless of whether the di-
agnosis 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 fa-
cilities for clinically suspected deep-vein thrombo-
sis.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 be-
fore diagnostic testing was conducted. The relative
risk of confirmed venous thrombosis associated with
oral contraceptives was 6.4 (95 percent confidence in-
terval, 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 surveil-
ance bias.

THE EFFECT OF PROGESTINS
IN COMBINED PREPARATIONS

Before 1995, the progestin component of oral
contraceptives was not generally thought to contrib-
ute to the risk of thrombosis. However, more recent
data showing a higher risk of venous thrombosis with
third-generation progestins (desogestrel and gesto-
dene) 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 demon-
strated 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-genera-
tion preparations, with estimates of risk ranging from
1.4 to 4 times as high as that associated with second-
generation preparations.15,20,22,23,36 In a prospective
study involving a pharmacy data base in the Nether-
lands, the absolute risk associated with third-genera-
tion contraceptives approached 1 per 1000 new users
per year during the first year of use.22 This finding is
consistent with those of earlier studies that also found
higher risks among first-time users.22-24

Findings of an increased risk with third-genera-
tion contraceptives led to a protracted debate about
possible bias and confounding.6,16,37-47 Some suggest-
ed that oral contraceptives were being differentially
prescribed on the basis of the patient’s underlying risk
factors,41 but the appropriate stratification for risk fac-
tors such as obesity and age did not eliminate the dif-
fERENCE in risk between third-generation and second-
generation contraceptives.6,46 The possibility that the
findings were due to selective “attrition of suscepti-
bles”16,41 was addressed by the confirmation of the
findings in a separate analysis of the first year of use.6,46
Reanalyses according to the duration of use were
suggested,41-43 but they failed to reverse the find-
ings 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</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>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</td>
<td>Nonfatal deep venous thromboembolism and pulmonary embolism</td>
<td>132 from Europe, &lt;35 yr old 42 from Europe, ≥35 yr old</td>
<td>4.3 (2.9–6.5) 3.9 (2.3–6.6)</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>93 from developing country, &lt;35 yr old 28 from developing country, ≥35 yr old</td>
<td>2.5 (1.5–4.5) 2.2 (1.3–4.0)</td>
</tr>
<tr>
<td>Lewis et al.16</td>
<td>1993–1995</td>
<td>16–44</td>
<td>Case–control</td>
<td>Fatal and nonfatal deep venous thromboembolism and pulmonary embolism</td>
<td>75</td>
<td>6.1 (2.5–15.1)</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. The prevalence of previously recognized prothrombotic defects includes 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.

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. 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.

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 F1+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 (those containing desogestrel) than with the use of second-generation oral contraceptives.60 Furthermore, third-generation oral contraceptives cause more pronounced resistance than do second-generation oral contraceptives.76-78 The clinical relevance of acquired resistance to activated protein C during the use of oral contraceptives is evidenced by the observation that the 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 fibrinolytic 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.85 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

Figure 1. Cases of Deep-Vein Thrombosis per 10,000 Person-Years, According to the Use of Oral Contraceptives and the Presence of Factor V Leiden.
fibrinolysis with the former type of contraceptive.\textsuperscript{83} 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.\textsuperscript{87}

**CONCLUSIONS**

Hormonal contraception is used by more than 100 million women worldwide.\textsuperscript{10} The number of excess deaths from cardiovascular disease (venous and...
arterial combined) among young, low-risk users — nonsmoking women between 20 and 24 years of age — ranges from 2 to 6 per million per year worldwide, depending on the region of the world, the underlying cardiovascular risk, and the extent of the screening for risk factors that is performed before the contraceptives are prescribed. Whereas the risk of venous thrombosis is more important for younger users, the risk of arterial thrombosis becomes more important at older ages. Among older smokers who use oral contraceptives, the number of excess deaths is estimated to vary from 100 to slightly more than 200 per million per year.88

The reduction of the dose of estrogen has had a limited effect on reducing the risk of venous thrombosis. 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 thrombosis. 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 contraceptives are older and either smoke or have other risk factors for arterial disease — in particular, hypertension.5 The avoidance of the use of oral contraceptives 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 theoretically 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 personal history of venous thrombosis to be an absolute contraindication, although little is known about the risk of recurrence during the use of oral contraceptives. 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 containing low doses of progestin alone (first-generation or second-generation) are associated with a lower risk of venous thrombosis than are combined preparations33,93; however, the risk among women with a history 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. Obesity 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 sensitivity of a family history as a marker for identifying persons at high risk remains unclear. A personal history of superficial thrombophlebitis might also suggest 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 mutations 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 factor 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 thrombosis — including the post-thrombotic syndrome that occurs in up to one third of patients96 — were considered, and if the cost of screening became very low (less than about $9), screening might be rationalized on economic grounds.97 Such cost–benefit calculations, however, might be too general to be of use, since the risk of carrying the factor V Leiden mutation 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 percent of young women without access to the most efficacious form of contraception. Moreover, the implications of a prothrombotic genetic defect in a woman without a history of thrombosis are unclear, and awareness of the presence of the defect has daunting 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 absence of decisive data regarding the risks and benefits of genetic screening before prescribing oral contraceptives, either in the general population or in high-risk families, decisions regarding screening and prescribing 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.

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REFERENCES

evidence shows they are less safe than second generation pills. BMJ 1999; 319:795-6.


74. Pabinger I, van der Meer FJM, Helmerhorst FM, Rosendaal