The Risk of Deep Venous Thrombosis Associated With Injectable Depot–Medroxyprogesterone Acetate Contraceptives or a Levonorgestrel Intrauterine Device

Astrid van Hylckama Vlieg, Frans M. Helmerhorst, Frits R. Rosendaal

Objective—To assess the risk of venous thrombosis associated with nonoral contraceptives (ie, injectable depot–medroxyprogesterone acetate contraceptives, hormone [levonorgestrel]–releasing intrauterine devices, a contraceptive patch, or a contraceptive implant).

Methods and Results—Analyses were performed in the Multiple Environmental and Genetic Assessment study, a large case-control study on risk factors for venous thrombosis. For the current analyses, we selected premenopausal women, aged 18 to 50 years, who were not pregnant nor within 4 weeks postpartum and were not using oral contraceptives; 446 patients and 1146 controls were included. Injectable depot–medroxyprogesterone acetate contraceptives were associated with a 3.6-fold (95% CI, 1.8- to 7.1-fold) increased risk of venous thrombosis compared with nonusers of hormonal contraceptives. The use of a levonorgestrel intrauterine device was not associated with an increased risk (odds ratio, 0.3; 95% CI, 0.1 to 1.1). Unfortunately, the few women using a contraceptive patch or an implant prevented a reliable estimate of the risk of thrombosis.

Conclusion—The risk of venous thrombosis was increased for injectable depot–medroxyprogesterone acetate contraceptive users, while we were able to reliably exclude an increased risk associated with levonorgestrel intrauterine device use. Therefore, the latter seems to be the safest option regarding the risk of venous thrombosis. (Arterioscler Thromb Vasc Biol. 2010;30:2297-2300.)

Key Words: risk factors ▪ venous thrombosis ▪ injectable DMPA ▪ hormone-releasing IUD ▪ nonoral contraceptives

Oral contraceptive use is a well-established risk factor for the development of a first deep venous thrombosis, with risk estimates ranging from a 2- to 6-fold increased risk for users compared with nonusers.1–4 Combined oral contraceptive preparations contain an estrogen (generally ethinyloestradiol) and a progestogen. The increased risk of venous thrombosis associated with combined preparations was mainly attributed to the estrogen component of the contraceptive. However, the progestogen component alone or in combination with ethinyloestradiol has also been associated with the risk of venous thrombosis. Different types of progestogens in combined preparations yield a different risk of deep venous thrombosis, with the highest risk associated with the third-generation progestogen desogestrel and the more recently introduced progestogens cyproterone acetate and drospirenone.5,6

Although there has been much research regarding combined oral contraceptives, few data are available on the risk of venous thrombosis associated with hormonal contraceptives with other routes of administration (eg, transdermal or intrauterine). Depot–medroxyprogesterone acetate (DMPA) is a long-acting injectable progestogen-only contraceptive. In 1998, the World Health Organization reported a small increased risk of venous thrombosis for women using injectable progestogen-only contraceptives (odds ratio [OR], 2.2; 95% CI, 0.7 to 7.3).7 In contrast, Goldstein et al8 performed a study on the risk of venous thrombosis associated with injectable progestogen-only contraceptives, using surrogate end points (eg, coagulation factor levels, D-dimer, and activated partial thromboplastin time) as markers of coagulation risk. They reported no adverse effects on other coagulation markers.8 Furthermore, Walsh et al9 reported a decrease in sex hormone–binding globulin (SHBG) levels, a probable marker of venous thrombosis risk, associated with injectable DMPA-only contraceptive use.

The levonorgestrel (LNG)–releasing intrauterine device (IUD) is a T-shaped plastic contraceptive that is inserted in
the uterine cavity. The LNG IUD releases a daily lower dose of LNG compared with systemic hormonal contraceptives as combined oral preparations and is, therefore, thought to be associated with a lower risk of venous thrombosis. Indeed, the use of the LNG IUD appeared not associated with an increased risk of venous thrombosis in a recently reported large follow-up study on venous thrombosis (relative risk, 0.9; 95% CI, 0.6 to 1.3). Regarding the effect of this contraceptive method on activated protein C resistance, a similar or even increased sensitivity to activated protein C was reported 3 months after the insertion of an LNG IUD, also indicating that this contraceptive does not have a prothrombotic effect.

Contraceptive methods with other routes of administration (eg, a hormone-releasing vaginal ring, transdermal hormonal contraception [contraceptive patch], or a hormonal implant) have been introduced more recently; little information is available regarding the risk of venous thrombosis or conflicting results have been published.

Because it does not contain estrogen, injectable progestogen-only contraceptives are often prescribed to women with a contraindication for oral contraceptives (ie, postpartum or lactating women) and those whose medical status precludes use of contraceptive doses of estrogen (eg, women with an increased risk of venous thrombosis). However, there is not sufficient evidence to make robust recommendations regarding oral and nonoral estrogen-containing contraceptives based on the risk of venous thrombosis. Therefore, we conducted a study to determine the venous thrombotic risk associated with nonoral hormonal contraceptives.

Methods

This study was performed within the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (MEGA) study, a large population-based case-control study on risk factors for venous thrombosis.

The design of this study was described previously. In brief, between March 1999 and September 2004, consecutive patients younger than 70 years with a first episode of deep venous thrombosis (leg or arm) or pulmonary embolism were included from the files of 6 participating anticoagulation clinics in the Netherlands (Amersfoort, Amsterdam, The Hague, Leiden, Rotterdam, and Utrecht). Exclusion criteria were severe psychiatric problems and the inability to speak Dutch. Partners of patients younger than 70 years were invited to participate as control subjects. From January 2002 until September 2004, additional control subjects were recruited by random digit dialing. Telephone numbers were dialed at random within the geographical inclusion area of the patients. The random controls were frequency matched to the patients for age and sex. Only control subjects between the ages of 18 and 70 years, with no history of deep venous thrombosis, were included; the same exclusion criteria were applied as for the patients. All participants gave written informed consent. The study was approved by the Medical Ethics Committee of Leiden University Medical Center, Leiden, the Netherlands.

For the current analysis, only women aged 18 to 50 years were included. Women who were using oral contraceptives, who were postmenopausal, pregnant, or within 4 weeks postpartum at the thrombotic event or index date were excluded. For 3 patients and 3 control subjects, the type of IUD (hormonal or copper) was unknown; therefore, these women were excluded from the analysis. In total, 446 patients and 1146 control subjects were included in the current analyses.

Table. Characteristics of the Study Population and the Risk of Venous Thrombosis Associated With the Use of Nonoral Contraceptives

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (n=446)*</th>
<th>Control Subjects (n=1146)*</th>
<th>OR (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT leg only</td>
<td>208 (46.6)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>PE only</td>
<td>178 (39.9)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>DVT leg plus PE</td>
<td>33 (7.4)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>DVT arm</td>
<td>27 (6.1)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Age, mean (range), y</td>
<td>39.9 (18–49)</td>
<td>39.5 (18–49)</td>
<td></td>
</tr>
<tr>
<td>Nonoral contraceptives, No. of individuals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injectable DMPA contraceptive use</td>
<td>20</td>
<td>15</td>
<td>3.6 (1.8–7.1)</td>
</tr>
<tr>
<td>Hormone-releasing IUD</td>
<td>3</td>
<td>26</td>
<td>0.3 (0.1–1.1)</td>
</tr>
<tr>
<td>No contraceptives, No. of individuals</td>
<td>421</td>
<td>1102</td>
<td>1.00</td>
</tr>
<tr>
<td>Contraceptive use per age category, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>4 (7.7)</td>
<td>10 (7.4)</td>
<td></td>
</tr>
<tr>
<td>30–40</td>
<td>12 (8.6)</td>
<td>18 (4.5)</td>
<td></td>
</tr>
<tr>
<td>40–50</td>
<td>9 (3.5)</td>
<td>16 (2.6)</td>
<td></td>
</tr>
<tr>
<td>BMI, mean (range), kg/m²‡</td>
<td>26.8 (16.0–48.4)</td>
<td>24.8 (15.8–45.4)</td>
<td></td>
</tr>
<tr>
<td>Positive family history§</td>
<td>94 (23.5)</td>
<td>130 (12.3)</td>
<td></td>
</tr>
</tbody>
</table>

DVT indicates deep vein thrombosis; PE, pulmonary embolism.
*Data are given as number (percentage) of individuals in each group unless otherwise indicated.
†The OR was adjusted for age.
‡Data are available for 392 (87.9%) patients and 1031 (90.0%) control subjects.
§Data are available for 400 (89.7%) patients and 1055 (92.1%) control subjects.

Because a positive family history of venous thrombosis has been hypothesized to lead to preferential prescription of specific types of oral contraceptives, we accounted for a positive family history. A positive family history was defined as a participant having at least 1 parent or sibling with a history of venous thrombosis as reported by the participants. Body mass index (BMI), also a potential confounder in the association between different types of oral contraceptives and the risk of venous thrombosis, was calculated using weight and height (kg/m²), as stated by the participants in the questionnaire. Smoking was defined as current smoking (versus never smoking and past smoking combined).

We calculated ORs with 95% CIs as an estimate of the relative risk per type of contraceptive compared with nonusers of a hormone-containing contraceptive method. All ORs were adjusted for age unless stated otherwise using unconditional logistic regression analysis.

Results

Details of the patients and control subjects are shown in the Table. Patients were comparable for age. In the control group, the BMI was lower than in the patients (mean difference, 2.0; 95% CI, 1.4 to 2.6). Furthermore, in the control group, contraceptive users were somewhat older than nonusers (ie, mean difference, 3.4 years; 95% CI, 1.2 to 5.6 years).

In the control group, we assessed possible differences between users of different hormonal contraceptives and nonusers...
for BMI, smoking habits, and positive family history of deep venous thrombosis. Women who were using an injectable DMPA contraceptive had a mean BMI of 25.5 (95% CI, 23.6 to 27.5); LNG IUD users, a mean BMI of 23.4 (95% CI, 22.1 to 24.7); and nonusers a mean BMI of 24.8 (95% CI, 24.6 to 25.1). Women who were using the injectable DMPA contraceptive were more often smoking compared with users of the LNG IUD or nonusers of hormonal contraception (those smoking for injectable DMPA contraceptives, 50%; LNG IUD, 29.6%; and nonusers, 30.9%). We found that 11.1% of women using injectable DMPA contraceptives and 8.7% of women using an LNG IUD had a positive family history of deep venous thrombosis compared with 15.7% of women who did not use hormonal contraception.

In a previous analysis on the risk of venous thrombosis associated with oral contraceptives in the Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (MEGA) study, we reported that 72.4% of the female patients and 37.4% of the female control subjects were using oral contraceptives.\(^5\) In comparison, only a few women were using injectable DMPA contraceptives or LNG IUDs. A total of 20 patients and 15 control subjects were using the injectable DMPA contraceptive that was associated with a 3.6-fold increased risk of venous thrombosis compared with women not using hormone-containing contraceptives (OR, 3.6; 95% CI, 1.8 to 7.1). The use of an LNG IUD was not associated with an increased risk of venous thrombosis (OR, 0.3; 95% CI, 0.1 to 1.1). Further adjustment for BMI (as a continuous variable), positive family history of deep venous thrombosis (yes versus no), or smoking habit (current versus never and ever combined) only marginally affected the risk estimates (adjusted OR for injectable DMPA, 3.0 [95% CI] 1.2 to 7.5; and adjusted OR for LNG IUD, 0.3 [95% CI], 0.1 to 1.3).

None of the patients and control subjects in this study were using a contraceptive patch. Also, not enough women were using a contraceptive implant (1 patient and 0 control subjects) or a contraceptive ring (1 patient and 3 control subjects) for an adequate estimation of the risk of venous thrombosis.

**Discussion**

These results indicate that injectable DMPA contraceptives are associated with an increased risk of venous thrombosis (OR, 3.6; 95% CI, 1.8 to 7.1); an increased risk for the LNG IUD can be reliably excluded (OR, 0.3; 95% CI, 0.1 to 1.1).

There was limited information on the thrombotic risk associated with the use of injectable DMPA contraceptives. In a study\(^7\) by the World Health Organization, a mild and nonsignificant increased risk was reported (OR, 2.2); it was concluded that, although the study was limited by the small number of patients and control subjects, there was little or no increased risk of venous thrombosis associated with injectable progestogen-only contraceptives. Although few women use an injectable progestogen-only contraceptive in the current study, the risk of venous thrombosis was clearly increased. In contrast, Walsh et al\(^9\) reported a decrease in SHBG levels associated with injectable DMPA contraceptive use. Oral contraceptives with the highest risks of venous thrombosis were also associated with the highest levels of SHBG and SHBG levels were positively associated with resistance to activated protein C.\(^{15,16}\) Therefore, because SHBG levels have been seen as a potentially useful marker for the risk of venous thrombosis, a decrease in SHBG associated with injectable DMPA-only contraceptives, as reported by Walsh et al,\(^9\) suggests that these contraceptives are not associated with an increased risk of venous thrombosis, contrary to our findings. However, other studies\(^8,17,18\) on the effect of DMPA contraceptives showed little or no effect on coagulation or inflammation markers.

Interestingly, 2 clinical studies available (ie, 1 by the World Health Organization and the present study) showed an increased risk of venous thrombosis while studies using intermediate end points do not support this finding.

No increased risk was found for women using an LNG IUD. These results are in line with previous findings from studies using intermediate end points. In 1991, factor VIII activity in the endometrium remained unchanged after 3 to 6 months of use of an LNG IUD,\(^19\) van Vliet et al,\(^11\) who showed that after insertion of an LNG IUD, there was no increase in activated protein C resistance, suggested that this contraceptive did not have a prothrombotic effect. In addition, oral LNG-only contraceptives were associated with slightly less resistance to activated protein C.\(^20\)

In this study, only a limited number of women used injectable DMPA contraceptives or an LNG IUD; therefore, the results may have been affected by the presence of bias or confounding. In our analyses, we adjusted for age, BMI, a positive family history of venous thrombosis, and smoking habits; this did not affect the risk associated with the use of injectable DMPA or LNG IUD. Although unknown confounding may still be present in our study, it is unlikely that this would lead to an entirely different conclusion.

Although observational studies are prone to bias, it is unlikely that this may have led to our findings. We found no increased risk of thrombosis associated with the use of an LNG IUD and an increased risk of thrombosis associated with the use of DMPA-only contraceptives. The presence of selection bias would indicate an overrepresentation of LNG IUD users and an underrepresentation of DMPA contraceptive users because of our selection of control subjects. Also, information bias is unlikely to have occurred because information regarding hormonal contraceptive use and potential confounders was obtained in a similar way for patients and control subjects (ie, via a mailed questionnaire). Because none of the patients or controls had a personal history of venous thrombosis and adjustment for a positive family history of venous thrombosis did not affect the results, prescription bias is unlikely.

Frequently, hormone IUDs are prescribed for women after a first venous thrombotic event to replace oral contraceptives. Our results suggest that it seems a safe contraceptive method regarding the risk of venous thrombosis, although our study is limited to first thrombotic events. Only 1 patient and 3 control subjects were using a contraceptive ring, and only 1 patient and 0 control subjects were using a contraceptive implant. Therefore, we were unable to estimate the risk of deep venous thrombosis associated with these contraceptive methods reliably. Furthermore, because of the fact that none of the
participants were using a contraceptive patch, we were unable to assess the associated thrombotic risk.

In conclusion, the risk of venous thrombosis was increased for injectable progestogens. Therefore, this may not be the safest option regarding thrombosis risk. An LNG IUD was not associated with the risk of thrombosis. Our results suggest that this is a safe contraceptive method regarding the risk of venous thrombosis, although our study is limited to first thrombotic events.

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