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Hormone-based Contraceptive Therapy and Risk of Venous Thromboembolism in Young Women

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H&O What do we know of the association between venous thromboembolism (VTE) and hormone contraception?

HR Although rare, VTE is one of the most serious side effects of combined hormonal contraception and causes death in 1–2% of combined pill users. Case reports of VTE started to appear in the early 1960s, shortly after the introduction of the pill. The type of estrogen was changed from mestranol to ethinyl estradiol, and the estrogen content was lowered from 100 to 50 µg ethinyl estradiol, with reduction of risk. More recent studies have shown further decrease in risk with even lower doses of estrogen. However, the introduction of newer types of progestin in the combined pill did not lead to further decrease in VTE incidence. These pills, containing desogestrel and gestodene, were commonly called *third-generation pills*, as opposed to the older, second-generation pills containing levonorgestrel and norethisterone. The baseline incidence of deep venous thrombosis among young women who do not use oral contraception is 0.5–1 per 10,000 women years. This is increased 3- to 4-fold by second-generation contraceptive pills and a further 2 times by third-generation pills. Studies have also shown that combined pills containing newer progestins, such as cyproterone acetate and drosperinone, have a similar further increased VTE risk as the third-generation pills.

In general, most women wishing to use a pill would initially be started with a second-generation pill. VTE risk from combined pills is low in absolute terms, appears soon after initiation of use, and disappears a few months after stopping the pill. Progestogen-only contraceptives do not appear to have an effect on VTE risk.

H&O Can you explain some of the most important studies that investigated the connection between VTE and hormone contraception?

HR Unlike the randomized evidence available for VTE risk with menopausal hormone replacement, the association between VTE and hormonal contraceptives comes from observational studies. Prior to the reduction of the estrogen dose, the early epidemiologic data showed that the combined pill increased VTE risk by a factor of 4–8. Between 1995 and 2001, second- and third-generation formulations were compared in 16 studies, including the worldwide case control study from the World Health Organization (WHO), the United Kingdom General Practice Research Database, and an industry-funded European transnational study. Thirteen of these studies found that third-generation pills carried a higher risk of VTE. A large amount of discussion subsequently appeared in the literature criticizing these studies and pointing out poten-

tial biases and confounders. One of these points was the "starter" or "healthy user" bias, which suggested that the VTE risk with third-generation pills would mainly occur in young first-time users who started with the newer pills. These new users may be more susceptible to the thrombogenic effects of contraceptives because they have never been challenged by previous pill use. On the other hand, women using second-generation pills have already used them for a long time, and if they had not had an adverse event such as VTE, continued to use them (healthy users). However, in a further separate analysis for first-time users, the difference was still apparent in these studies. Risk with all pills was always higher in the first year of combined pill use, reaching an absolute risk of 12 per 10,000 women per year for second-generation pill use. The WHO analysis also showed that the 2-fold differential increase in VTE risk with first-time third-generation users was apparent from the first year of pill use (ie, the "starter" effect was stronger for these pills).

Most of the biases and confounders were addressed by the WHO study, and during a WHO-organized conference in November 1997, a committee of independent and uninvolved researchers discussed all published and many unpublished studies. The conclusion was that combined oral contraceptives containing desogestrel or gestodene probably carry a small risk of VTE beyond that which is attributable to combined oral contraceptives containing levonorgestrel.

In addition to coagulation research, investigation from the Netherlands has now shown that women who use third-generation pills acquire a degree of resistance to the blood's own anticoagulation system, which is similar to the degree of activated protein C resistance in carriers of the factor V Leiden mutation. Women using second-generation pills, however, only show approximately half of this effect.

A recent Danish cohort study by Lidegaard also assessed the risk of VTE in current users of different types of hormonal contraception using the National Registry. Hormonal contraception included combined pills, progestin-only pills, and the progestin-releasing intrauterine system. The study population included all non-pregnant women with no previous cancer or cardiovascular disease. The endpoint was first-ever VTE event. This large study had 4,213 events observed for an overall 10.4 million women-years and 3.3 million women-years of oral contraceptive use. VTE risk in contraceptive users was double that of non-users (6 vs 3 per 10,000 women-years). The risk was higher in the first few years of use and with higher doses of estrogen. Combined pills containing the progestins desogestrel, gestodene, and cyproterone acetate had almost double the VTE risk compared to those containing levonorgestrel, norethisterone, and norgestimate. As most of the women in this study were users of low-dose combined pills, and women with a history of cancer or cardiovascular disease were excluded, the overall VTE risk estimates were lower than those found in some earlier studies. Although the European Active Surveillance (EURAS) study did not find a higher VTE risk with combined pills containing the progestin drosperinone, this larger study found a doubling of risk similar to that with third-generation pills.

H&O What do we know now of the pathophysiology of the mechanism by which female hormones may lead to a prothrombotic state? Is there a difference between estrogen-based therapy and progestin-based therapy?

HR Combined oral contraceptive pills have varying effects on hemostatic variables. As procoagulation and fibrinolysis are stimulated and anticoagulation is inhibited, it can be difficult to determine the net effect. Procoagulation may be clinically counterbalanced by an increase in fibrinolysis, but fibrinolysis probably plays a minor role in the etiology of thrombosis. However, even small functional differences in hemostatic variables, such as elevated levels of factor II, factor VIII, and fibrinogen, can be considered risk factors for venous thrombosis.

Overall, the use of the combined pill seems to influence all parts of the hemostatic system towards a prothrombotic state. Thrombosis has multiple determinants, and disease usually only develops with the presence of several interactions among these determinants. The real net effect can only be assessed by epidemiologic studies with clinical endpoints instead of the surrogate endpoints of plasma levels of hemostatic variables. New research looking at the interaction of hormones with the gene environment and inherited and acquired clotting tendencies may give further explanations regarding the cause of thrombosis.

Hemostatic changes from progestogen-only contraception, such as subcutaneous implants (eg, Implanon [Schering-Plough; 1 rod up to 3 years] or Jadelle [Schering Oy; 2 rods up to 5 years]), are minor, and few of the alterations are outside the normal range. In the WHO studies, VTE risk was not increased when progestins were used alone for contraception, compared with when they were used in higher doses for gynecologic disorders. The Lidegaard study also did not find an increased VTE risk with low- or high-dose progestin-only pills or the progestin-releasing intrauterine system.

H&O In your practice, what are the risk factors you look for before deciding whether or not to prescribe hormone contraception to a patient?

HR A full personal and family medical history is taken in order to assess risk factors for combined pill use, along with body mass index and blood pressure measurement. Combined hormonal contraception would normally not be prescribed for women over the age of 35 years who smoke. A personal history of venous thrombosis is considered an absolute contraindication to any combined hormonal use with a WHO medical eligibility criteria of 4 (unacceptable health risk). The existing evidence is indirect; VTE that occurred during the use of combined pills was less likely to recur when the contraceptives were stopped. Similarly, women with systemic lupus erythematosus with positive antiphospholipid antibodies have a higher VTE risk and are also designated WHO criteria 4. Both of these groups can use progestin-only methods, which are WHO 2 (advantages of using the method generally outweigh the theoretical or proven risks).

Inherited thrombophilias can increase the risk of VTE with combined hormonal use. The development of venous thrombosis during the first year of use can be an indication of an inherited clotting defect. The most common of these is the factor V Leiden, with a prevalence of 5% in Caucasians. The presence of factor V Leiden increases the risk of venous thrombosis by a factor of 4–10 in heterozygotes and by a factor of 50–100 in homozygotes. 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 35 in women who carry the mutation and also use oral contraceptives, with an even higher risk in homozygotes.

However, thrombophilia screening prior to commencing combined hormonal contraception is only undertaken in women with a family history of VTE. In our clinical situation, we would consider women with a first-degree relative with 1 event under the age of 45 years, or more than 1 event in second-degree relatives under the age of 45 years, to be at moderate risk, and undertake activated protein C resistance and prothrombin mutation. A woman with a first-degree relative with 2 or more events under 45 years old would be considered as high risk, and additional antithrombin III, protein C, and protein S measurements would be ordered. Known thrombogenic mutations are designated WHO 4 for combined hormone use but WHO 2 for progestin use.

H&O Are there new agents being investigated that may resolve this issue of increased VTE risk, if in fact there is increased risk?

HR It is likely that variation in the genetic susceptibility of the individual woman holds the key to the understanding of increased thrombotic risk with combined hormonal use. As well as the combined pill, other delivery systems, such as the combined transdermal patch and vaginal ring, are now available. However, these are at present considered to carry a similar potential for VTE risk as the pill. Indeed, the contraceptive patch, which was designed to deliver a relatively low dose of ethinyl estradiol (20 µg daily), was unexpectedly found to produce 60% higher concentrations in the serum than an oral 30 µg pill. Also, 2 of the 3 postmarketing studies comparing the patch with a 30 µg or 35 µg oral contraceptive showed a doubling of VTE risk with transdermal delivery. Newer pills, with estradiol instead of ethinyl estradiol, are now becoming available on the market. Ongoing follow-up will determine if this leads to reduction in VTE risk.

Suggested Reading

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