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How does VTE risk for the patch and vaginal ring compare with oral contraceptives?

Evidence-based answer

Evidence is conflicting with regard to the comparative frequency of venous thrombolic events (VTE) among women using the transdermal patch when compared to an oral contraceptive (OC), even though the patch produces a relatively high serum ethinyl estradiol (EE) level (strength of recommendation [SOR]: **C**, conflicting cohort case-control studies).

The vaginal ring has a risk of VTE comparable to that of an OC (SOR: **B**, 1 comparative study).

Clinical commentary

For now, base decisions on patient preference

This review points out that we don't have enough evidence to make a strong recommendation about oral or nonoral estrogen-containing contraceptives based on the risk of thromboembolic disease. All estrogen-containing contraceptives have similar side-effect profiles, regardless of the route of administration.

In my experience, the patch or ring appeals to women who have had difficulty with OCs and need a simpler dosing regimen to improve compliance. The choice between an oral estrogen-containing contraceptive and the patch or ring should be based on the patient's preference, not the risk of thromboembolic disease, until we have evidence to suggest otherwise.

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FAST TRACK

All estrogen-containing contraceptives have similar side-effect profiles, regardless of the route of administration

Evidence summary

Two nonoral estrogen-progestin contraceptives have been approved by the US Food and Drug Administration (FDA). OrthoEvra is a transdermal patch applied weekly for 3 consecutive weeks, followed by 1 patch-free week per cycle.[1] The NuvaRing is a vaginal ring worn for 3 consecutive weeks in a 4-week cycle.[2]

The patch causes greater estrogen exposure than OCs or the ring

In November 2005, the FDA issued an update to the labeling of the Ortho-Evra contraceptive patch, reporting increased systemic estrogen exposure, which may increase the risk of blood clots.[3] The FDA warned that the transdermal patch exposes the user to 60% more estrogen than the typical birth control pill containing 35 µg EE.[3] In January 2008, the FDA approved an additional update to include the results of a new study that found users of the patch to be at higher risk of developing VTE than OC users.[3,4]

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One pharmacokinetic study found that exposure to EE differed among delivery systems. The area under the EE concentration-vs-time curve in the patch group was 1.6 times higher than in the OC group ($P<.05$) and 3.4 times higher than in the vaginal ring group ($P<.05$).[2]

So what's the VTE risk? Two studies, contrasting conclusions

A nested case-control study—based on a PharMetrics longitudinal database of information from paid claims by managed care health plans—included 215,769 women between the ages of 15 and 44 years who had started using the patch or a norgestimate-EE combination OC since April 1, 2002, when OrthoEvra was first introduced on the US market.[5] Investigators identified 68 diagnosed cases of VTE with no identifiable risk factors.

The overall incidence of VTE in this study was 52.8 per 100,000 women-years (95% confidence interval [CI], 35.8-74.9) among patch users and 41.8 per 100,000 women-years among OC users (95% CI, 29.4-57.6).[5] The study concluded that the risk of nonfatal VTE for the patch isn't higher than the risk for an OC containing 35 µg EE and norgestimate (odds ratio [OR]=0.9; 95% CI, 0.5-1.6; incidence rate ratio [IRR]=1.1; 95% CI, 0.7-1.8).

A recent update to the study evaluated an additional 17 months of data on new cases of women meeting the same criteria. The supplementary results proved consistent with earlier conclusions, indicating that the risk of nonfatal VTE for the patch is similar to the risk for the OC (OR=1.1; 95% CI, 0.6-2.1).[6] Combined data from the original study and the update show that the OR for VTE is 1.0 (95% CI, 0.7-1.5) in users of the patch compared with users of the OC. [6]

Another nested case-control study—based on UnitedHealthcare insurance claims data and confirmatory chart reviews—showed contrasting results. The study included 340,377 women between the ages of 15 and 44 years who were new users of the patch or new and previous users of a norgestimate-EE combination OC from April 1, 2002 through December 31, 2004.[3] Investigators verified 57 diagnoses of VTE, controlling for confound-

ing factors. The incidence of VTE in this study was 40.8 per 100,000 women-years among patch users and 18.3 per 100,000 women-years among users of the norgestimate-35 µg EE OC. The study reported a more than 2-fold increased risk of VTE in patch users compared to OC users (OR=2.4; 95% CI, 1.1-5.5; IRR=2.2; 95% CI, 1.3-3.8).[3,7]

Do the differences between studies make a difference?

The 2 studies appear similar in design but have 2 major identifiable differences:

- The first study verified VTE diagnoses by claims for systemic anticoagulants, whereas the second study expanded its analysis by performing confirmatory chart reviews for VTE diagnoses.
- The first study included only new OC and patch users as of April 1, 2002, whereas the second study included new and experienced users of the OC as of April 1, 2002.

The significance of the differences in these studies is debatable; the results have yielded controversial, conflicting evidence.

Safety and tolerability are similar for the vaginal ring and OCs

A 1-year, open-label, randomized Phase III study of 1030 women compared the NuvaRing with a combination OC containing levonorgestrel and 30 µg EE. One case of deep venous thrombosis occurred in the NuvaRing group.

In reviewing the data, the authors concluded that the NuvaRing demonstrated comparable safety and tolerability to the OC.[8] NuvaRing users experienced similar side effects compared with OC users.[9]

Recommendations

The World Health Organization Medical Eligibility Criteria for Contraceptive Use (WHOMEC) reports that long-term safety data for the estrogen-progestin contraceptive patch are not available.[10] However, the limited studies that are available suggest a safety profile similar to that of combination OCs with comparable hormone formulations.

WHOMEC suggests that the guidelines for combination OCs also should apply to the patch and the ring. Women shouldn't use these contraceptive methods if they have a history of VTE or current VTE or if they are undergoing major surgery that may include prolonged immobilization.[10] ■

FAST TRACK

The patient's preference should determine the choice between an estrogen-containing OC and the patch or ring

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