



**BRIEF ANSWERS  
TO SPECIFIC  
CLINICAL  
QUESTIONS**

## **Q:** How should we advise patients about the contraceptive patch, given the FDA warning?

### **HOLLY L. THACKER, MD**

Director, Women's Health Center at The Gault Women's Health and Breast Pavilion, Department of General Internal Medicine, Department of Obstetrics and Gynecology, The Cleveland Clinic Foundation; Associate Professor of Medicine, Cleveland Clinic Lerner College of Medicine of Case-Western Reserve University

### **TOMMASO FALCONE, MD**

Chairman, Department of Obstetrics and Gynecology, The Cleveland Clinic Foundation; Professor of Medicine, Cleveland Clinic Lerner College of Medicine of Case-Western Reserve University

### **ASHISH ATREJA, MD, MPH**

Associate Program Director, Medical Informatics Fellowship, Department of General Internal Medicine, The Cleveland Clinic Foundation

### **ANIL JAIN, MD**

Department of General Internal Medicine, The Cleveland Clinic Foundation

### **C. MARTIN HARRIS, MD, MBA**

Chief Information Officer, Chairman, Information Technology Division, Department of Internal Medicine, The Cleveland Clinic Foundation

**A:** On November 10, 2005, the US Food and Drug Administration (FDA) approved an update to the labeling of the Ortho Evra contraceptive patch, warning providers and patients that it exposes women to higher levels of estrogen than most birth control pills.<sup>1</sup> In theory, this pharmacokinetic observation could translate into a greater risk of venous thromboembolism (more about this below).

The FDA's announcement puts physicians and other health care providers in a dilemma as to what to tell their patients who use the patch. On one hand, the patch is popular, convenient, and effective. It has not been withdrawn. Further, no one knows whether the risk with the patch is truly greater than with oral contraceptives. On the other hand, all hormonal contraceptives pose some risk of venous thromboembolism (although the risk is considerably higher in pregnancy), and some women should not use any type of hormonal contraceptive.

Most of all, we want to urge patients not to simply go off their contraception and face the risk of unplanned pregnancy. Rather, if they are concerned, they should discuss their contraceptive options with their health care providers.

### ■ **CONVENIENT AND EFFECTIVE**

Ortho Evra is a prescription patch that releases ethinyl estradiol (the most commonly used estrogenic hormone in hormonal contraceptives) at a rate of 20 µg/day, and norelgestromin (a third-generation progestin) at a rate of 0.15 mg/day. These are absorbed through the skin directly into the bloodstream.

Applied once a week, the patch is a good option for patients who might have trouble remembering to take a daily pill. Many studies have shown that compliance with the weekly contraceptive patch is significantly better than with an oral contraceptive.<sup>2,3</sup> Studies have also shown that many patients prefer the patch and are satisfied with it, and that use of the patch could be cost-effective, with a net savings of \$249 per woman over 2 years compared with oral contraceptives, and preventing three more pregnancies per 100 users over the same period.<sup>4,5</sup>

### ■ **MORE ESTROGEN EXPOSURE**

The new labeling is a result of an analysis done by the FDA and the manufacturer that directly compared the blood levels of estrogen and progestin in users of Ortho Evra vs a typical 30-µg ethinyl estradiol birth control pill.

With the pill, the hormone levels reach a peak after the patient takes the pill, and then decline. With the patch, the blood levels

**Any higher risk with the patch vs the pill has not been directly demonstrated**

remain fairly steady at a level about 25% lower than the peak levels with the pill. However, if we look at the area under the curve, ie, the hormone level averaged out over 24 hours, women who use Ortho Evra are exposed to about 60% more estrogen in their blood than if they were taking the pill.

NuvaRing, another hormonal contraceptive option, delivers ethinyl estradiol 15 µg/day and etonogestrel 0.120 mg/day in a vaginal ring that is changed once a month. van den Heuvel et al<sup>6</sup> found that the area under the curve was 3.4 times lower with the ring than with the patch, and 2.1 times lower than with the pill.

### ■ IS THE RISK HIGHER WITH THE PATCH THAN WITH THE PILL?

Oral contraceptive therapy is associated with a risk of venous thromboembolism about four times higher than in age-matched nonusers.<sup>7</sup> Since the increased risk of venous thromboembolism has primarily been attributed to the estrogen dose, it is possible that the transdermal patch may result in more vascular events than the oral contraceptives, based on continuous steady-state estrogen levels.

Although cases of stroke and death in young, otherwise healthy women who used the patch have been reported, they have also been reported with oral hormonal contraception. No trials to date have specifically looked into whether Ortho Evra carries an increased risk of thromboembolism (or other vascular events) compared with widely used second-generation or third-generation oral contraceptives.

Further, the progestin component of hormonal contraceptives may also affect risk. It is possible that norelgestromin, the progestin in Ortho Evra (as well as the third-generation progestins contained in the contraceptives Desogen, Ortho Tri-Cyclen, Ortho-Cept, and NuvaRing), may pose a higher risk of thromboembolism than the progestins contained in second-generation pills. Many studies have suggested that the third-generation progestin birth control pills are associated with a two times higher risk of deep venous thrombosis compared with second-generation oral contraceptives.<sup>8,9</sup> Because of this, some experts have suggested that women who have never used

hormonal contraceptives and women with other risks for venous thromboembolism should generally initially avoid all third-generation progestins. We would extend that to include the Ortho Evra patch in its current formulation pending additional study, provided that another contraceptive option is acceptable to the woman.

The risks of thromboembolism with any hormonal contraceptive agent (including Ortho Evra) have to be balanced with the known, very real risks of pregnancy. Thromboembolic disease is the leading cause of nonobstetric postpartum maternal death. The risk of deep venous thrombosis is approximately five times higher than in nonpregnant women, with the risk being highest in the immediate postpartum state and the risk of deep venous thrombosis and pulmonary embolism highest in women who underwent cesarean section. This contrasts with a two to four times higher risk of deep venous thrombosis in hormonal contraceptive users.

### ■ SOME WOMEN SHOULD NOT USE ANY HORMONAL CONTRACEPTIVE

Whether to prescribe any exogenous hormonal contraception depends on the net benefit for the woman after risk factors are taken into account.<sup>10</sup> Risk factors include:

- A family history or especially a personal history of venous thromboembolism
- Known factor V Leiden mutation
- Any other environmental factors such as smoking, immobility, or advanced age.

Any smoker older than 35 years should be strongly discouraged from using any form of estrogenic hormonal contraception, as should women who have already had a thromboembolic event. These may be candidates for progestin-only methods of contraception, such as depot medroxyprogesterone acetate (Depo-Provera) or the levonorgestrel intrauterine system.

### ■ PATIENTS SHOULD NOT STOP THEIR CONTRACEPTION

Ortho Evra has not been withdrawn from the market, nor have any systematic attempts been made by professional medical societies to

**Women older than 35 who smoke should not use the patch or the pill**



warn patients and providers of the possible risk from continued use of Ortho Evra. However, we were concerned that women, upon hearing media reports, may just stop using Ortho Evra without considering alternative contraceptive methods.

Hence, we decided to take proactive steps to inform our patients who are using the patch of this development and help them make an informed decision regarding continuing Ortho Evra vs switching to alternative contraceptive medications or methods. We used our hospital's computer system<sup>11</sup> to identify all 2,468 Cleveland Clinic patients who have a prescription for Ortho Evra. We sent each a letter outlining the specifics of the FDA announcement and recommending that she call her prescribing physician to discuss the issue.

We also sent an e-mail message to the 489 physicians and nurse practitioners who wrote the prescriptions, along with a list of their patients who have been documented to be using Ortho Evra and a copy of the letter we mailed to the patients. Furthermore, whenever anyone at our hospital uses the computer system to write a new prescription for Ortho Evra, he or she also gets a "Clinical Alert," which we also posted on our institutional Intranet.

## REFERENCES

1. **FDA News.** FDA updates labeling for Ortho Evra contraceptive patch. [www.fda.gov/bbs/topics/news/2005/NEW01262.html](http://www.fda.gov/bbs/topics/news/2005/NEW01262.html). Accessed December 6, 2005.
2. **Archer DF, Cullins V, Creasy GW, et al.** The impact of improved compliance with a weekly contraceptive transdermal system (Ortho Evra) on contraceptive efficacy. *Contraception* 2004; 69:189–195.
3. **Audet MC, Moreau M, Koltun WD, et al.** Evaluation of contraceptive efficacy and cycle control of a transdermal contraceptive patch vs an oral contraceptive: a randomized controlled trial. *JAMA* 2001; 285:2347–2354.
4. **Weisberg F, Bouchard C, Moreau M, et al.** Preference for and satisfaction of Canadian women with the transdermal contraceptive patch versus previous contraceptive method: an open-label, multicentre study. *J Obstet Gynaecol Can* 2005; 27:350–359.
5. **Sonnenberg FA, Burkman RT, Speroff L, et al.** Cost-effectiveness and contraceptive effectiveness of the transdermal contraceptive patch. *Am J Obstet Gynecol* 2005; 192:1–9.
6. **van den Heuvel MW, van Bragt AJ, Alnabawy AK, Kaptein MC.** Comparison of ethinyl estradiol pharmacokinetics in three hormonal contraceptive formulations: the vaginal ring, the transdermal patch and an oral contraceptive. *Contraception* 2005; 72:168–174.
7. **Girolami A, Spiezia L, Rossi F, et al.** Oral contraceptives and venous thromboembolism: which are the safest preparations available? *Clin Appl Thromb Hemost* 2002; 8:157–162.
8. **Jick H, Kaye JA, Vasilakis-Scaramozza C, et al.** Risk of venous thromboembolism among users of third generation oral contraceptives compared with users of oral contraceptives with levonorgestrel before and after 1995: cohort and case-control analysis. *Br Med J* 2000; 321:1190–1195.
9. **Weiss G.** Risk of venous thromboembolism with third-generation oral contraceptives: a review. *Am J Obstet Gynecol* 1999; 180:295–301.
10. **Budev M, Thacker, HL.** Hormone replacement therapy. [www.clevelandclinicmeded.com/diseasemanagement/women/exogenous/exogenous1.htm](http://www.clevelandclinicmeded.com/diseasemanagement/women/exogenous/exogenous1.htm). Accessed December 6, 2005.
11. **Jain A, Atreja A, Harris CM, et al.** Responding to the rofecoxib withdrawal crisis: a new model for notifying patients at risk and their health care providers. *Ann Intern Med* 2005; 142:182–186.

**ADDRESS:** Holly L. Thacker, MD, Gault Women's Health and Breast Pavilion, A10, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail [thackeh@ccf.org](mailto:thackeh@ccf.org).