

## **Rethinking Hormone Therapy -- Again --- Despite Concerns, The Range of Options For Women Is Growing**

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### **WHAT NOW?**

The decision by the National Institutes of Health to halt a clinical trial of estrogen therapy a year early will likely lead to even more confusion among female patients and their doctors. Women struggling with troublesome symptoms of menopause have been in a quandary over whether to take hormones since the summer of 2002, when researchers linked a widely used form of hormone-replacement therapy, Wyeth's Prempro, to increased risk of heart disease, breast cancer and stroke. While the research findings announced yesterday indicated that estrogen alone has fewer dangerous side effects than the more-common regimen of estrogen combined with progestin, researchers still reiterated frustratingly vague advice. In effect, they told women it is up to them and their doctors to sift through the science.

The federal Food and Drug Administration "advises women to use hormone therapy at the lowest dose and for the shortest period of time," said Barbara Alving, director of the massive hormone-replacement study, known as the Women's Health Initiative. "Women can work with their doctors to determine how long they want to be on these medications and also what type of medication they want to be on."

But despite the overall concerns, there are an increasing number of treatment options for menopausal women, some of which may have fewer side effects than Prempro or Wyeth's Premarin, the popular therapies in the widely-publicized studies. The new landscape is turning hormone therapy from an easy off-the-rack prescription into more of a couture therapy, customized by each doctor to minimize side effects and maximize benefit for an individual patient.

The new forms of HRT include lower-dose estrogens and progestins and estradiol, a synthetic hormone. Wyeth introduced a version of Prempro last month that has 52% less estrogen and 40% less progestin than its earlier version. Berlex Laboratories, the U.S. unit of Schering AG, also launched a low-dose product last month.

New patches, creams and vaginal rings have also been unveiled, which supporters say deliver their drugs more efficiently and possibly with fewer side effects. In August, Novartis Pharmaceuticals Inc. and its partner Noven Pharmaceuticals Inc. launched Vivelle-Dot, a low-dose patch that contains a different version of estrogen, called estradiol. In June, Femring, a vaginal ring made by Galen Holdings PLC was launched in the U.S.

Further down the road are so-called designer estrogens, which scientists are just beginning to research. Called selective estrogen receptor modulators, or Serms, these are medicines that would turn on the desirable receptors that estrogen affects in a woman's body, while at the same time turning off the undesirable ones such as those that increase risk of cancer.

Katherine Munn, a 44-year-old in Massachusetts, is one patient who has spent time hormone shopping. Ms. Munn was pushed into menopause by chemotherapy in her mid-30s. She took a number of different hormones over the years to calm mood swings, but was dissatisfied. Finally,

she went to an alternative doctor who customized a cocktail of hormones and mixed it into a cream for her. "My doctor tested my blood and we spent a year fine-tuning" the hormone mix, Ms. Munn says. Ms. Munn is one of a small number of women turning to compounding pharmacies. These pharmacies blend together different hormones, including estrogens, testosterone and progestins among others, into customized creams.

Many women abandoned hormone therapy altogether after the initial study results. Some were scared off after the FDA and the American College of Obstetricians and Gynecologists said taking hormones for prevention of age-related ailments like heart disease and osteoporosis, a practice once standard, is too risky. Now the organizations advise that only women with temporary symptoms of menopause should turn to hormones -- and always at the lowest dose, for the shortest time possible.

As a result of the warnings, sales of the two hormone therapies in the study, both made by Wyeth, have fallen markedly. Sales of Prempro, an estrogen and progestin combination, fell to \$20.4 million in December 2003 from \$60.7 million in July 2002. Sales of Premarin, which contains only estrogen, fell to \$82.1 million in December from \$116.2 million in July 2002.

But a growing number of women who went off hormones have come back to them. A survey of 670 women in the Kaiser Permanente Health Plan showed that about half stopped or tried to stop taking hormones after the study results came out. A quarter of those who stopped ended up going back when their symptoms returned. The study was funded by Eli Lilly & Co., which markets Evista, an osteoporosis drug whose sales have been affected by the hormone debate.

Here is a rundown on some alternatives to Prempro and Premarin:  
Low-dose estrogens and progestins: The theory is that lowering the dose of hormones will reduce the risks. For example, less estrogen may reduce the risk of blood clots and deep vein thrombosis. "We don't have good data on it, but everyone believes that less hormone would mean a better risk/benefit ratio," said James A Simon, president of the North American Menopause Society.

Estradiol: One product that is gaining new interest is estradiol, a synthetically produced copy of the estrogen that women's ovaries make before menopause. While Prempro and Premarin are made from horse urine, estradiol more closely resembles the estrogen that a woman's body naturally makes. Estradiol products came on the U.S. market in the mid-1970s, but haven't been as widely used here as in Europe. They come in oral form, such as the brand Estrace, and patches, such as Estraderm.

While demand for many other HRT products has fallen, sales of estradiol products have held up, though they still account for a small portion of the market, according to prescription data from NDC Health. Sales of all estradiol products rose \$3.3 million to \$27.5 million in December 2003 from July 2002.

For Becky Simpson, a 52-year-old who runs a public-relations firm in Louisville, Ky., an estradiol patch was the answer for the insomnia, hot flashes and depression that she endured for three years. "For a year, I slept only two hours a night," said Ms. Simpson, who is a long-distance runner. The day after she began using an estradiol patch, she slept for eight hours and says she's felt great since.

Patches, creams and rings: Some doctors think that delivering hormones through the skin may have fewer side effects. While oral hormones have to be processed by the liver first, patches and creams go directly to the blood stream. Some doctors feel that so-called transdermal products may pose a lower risk of blood clots, deep vein thrombosis and even cardiovascular events.

Still, federal researchers debate that view. In January 2003, the FDA decided that all kinds of hormone replacement products should carry warning labels describing the increased risk of

cancer and heart disease seen in the WHI study. All hormones would be assumed to have the same risks unless proved otherwise, the agency said.

Other alternatives: Women and their doctors have also been experimenting with alternative products, such as soy supplements and the herb black cohosh, that may help with hot flashes.

Others are deciding to tackle individual symptoms with therapies besides hormones, such as antidepressants for mood and sleep issues and other drugs specifically targeted to fight osteoporosis.

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### **Choosing a Treatment**

Some hormone-therapy options.

-- Patches: Skin patches tend to have fewer side effects than pills, and may provide more even hormone levels

-- Vaginal rings: Like patches, rings aren't known to increase blood-clot risk because the estrogen isn't processed by the liver

-- Vaginal Creams: Again, fewer side effects than oral varieties; some brands may cause vaginal irritation

-- Oral: Women in one new study who were taking estrogen orally showed a slightly increased risk of stroke and blood clots

Source: WSJ Research

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### **Options for Women**

A look at the pros and cons of some current hormone-replacement treatments.

#### **Patches**

BRAND/COMPANY: Vivelle-Dot/Novogyne

DESCRIPTION: A skin patch that releases estradiol. Used to treat vaginal atrophy and prevent osteoporosis. Comes in several strengths. Patch should be changed twice weekly.

COMMENT: Patches may have fewer side effects than pills because the estrogen is not processed through the liver. They may also provide more even hormone levels than pills. Like any estrogen, possible side effects include breast tenderness, fluid retention and back pain.

BRAND/COMPANY: Climara/Berlex

DESCRIPTION: Estradiol patch used to treat hot flashes, vaginal dryness and to prevent osteoporosis. Available in various strengths. Patch changed once a week.

COMMENT: Benefits and risks are similar to Vivelle-Dot. Also comes in Climara Pro, which combines estradiol and progestin into a patch. Progestin can protect against the uterine cancer risk posed by taking estrogen on its own.

#### **Rings**

BRAND/COMPANY: Femring/Galen

DESCRIPTION: A flexible vaginal ring that releases estradiol. Used for hot flashes, night sweats, and vaginal dryness. Does not need to be removed for intercourse.

COMMENT: Like patches and cream, rings are not known to pose a blood clot risk because the estrogen doesn't go through the liver. Side effects may include vaginal discharge and breast tenderness.

BRAND/COMPANY: Estring/Paladin

DESCRIPTION: A soft plastic ring used specifically to treat vaginal dryness and atrophy, and pain during intercourse.

COMMENT: Unlike Femring, the drug is not absorbed into blood stream. The ring provides vaginal benefits without the systemic risks posed by taking estrogen throughout the body.

### **Gels/Creams**

BRAND/COMPANY: EstroGel/Solvay

DESCRIPTION: An estrogen gel applied to the arm used to treat hot flashes and vaginal dryness.

COMMENT: Will be available soon in the U.S.. The gel is not processed through the liver, which reduces blood clot risk. Like all estrogens, may cause breast tenderness and bloating.

BRAND/COMPANY: Premarin Vaginal Cream/Wyeth

DESCRIPTION: Used specifically to treat vaginal dryness associated with menopause.

COMMENT: May cause vaginal irritation or discharge.

BRAND/COMPANY: Personalized Hormone Creams/Compounding pharmacies

DESCRIPTION: Some doctors will order "hormone cocktails" that combine drugs like estrogen and progesterin into a cream form.

COMMENT: These products have not been tested for safety or efficacy.

### **Oral**

BRAND/COMPANY: Prempro/Wyeth

DESCRIPTION: A estrogen and progesterin combination product used to treat a wide range of menopausal symptoms and to prevent osteoporosis. The estrogen is derived from the urine of pregnant mares.

COMMENT: A major 2002 study linked it to increased risk of heart attacks and breast cancer in older women. But the progesterin in the product can protect against the increased risk of uterine cancer caused by taking estrogen alone.

BRAND/COMPANY: Premarin/Wyeth

DESCRIPTION: Same as Prempro, but without the progesterin. Taken mostly by women who have had hysterectomies for relief of menopausal symptoms.

COMMENT: This week, a major Premarin study was stopped early when it showed no heart benefit for women and a slight increase in risk of strokes.

BRAND/COMPANY: Cenestin/Duramed

DESCRIPTION: A plant-based estrogen product used to treat menopausal symptoms, vaginal dryness and to prevent osteoporosis.

COMMENT: Similar to the other oral estrogens, but it's plant-based. Some people feel more comfortable with products that are derived from plants, instead of animal urine.

BRAND/COMPANY: Prometrium/Solvay

DESCRIPTION: A natural progesterone that can be used in combination with estrogen treatments to protect against uterine cancer.

COMMENT: A natural, non-synthetic progesterone.

-- Jane Spencer