Transdermal Hormones Yield CV Benefits in Menopause

BY BRUCE JANCIN
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NEW ORLEANS — Compounded transdermal hormone therapy relieves menopausal symptoms while improving cardiovascular risk factors and inflammatory and thrombotic biomarkers, according to a preliminary study.

"By replacing the hormone that's deficient via transdermal dosing it may be possible to more closely mimic normal physiology and favorably impact cardiometabolic clinical biomarkers. Despite FDA concerns of dangers of compounded hormone use, our data suggest that transdermal compounded hormones may offer a safe and effective treatment for hormone-related symptoms when utilizing dosages targeting physiologic reference ranges and compounds, which meet USP standards for potency," Dr. Kenna Stephenson, a family physician active in clinical research in women's health at the University of Texas Health Science Center at Tyler, said at the annual scientific sessions of the American Heart Association.

Her study involves 150 women, mean age 51.9 years, with menopausal symptoms, who were randomized to usual care or individualized transdermal plant-derived estrogen, progesterone, testosterone, and dehydroandrostenidione therapy prepared by a compounding pharmacist.

After 12 months of follow-up, women on transdermal therapy showed significant reductions in triglycerides, blood pressure, fasting blood glucose, C-reactive protein, plasma fibrinogen, insulin-like growth factor–I, and factor VII along with significant symptomatic and quality of life improvements (see chart). The study will continue through 3 years of follow-up.

Ever since the Women's Health Initiative linked oral hormone replacement-therapy to increased risks of breast cancer and cardiovascular events, women with menopausal symptoms have expressed growing interest in alternative forms of hormonal therapy.

As in the ongoing study, Dr. Stephenson's clinical practice is to take a history of hormone-related symptoms such as hot flashes, night sweats, mood changes, sleep deprivation, and unexplained fatigue, measure the patient's sex hormone levels, and then prescribe a low-dose transdermal hormone compounded specifically for her. Transdermal therapy avoids first-pass hepatic metabolism, thereby preventing buildup of atherogenic sex hormone metabolites, said Dr. Stephenson.

"What I see in clinical practice and my research studies is their biomarkers improve. They have adequate symptom relief, which is what's most important to them. And once their symptoms are relieved they're more likely to make positive nutritional and lifestyle changes: They feel like exercising; they feel like eating the way they're supposed to," she said.

Dr. Stephenson uses the university medical center's compounding pharmacy. There are a growing number of such pharmacies as a result of increasing applications for compounded transdermal therapy in pain medicine, oncology, dermatology, and sports medicine, as well as hormone therapy. Physicians can locate a compounding pharmacist through the member registry maintained by the International Academy of Compounding Pharmacists (www.iacprx.org).

A home salivary specimen shipped to a CLIA-certified laboratory provides the most accurate way to assess a woman's hormone status. "The reference ranges in serum testing for sex hormones are too broad," Dr. Stephenson explained.

In January 2008, the Food and Drug Administration announced a new policy of restricted access to medications containing estriol that could have a negative impact on compounded transdermal hormone therapy for women, since prescribing physicians are required to fill out an Investigational New Drug application. Resolutions have been introduced in both the Senate (S.Con.Res. 88) and House of Representatives (H.Con. Res. 342) calling on the FDA to reverse this policy.

To watch a video interview with Dr. Stephenson, go to http://www.youtube.com/familypracticenews. ■

Changes in Women Placed on Transdermal Hormone Therapy

	Baseline	8 weeks	1 year
Blood pressure (mm Hg)	133/80	126/79	121/76
C-reactive protein (mg/mL)	6.2	5.8	3.9
Triglycerides (mg/dL)	175	154	120
Fasting blood glucose (mEq/L)	110	89	92
Fibrinogen (mg/mL)	4.6	4.4	4.0
Factor VII (mcg/mL)	1.1	1.1	0.9
Insulinlike growth factor-1 (ng/mL)	171	NA	151
Antithrombin (ng/mL)	341	341	329
Hamilton Depression score	6.6	4.9	5.0
Hamilton Anxiety score	9.6	7.0	6.5
Visual analog pain scale	1.5	1.2	0.9
Greene Climacteric Scale score	17.7	13.7	12.9

Note: Study comprised 150 women with menopausal symptoms.
Source: Dr. Stephenson

ELSEVIER GLOBAL MEDICAL NEWS

DRUGS, PREGNANCY, AND LACTATION

Drug Exposure and the Media

Over the past several decades, media coverage of medical journal studies has played a powerful role in perpetuating the bias against the use of certain medications during pregnancy.

As physicians, we read medical journals and other professional materials, but we also pay attention to the media. We may not necessarily have an opportunity to check the veracity and quality of a study we read or hear about, so the message we get may influence some of our perceptions and even our practices.

BY GIDEON KOREN, M.D.

The impact on the public is enormous. At Motherisk, we are often contacted by pregnant women who are afraid of taking a medication because they heard about a study indicating a drug was not safe during pregnancy. It's not unusual for such reports to lead a woman to seek termination of an otherwise wanted pregnancy.

The thalidomide disaster heightened the public's awareness and sensitivity to the concept that every drug is potentially a human teratogen. But the reality is that, almost 50 years later, very few drugs have been shown to be human teratogens. Still, physicians and women are hesitant about the use of medications during pregnancy, even when the drug is highly needed.

The notable examples in the medical literature date back to a study published in the early 1970s that reported an association between prenatal exposure to the hormones in oral contraceptives and congenital malformations (Lancet 1973;1:941-2). At that time, the study caused huge anxiety, resulting in oral contraceptives' being labeled as pregnancy category X. But in the 1990s, a large number of studies and two meta-analyses, including one we conducted at Motherisk, failed to show any increased risk of malformations associated with prenatal exposure to OCs, which, by far, are the most common prescription product inadvertently taken by women during pregnancy.

The anxiety created by the initial paper continued until a few years ago, when OCs were switched to category D. It is not possible to estimate how many women may have terminated their pregnancies because of such exposures, but this is clearly an example of how one study in a major journal led to an unwarranted degree of anxiety.

Another example is the story of spermicidal contraceptives. It made biologic sense that spermicide may not destroy all sperm and that a damaged sperm that fertilizes an egg could possibly cause congenital malformations. In the early 1980s, a study using an HMO database reported finding an association between spermicide prescriptions and malformations (JAMA 1981;245:1329-32). The number of children with malformations thought to have been exposed to spermicide, although significant, was small. The study used data from the HMO records of women who were prescribed a spermicide. But this information did not prove the women actually took it into pregnancy; some may have stopped using it before they got pregnant, or may have never taken it at all.

A large number of subsequent studies could not confirm this finding, but this was a positive study in a major journal that caused huge anxiety for many years. Letters to the editor included suggestions to track down the women and confirm whether they took the spermicide into pregnancy; a few years later, one of the original authors indeed interviewed those women and found no association. It turned out that most of the women did not take it into pregnancy. The original study provides a notable example of how anxiety triggered by a poorly conducted study can blow a potential risk out of proportion. (JAMA 1986;256:3095-6; JAMA 1987;258:2066).

Very often major journals that publish studies of positive associations do not publish subsequent studies involving negative findings. While some of these studies are eventually published in less-prominent journals, the biases are perpetuated nonetheless.

Physicians should keep in mind that for every positive study published, there also may be negative studies published that may go unnoticed. Moreover, research that we and others have conducted shows that negative studies are less likely to be published than positive studies. At Motherisk, when we evaluate the reproductive safety of a drug, our analysis always includes an attempt to determine whether negative studies exist, and how many unrecognized negative studies could have changed an apparent positive result.

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