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Weighing Risks and Benefits

By DENISE GRADY

The patient is 60, and she has been happily taking estrogen for 20 years, ever since her uterus and ovaries were removed. Now, she would like to stop. But when she tries, she is miserable. Hot flashes leave her drenched in sweat, sometimes as often as every half hour, and she seems to be getting more uncomfortable every day.

Much as she wants to get off the hormone, she tells her doctor, "Right now, I'm ready to just scream and say, 'Oh, please, just put me back on it.'"

Frequent hot flashes can be debilitating; if they play havoc with sleep, fatigue can then lead to depression and forgetfulness. There is no better treatment for hot flashes than estrogen, most doctors agree. Why, then, does this woman want to quit?

According to an article last week in *The Journal of the American Medical Association*, the patient, Mrs. W., is concerned about the possible risks of long-term hormone therapy. Her biggest fear is breast cancer, because her sister and grandmother have had the disease and she herself has had several breast cysts. Although there is no evidence of an increased breast cancer risk for women who use hormones for less than five years, studies suggest that taking them longer is associated with a 30 to 60 percent increase in risk.

For women like Mrs. W., who have had their uteruses removed, hormone replacement therapy consists of estrogen alone. But for other women, estrogen alone can cause uterine cancer, and so the estrogen is given along with another hormone, progesterin.

Breast cancer is not the only concern for women taking either type of hormone therapy. The article in the medical journal, by Dr. Deborah Grady, a professor of epidemiology and medicine at the University of California in San Francisco, describes several other side effects, including relatively minor ones like uterine bleeding and breast soreness, and more serious problems like a tripling of the risk of blood clots and a 40 percent increase in the risk of gallbladder disease, which affects 1 in 10 Americans; the risk increases with age, and in women is twice as great as in men.

Blood clots are far less common, though; over all, they occur in only 1 to 2 women in 10,000 who do not use hormone therapy, so a tripling of the risk does not result in a huge number. But the risks are higher in women who already have coronary artery disease. Estrogen increases the risk by stimulating the liver to produce more of the substances that it normally makes to promote clotting.

Estrogen's risks have long been recognized, but until recently many doctors and patients assumed the risks were outweighed by benefits, which were thought to include a decreased risk of heart attacks, strokes, broken bones, urinary incontinence, severe depression and Alzheimer's disease.

But rigorous studies in recent years have cast doubt on some of the benefits that many women and their doctors took for granted. Most of the data comes from studies involv-



Susan Spann for The New York Times

"Hormone treatment is reasonable therapy," says Dr. Deborah Grady of the University of California at San Francisco. "But you don't have to take it for the rest of your born days."

arin, the most widely used brand of hormone replacement in the United States. The hormone, conjugated equine estrogen, is extracted from the urine of pregnant horses.

An international panel of experts who evaluated hormone therapy released part of a position paper last month stating that clinical trials had found no evidence that estrogen could treat or prevent urinary incontinence, major depression or memory loss in Alzheimer's disease. It is still being studied in Alzheimer's, however, the paper noted. And the paper added that although estrogen clearly prevents bone loss, whether that translates into preventing fractures has not been studied in a large controlled trial. For treating osteoporosis and preventing fractures, there is stronger evidence for other drugs: raloxifene and a class of drugs called bisphosphonates, which includes Fosamax.

As for cardiovascular disease, three studies have suggested that rather than protecting women from heart attacks and strokes, hormone therapy may increase their risk in the first few years. Women with heart disease or risk factors for it, like high blood pressure or high cholesterol, are now advised not to depend on estrogen but to take drugs meant specifically to lower blood pressure and cholesterol.

But one of the studies that found signs of a heart risk, the Women's Health Initiative, a clinical trial involving more than 27,000 women, is still under way and is expected to provide more information about cardiovascular disease and hormones in 2006.

"We haven't had the last word on this," said Dr. Nanette Wenger, chief of cardiology at Grady Memorial Hospital in Atlanta and an editor of the International Position Paper on Women's Health and Menopause, to be issued in June by the National Institutes of

Drugs for Menopause

FOR TREATMENT OF HOT FLASHES

DRUG	REDUCTION IN HOT FLASHES
Estrogen	80-100%
Megestrol	80
Venlafaxine or paroxetine	60
Clonidine	40

FOR PREVENTION OF BROKEN BONES

DRUG	REDUCED RISK OF FRACTURES FROM OSTEOPOROSIS
Estrogen	27%
Alendronate	40-50
Risedronate	40-50
Raloxifene	SPINAL: 40 OTHERS: None

Sources: Dr. Deborah Grady; *Journal of the American Medical Association*

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Medical Science Foundation of Italy.

But women want advice now. Many doctors say that given hormone therapy's known risks and the dearth of evidence for life-saving benefits, they can recommend it only to women who have severe symptoms like hot flashes and vaginal dryness, or low bone density — and who do not have known risk factors like a history of heart disease, strokes or blood clots. And then, doctors say, the best course may be to use the hormones for a few years at the height of their symp-