

Q&A

Hormone Replacement Therapy

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As women of the baby boom generation are all too aware these days, bodies start to change after 50. After a long career of producing eggs and estrogen, the ovaries take an early retirement, and the body goes through the hormone withdrawal process—hot flashes and all—known as menopause.

To many women, living with little estrogen is an unappealing prospect, so every year doctors write about 60 million prescriptions for the hormone. Although no other drug is more widely prescribed in the U.S., scientists still debate the risks and merits of hormone replacement therapy. That debate is taken up here as **REBECCA ZACKS**, special correspondent for *SCIENTIFIC AMERICAN*, talks with two experts in women's health: **ROGERIO A. LOBO, M.D.**, and **GRAHAM A. COLDITZ, M.D.** Lobo is the chief of obstetrics and gynecology at Columbia-Presbyterian Medical Center and a self-proclaimed advocate of estrogen, which he recommends regularly in his capacity as head of the hospital's Menopause Treatment Center. Colditz, an epidemiologist at Harvard Medical School, is an outspoken critic of estrogen therapy. He has investigated its effects while working as a lead researcher on the Nurses' Health Study, which has been following more than 120,000 American women since 1976. Although Lobo and Colditz agree on many of the basics about estrogen, when it comes to the connection between estrogen therapy and cancer, they just don't see eye to eye.

Q What are the hormones in "hormone replacement therapy"?

A **LOBO:** Estrogen is the mainstay. There are many dosages and different forms, from synthetic to natural, given as oral formulations or through skin patches. It can also be administered vaginally.

COLDITZ: More recently, there's been growing use of progestin along with the estrogen, particularly among women who still have their uterus, to counter the risk of getting uterine cancer. Taken alone, estrogen increases a woman's risk of uterine cancer fourfold to sixfold. And, like estrogen, there are a number of different formulations of progestin on the market.

Why do some women decide to try hormone replacement therapy as they enter menopause?

COLDITZ: Traditionally, the major reason for use has been relief of menopausal symptoms—preventing hot flashes and other problems. More recently, there's been a push to consider the decrease in bone density associated with menopause as an indication for starting estrogen at the time of menopause to prevent loss of calcium and ultimately to prevent osteoporosis. Also very recent is the notion of using hormones for preventing heart disease. And so some women may be advised to take hormones for the preventive benefit, not just for the relief of menopausal symptoms.

Why do other women choose not to use hormones during menopause?

COLDITZ: There's a huge spectrum of reasons. There's one extreme of a woman who doesn't want to take any unnecessary hormones or drugs or to put anything in her body that she doesn't need to. There's the attitude "If I'm not having symptoms, why should I take a drug?" And some women really don't tolerate estrogen plus progestin. They get premenstrual symptoms, and when you've not had them for 10 years, you don't sign up to take a pill to induce symptoms on a monthly basis.

If a woman goes through menopause without using hormones, why might she still choose to begin replacement therapy later in life?

LOBO: If we take an extreme—a woman with a strong family history of both osteoporosis and cardiovascular disease and, for the sake of argument, no history or risk factors for breast cancer—then I think she is a very good candidate for estrogen in her later years.

COLDITZ: Again, there's been a shift in philosophy as we've moved from use of hormones primarily for relief of menopausal symptoms, such as hot flashes and vaginal dryness, to use of hormones long term for prevention.

What concerns women most about taking hormones?

LOBO: The overriding risk that concerns women is that of breast cancer. The perception is that most women die of breast cancer and that only a few die of cardiovascular disease. But the lifelong mortality related to breast cancer is about 3 percent, and for cardiovascular disease it's in the range of about 30 percent. It's actually the reverse of what women perceive.

COLDITZ: My sense is that women are most concerned about the risk of cancer. Even though the evidence that estrogen causes breast cancer—evidence that is now quite powerfully conclusive—has not yet fully reached women and the clinicians prescribing the hormone, it is clear that women are particularly concerned about breast cancer.

The Benefits of Hormones

You mentioned that estrogen helps to prevent osteoporosis in postmenopausal women. How does it do so?

COLDITZ: In a simple sense, estrogen works to prevent osteoporosis by stimulating cells in the bone to maintain their function to retain calcium and to maintain the actual structure of the bones, keeping them strong and thereby reducing the risk of breaking bones.

So how much protection does estrogen provide for a woman's bones?

LOBO: If you're talking about hip fractures, it's probably in the range of about a 50 percent reduction of fracture risk—I mean that's the bottom line.

Let's turn to estrogen and cardiovascular disease. How does estrogen replacement therapy reduce a woman's risk of heart disease and heart attack?

COLDITZ: Estrogen influences cholesterol metabolism and leads to a higher HDL—the good cholesterol—and a lower LDL cholesterol, the bad cholesterol. Estrogen also causes the muscles in the artery walls to relax a little bit so blood flows better.

People have studied blood flow to the brain in women exercising on treadmills, comparing women when they're taking estrogen to when they're not. And when they're taking estrogen, they can exercise longer and have better blood flow. People have also been looking at the antioxidant effects of estrogen. So those mechanisms together account for most of the protection that's seen, though probably not all of it.

How much does estrogen replacement therapy reduce a woman's risk of heart attack?

COLDITZ: We see about a 50 percent reduction among high-risk women who are currently taking hormones compared with women who have never taken them. The effect is stronger among current users than among women who have stopped using hormones. So I'd say a woman's risk of heart attack is cut in half if she's currently taking estrogen and is cut by 25 percent after she stops.

Does adding progestin to hormone therapy alter any of the cardiovascular benefits?

LOBO: This is the difference between epidemiological observational studies and clinical trials. In the former, researchers study a population of women who have decided on their own whether to take hormones and what kinds to take. In the latter, researchers randomly assign volunteer participants to a course of treatment. Most clinical trials will show what I call some attenuation, some reduction of the benefits when progestin is combined with estrogen, depending on the route of the administration, the type of progestin and the specific regimen. But observational studies have suggested that there's no reduction in benefit.

Do women need to start taking hormone replacement therapy by a certain age to enjoy the benefits of estrogen for their hearts and bones?

LOBO: There are going to be benefits whenever you start. But the benefits are going to be less, obviously, if you start later. For bone loss, it's been shown that whenever you start estrogen therapy, you can stop bone loss. The effects on cardiovascular health and cognition have also been shown to be beneficial when estrogen is taken starting at a later age. There really haven't been studies of 80-year-old women. But certainly women through their 60s and 70s benefit from starting estrogen.

COLDITZ: This is a really central question that still hasn't been answered. If you start at age 65 rather than at age 50, is the benefit still there? Because, after all, the risk of heart attack and hip fracture between ages 50 and 60 is in fact still pretty small. Because few women have started taking hormones at older ages, there's not a lot of experience yet. But the heart benefits are thought to be there for women who start hormones at older ages, and bone benefits are probably going to be there as well. They may not be as pronounced as they would be for someone who began taking hormones earlier in life, but there should still be benefits. And the upside of starting later is that there is presumed to be less cancer risk if you haven't been using the hormones for 10 or 15 years from menopause to age 60 or 65.

Once a woman has started treatment, must she continue to take hormones indefinitely?

LOBO: Yes, that's the problem. Most data would suggest that as soon as you stop taking hormones you lose the benefit. So I think that long-term therapy really is better. But of course the

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Guide to Estrogen and Progestin Use

If you are considering hormone replacement therapy and you have had a hysterectomy, you should take estrogen alone. You and your doctor can choose from the following options:



Pills

Estrace (estradiol)
Estratab (sterified estrogen)
Menest (esterified estrogen)
Ogen (estropipate)
Ortho-EST (estropipate)
Premarin (conjugated equine estrogen)

Patches

Alora (estradiol)
Climara (estradiol)
Estraderm (estradiol)
Fempatch (estradiol)
Vivelle (estradiol)

Vaginal Ring

Estring (estradiol)



If you have not had a hysterectomy, you should take progestin with your estrogen. Ask your doctor about the following choices:

Pills

Aygestin (norethindrone acetate)
Cycrin (medroxyprogesterone acetate, or MPA)
Prometrium (micronized progesterone)
Provera (MPA)



Vaginal Gel

Crinone (micronized progesterone)

If you have not had a hysterectomy, you can also ask your doctor about taking a combination of progestin and estrogen:

Pills

Premphase (conjugated estrogens and MPA)
Prempro (conjugated estrogens and MPA)



If your primary concern is osteoporosis, you can consider a selective estrogen receptor modulator (SERM):

Pill

Evista (raloxifene)

risks are related to the duration of use. So that's the dilemma. **COLDITZ:** Historically, most women took their hormones for relief of symptoms during menopause and then stopped. The still unanswered question is: Can you take hormones short term for relief of symptoms at menopause, stop and then maybe 15 years later start again to get the preventive benefits when the risks of heart disease and bone fractures are big enough to justify the potential increased breast cancer risk?

Estrogen and Breast Cancer

There is so much controversy surrounding the impact of estrogen on a woman's risk of breast cancer. How has this been studied, and why do the data often seem to conflict?

LOBO: Well, it's been studied for 20-plus years, and it's been studied primarily in epidemiological trials. And there's no clear-cut association—at least in my view. That's largely because if there is a risk, the risk is relatively small. The fact that we really haven't completely figured this out in over 20 years of research shows that if there is an association, it is so small that it's very hard to prove statistically, unless you have a large number of women. And once you start looking at large numbers of women, then you have so many confounding variables: biases inherent about why these women are taking hormones to begin with, what the characteristics of the group are and so forth.

COLDITZ: Probably most of the literature on this question to date has had troubles with the precision of the analysis. At any given age, the earlier a woman went through menopause, the longer she is likely to have been using hormones. Which then comes back to a basic factor that has in large part been ignored. Since the 1950s we've known that a woman's age at menopause is a strong predictor of her risk of breast cancer: that the earlier a woman went through menopause, the lower her lifetime risk of breast cancer. So we have to control statistically for age at menopause when we start looking at use of hormones. And if we don't control tightly, then we start to mix up the effect of age of menopause and the effect of hormones. Some of the controversy really came from different studies using different techniques of analysis—some of which may control for age at menopause more tightly than others—and so they get different results.

In part, this controversy is fed by the groups who are pro-estrogen picking out studies that didn't find any adverse effect and ignoring the total body of evidence. And then I suppose it's fed by people like me on the other side saying it's unarguable now that estrogen causes breast cancer and therefore we really need to stop and think before we go willy-nilly prescribing a drug that's clearly going to cause cancer.

So in your interpretation of the data, how much is a woman's risk of getting breast cancer affected by estrogen replacement therapy?

LOBO: My bottom line is that there is no definitive answer about estrogen and breast cancer. There is suggestive evidence that there is a small increased risk. If a woman happens to have some abnormal breast cells during her menopausal years, taking estrogen, particularly at high doses and for long periods, may promote that cancer to develop. Not to say that if she were 70 or 80, she might not have developed the disease anyway. So that's the way I view it. If there is an increased risk, it's in the range of about 20 percent, even up to 30 percent among

the susceptible population. It's something that's just on the borderline of being significant.

COLDITZ: Well, we have to be careful. Estrogen causes breast cancer even if a woman doesn't take postmenopausal hormones. We know that women with higher estrogen levels after menopause have a higher risk of breast cancer than women with lower levels. We know that obese women have higher estrogen levels and are at increased risk of dying from breast cancer, so there's a lot of evidence now that just natural estrogen levels are related to breast cancer risk. And we know separately from a recent study that the risk of breast cancer goes up somewhere between 2 and 3 percent for each year a woman uses hormones, which really means that after 10 years of use we're looking at around a 30 to 35 percent increase in risk compared with a woman who has never used hormones. What this translates to is that if we have 1,000 women beginning the use of postmenopausal hormones at age 50 and taking the hormones for 10 years, there are going to be six excess cases of breast cancer caused by the estrogen therapy. If the same group of women uses hormones for 15 years, there'll be 12 excess cases.

Alternatives to Estrogen

In light of the various concerns about hormone replacement therapy, researchers are trying to create other options. What are the so-called designer estrogens that are currently in development and testing?

LOBO: This is the group of selective estrogen receptor modulators, or SERMs. The prototype of this group is raloxifene, although the anticancer drug tamoxifen is actually a SERM also. It's not as glamorous, but it's really the parent of this group. These compounds selectively bind in certain tissues to have either an estrogenlike effect, known as an agonist effect, or an estrogen-opposing effect, known as an antagonistic effect. The ideal designer estrogen would be one that does not stimulate the breasts or the uterus but would have estrogenlike effects on the heart, the brain, the bones and the vagina. And to date there is no ideal designer estrogen. There may or may not ever be a completely ideal designer estrogen.

Are there other ways besides taking estrogen that women can protect themselves from osteoporosis and heart disease?

LOBO: Certainly for osteoporosis there are natural things that a woman can do that are somewhat helpful—exercise, eat a decent diet, get enough calcium—but at the next level, which is taking medication, a woman's options include alendronate, calcitonin and raloxifene or tamoxifen.

For cardiovascular disease, it's the same thing: a low-fat diet, antioxidant vitamins, exercise, not smoking—all the things we know and read about. None of them is as good as estrogen for either osteoporosis or cardiovascular disease, but there certainly is some benefit. It's better than doing nothing.

COLDITZ: In the antioxidant area, folate is at least as strong as estrogen for fighting cardiovascular disease, as is vitamin E. For a smoker, quitting smoking will actually have as big an impact as taking estrogen. So in fact there are a number of comparable strategies, and those with equal benefits and low risks should come to the top of the list of strategies. To me, that's where some of these options clearly dominate the choice of estrogen for preventing heart disease.

Many women rely on their doctors for advice about hormone replacement therapy. How well does the information that those doctors provide reflect the latest research?

LOBO: It's gotten to the point where there's more information coming from the media than from anywhere else. One of the reasons women discontinue hormones is because there's a lack of information, and they are concerned about not being counseled adequately. But I think hormone replacement is becoming such a hot topic that people are beginning to stay on top of it—both physicians and patients. I think the information trickles down much faster than it did in the past.

COLDITZ: The benefits of hormones are pretty clearly communicated out there rather quickly. The adverse effects are, shall we say, less popular. On a Saturday morning in Buffalo not that long ago, I gave a lecture for a continuing education program directed primarily at gynecologists, and after I'd given my talk, one of them said, "It's almost irresponsible of you to publish your material in the *New England Journal of Medicine* because now I have to talk to all my patients about the breast cancer risk." Well, maybe that's why we publish, you know.

Realistically, how long do you think it will be before women and their doctors have enough information to make decisions about hormone replacement therapy with confidence?

LOBO: You'll never know everything. There will always be room for new studies, new information and refinements of what we know. I feel very comfortable with what information we already have. We'll know more in the next few years. Every year brings more new information. But I really think you can synthesize what you have now and make an informed choice.

COLDITZ: With these new drugs [SERMs] coming, maybe every year we've got to sit down and reassess where we are. So even if a woman is using estrogen right now for relief of menopausal symptoms, in a year's time she might want to stop and ask, "Should I stay on this, should I be taking an alternative, what's the new evidence?" I don't know if there's one date by which we'll have the answer, because when we have the answer on drug A, drug B will have been on the market for only two years, so we'll start to have answers for it, and then drug C will just have been approved. So my attitude is this: let's not use a drug blindly for the next 10 years. Let's instead stop every year or so to reassess the approach and ask if this is the right drug, if it's the right strategy to achieve the goal, be it preventing osteoporosis or heart disease or avoiding menopausal symptoms. ^{5A}

The ongoing Women's Health Initiative (WHI) is looking at, among other issues, the risks and benefits of hormone replacement therapy. For more information about the study and the location of the nearest participating facility, call 800-54-WOMEN or write the WHI Program Office, Room 6A09, Federal Building, 9000 Rockville Pike, Bethesda, MD 20892-9110. Information about the WHI can also be found at <http://www.nhlbi.nih.gov/nhlbi/whi1/> on the World Wide Web.

The National Institute on Aging (NIA) Information Center offers printed material about menopause, osteoporosis, heart disease and stroke. For more information, call 800-222-2225 (for TTY callers, the number is 800-222-4225). A variety of NIA materials are also available at <http://www.nih.gov/nia> on the World Wide Web.

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