Menopause and the risks and benefits of hormone therapy

As women age, their bodies undergo complex changes that affect many aspects of their health. Menopause is one such change, driven by altered hormonal levels.

The ovaries produce estrogens, estradiol and estrone, and around age 35 they begin to shrink. On average, by the age of 50, production of estrogen has significantly decreased while production of other hormones, LH and FSH, are on the rise. As women approach menopause, changing hormone levels cause symptoms such as the following:

- hot flashes
- night sweats
- irregular periods with changes in bleeding
- vaginal dryness

Some women have reported these symptoms as they transition through menopause:

- mood swings
- depression
- difficulty concentrating
- poor memory
- sexual dysfunction

The intensity and duration of these symptoms associated with the body’s entry to menopause can vary considerably.

Hormone therapy

One key part of the body affected by declining estrogen levels is the skeleton. The relatively high levels of estrogen in circulation during adolescence and early adulthood impair the body’s ability to tear down bone.

Discussing the risks and benefits of hormone therapy with a doctor is vitally important because well-designed clinical trials of hormone therapy in HIV-negative women have found some unfavourable effects. For instance, data from large randomized clinical trials have found that supplemental estrogen can help relieve some symptoms of menopause. However, some doctors suggest that antidepressants, vitamin E or eating a diet rich in soy-based products may also provide some relief from these symptoms without the risks associated with the use of estrogen therapy.

In this report we explore data from clinical trials of hormone replacement in HIV-negative women. Unfortunately, data from large randomized clinical trials in HIV-positive women assessing hormone therapy are not available. However, the risks and benefits seen with hormone therapy in HIV-negative women likely apply to women with HIV as well.

Estrogen and bone mineral density

Clinical trials have found that estrogen can significantly and quickly increase bone mineral density at the hip and spine. These increases are sustained while hormone therapy continues. During this time, rates of fractures significantly decline.

An alternative to the use of estrogen is a class of drugs called bisphosphonates, examples of which include the following:
• alendronate (Fosamax, Fosavance)
• risedronate (Actonel)
• zoledronic acid (Aclasta, Zometa)

All of these drugs can increase bone density and significantly reduce the risk of fractures. Bisphosphonates work by impairing the body’s ability to tear down bone.

Another possible product is parathyroid hormone (teriparatide), which can also increase bone density. Unlike other drugs, parathyroid hormone must be injected daily and stimulates new bone to grow. However, this drug must be used with caution and only for a limited time because of a possible increased risk for cancer. Once a person stops using pariparatide, bone density quickly falls.

Generally, neither bisphosphonates nor synthetic parathyroid hormone affects the breasts or genital tract.

**Estrogen risks - Endometrial cancer**

Analyses of observational studies have found that the risk of endometrial cancer triples with short- or medium-term (between one and five years) estrogen-based hormone therapy. This risk of cancer increases considerably (about 10-fold) when estrogen is used for 10 or more years. Using a small dose of the hormone progesterone together with estrogen greatly reduces the risk of this cancer developing.

**Estrogen risks - Breast cancer**

An increased risk of breast cancer has been seen in observational studies of estrogen therapy; the longer the use the greater the risk. For instance, among women who used estrogen for less than five years the risk was very low. However, among women who used estrogen for five or more years the risk increased by 35%.

Unlike the case with endometrial cancer risk, combining estrogen with a progestin appeared to increase the risk for breast cancer.

**Estrogen risks - Excessive blood clots**

The ability of blood to clot is useful, as it helps staunch the loss of this vital fluid. However, unnecessary blood clots can block the flow of blood and cause serious complications such as stroke and heart attack. The risk for these problems increased about threefold among estrogen users.

**Estrogen and cardiovascular disease**

Results from observational studies done in the 1980s and 1990s suggested that estrogen-based hormone therapy could help reduce the risk of cardiovascular disease. However, note that observational studies can have their conclusions skewed by factors that were not accounted for in analyses. Indeed, robust clinical trials have found that women with pre-existing CVD did not significantly benefit from reduced risk for stroke and heart attack with estrogen supplements. In one trial of estrogen-progestin, a 50% increased risk of heart attack and stroke occurred in the first five years of the study. Other well-designed trials have also found an elevated risk for these complications with estrogen-progestin, a 24% increased risk for coronary heart disease and a 31% increased risk for stroke compared to placebo.

Some researchers think that women who have minimal pre-existing risk for CVD may benefit from hormone therapy early in menopause. However, data are needed to support this.

Reanalyses of several hormone therapy clinical trials suggest that part of the reason for the increased risk for CVD may have been the relatively older age of the women and that they had pre-existing risk factors for CVD. Among women aged 50 to 59, estrogen seemed to reduce the risk for coronary artery disease. However, differences in risk between age groups were generally not statistically significant.

Researchers are not certain if different doses and formulations of hormone therapy will produce different cardiovascular risks.

**Other conditions**


Limited data suggests that hormone therapy appears to increase the risk for ovarian and lung cancers but appears to decrease the risk for type 2 diabetes.

**What happens when hormone therapy stops?**

In clinical trials, the elevated risk for heart attacks, stroke and excessive clotting associated with estrogen-progestin disappeared two years after this therapy ceased. Benefits associated with hormone therapy—suppression of hot flashes and increased bone density—also ended.

The risk for breast cancer was slightly elevated and there was a suggestion of elevated risks for lung cancer (and other cancers) and dying.

**Bear in mind**

Leading hormone experts caution: “Primary prevention of heart disease should not be viewed as an expected benefit of hormone therapy.” They also add that “an increase in stroke and a small early increase in coronary artery disease risk should be considered [as possible adverse effects of hormone therapy]."

Thus the risk and benefit of hormone therapy should always be carefully considered and discussed with health care providers.

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