

10. HORMONE REPLACEMENT THERAPY

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Initial background information for this review was obtained from the 1996 U.S. Preventive Services Task Force (USPSTF) chapter on postmenopausal hormone prophylaxis and the 1992 American College of Obstetricians and Gynecologists (ACOG) Technical Bulletin on hormone replacement therapy (HRT). In addition, a MEDLINE search was performed for review articles published from 1990 to 1997 on the topic of postmenopausal HRT. Topics for quality indicators were then developed and, when necessary, clinical trials specific to the indicators were reviewed. Because the areas of screening and diagnosis are not pertinent to the topic of hormone replacement, this chapter covers treatment only.

IMPORTANCE

With the average age of menopause in the United States being 51 years, and the average life expectancy for a woman after reaching menopause being 30 years, women today can expect to live approximately one-third of their lives after menopause (USPSTF, 1996). The decline in endogenous estrogen that occurs with menopause is associated with several important causes of morbidity in women, such as osteoporosis, bone fracture, and cardiovascular disease. Cardiovascular disease is the major cause of morbidity and mortality in postmenopausal women. Nearly 50 percent will develop coronary artery disease at some time, and 30 percent will die of this disease (Grady et al., 1992). It has been estimated that a 50 year old white woman has a 15 percent lifetime probability of hip fracture, a 1.5 percent probability of dying of sequelae of hip fracture, and a 32 percent lifetime risk of a vertebral fracture (Grady et al., 1992; USPSTF, 1996). Vasomotor symptoms, or "hot flashes," occur in 50 to 85 percent of women at the time of menopause, and symptoms of urogenital atrophy occur in up to 45 percent of women over the age of 60 (USPSTF, 1996).

TREATMENT

For purposes of this review, HRT refers to the systemic use of estrogen (most commonly in an oral or transcutaneous form) with or without the use of a progestin, after cessation of ovarian function. When discussing the use of estrogen alone, the term "unopposed estrogen" will be used. Post-menopausal HRT can be used for relief of vasomotor symptoms and urogenital atrophy caused by the decreased estrogen production associated with menopause. With the recognition of other potential benefits of HRT, such as reduction in the incidence of osteoporotic fractures and cardiovascular disease, more attention has been given to the use of estrogens as a preventive therapy for post-menopausal women (Grady et al., 1992). Questions about hormone replacement therapy concern the appropriate dosages and regimens, and the risks versus the benefits of its preventive use in various subgroups of post-menopausal women.

Benefits of Hormone Replacement Therapy

HRT is generally accepted to be highly effective for relief of both vasomotor symptoms and urogenital atrophy associated with menopause. Both estrogen alone and estrogen plus progestins produce significant relief of these symptoms (ACOG, 1992; Belchetz, 1994).

Several observational epidemiologic studies have reviewed the effect of post-menopausal estrogen use on the incidence of hip fracture, with the majority showing a decreased relative risk of fracture in "ever-users" of estrogen replacement. The overall decrease in risk has been estimated at 25 percent (Grady et al., 1992). There is also evidence from clinical trials that HRT can reduce the rate of bone loss and improve bone mineral density in postmenopausal women (USPSTF, 1996). Current use of HRT, long term use (>5 years), and use close to the time of menopause have all been associated with greater reductions in fractures. However, past estrogen use provides minimal or no protection from fracture to women over the age of 75 (USPSTF, 1996). Because the median age for hip fracture is 79 (Grady et al., 1992), long-term use of HRT would be required to obtain maximal benefit for osteoporosis.

An important area of controversy in HRT concerns the decrease in risk of coronary heart disease (CHD) in women using estrogen plus

progestin HRT. Many epidemiologic studies have evaluated the relationship of HRT with CHD, most of them finding a lower risk of CHD among estrogen users (Grady et al., 1992). The relative risk of CHD in ever-users of estrogen has been estimated at 0.65 (Grady et al., 1992). This estimate is based on studies where the majority of subjects were taking unopposed estrogen. Because systemic estrogen therapy decreases LDL cholesterol and increases HDL cholesterol, the effect of HRT on CHD risk is thought to be mediated at least in part by this beneficial effect on the lipid profile. However, progestins have been shown to attenuate this beneficial effect (PEPI, 1995) raising the possibility that estrogen plus progestin HRT may not lead to as great a reduction in CHD as unopposed estrogen therapy. In addition, the non-random nature of the studies of CHD risk and HRT introduces the possibility that women at lower baseline risk of CHD were prescribed estrogen therapy, leading to an over-estimate of the beneficial effects of HRT (Hemminki and Sihvo, 1993). A more conclusive estimate of the benefits of estrogen plus progestin HRT on CHD will not be available until results of randomized trials, such as the Women's Health Study, are published.

Risks of Hormone Replacement Therapy

Use of unopposed estrogen in women with intact uteri leads to a significant increase in the risk of endometrial cancer. A meta-analysis of 37 observational studies showed that unopposed estrogen use for five to ten years was associated with a six-fold increased risk of endometrial cancer, and use for more than ten years with a nine-fold increased risk (Grady et al, 1995). The addition of either continuous or cyclic progestins to the HRT regimen eliminates this increased risk of endometrial cancer (Belchetz, 1994; The Writing Group for the PEPI Trial, 1996; USPSTF, 1996). For women who do not tolerate the addition of progestins to the HRT regimen, reduction of the frequency of progestin administration or performance of annual endometrial sampling have been proposed as alternatives. However, no studies have evaluated the safety of these regimens for women on unopposed estrogen (Indicator 1).

Many epidemiologic studies have examined the association between HRT and breast cancer, with inconsistent findings (Grady et al., 1992;

USPSTF, 1996). Several overviews have reported a relative risk of 1.2 to 1.4 in current users of HRT and in women who have used estrogen for more than ten to 15 years, but no increased risk among women who had ever used HRT (USPSTF, 1996). The Nurses Health Study, a prospective cohort study, showed a 50 percent increased incidence of breast cancer in current long-term (>5 years) users of HRT compared with women who had never taken HRT (Colditz et al., 1995). No clear association between short-term HRT use and breast cancer has been documented (Grady et al., 1992). The inconsistent findings in at least 40 observational studies and six meta-analyses (USPSTF, 1996) suggest that any potential association between HRT -- especially short-term HRT -- and breast cancer is small, but the possibility of an increased risk of breast cancer with long-term use cannot be excluded.

Summary

Post menopausal HRT has well-documented beneficial effects on the vasomotor symptoms and urogenital atrophy associated with menopause. In addition, long-term use of HRT reduces the risk of fractures associated with osteoporosis and probably reduces the risk of CHD. Unopposed estrogens in women with intact uteri leads to a significant increase in endometrial cancer. A possible association exists between long-term use of HRT and breast cancer incidence.

Women with significant symptoms of menopause may find the improvement in quality of life conferred by HRT outweighs any possible risk. In asymptomatic women, it appears that the benefits of HRT are substantial, but the individual patient's preferences and feelings toward risk need to be considered (Indicator 2).

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RECOMMENDED QUALITY INDICATORS FOR HORMONE REPLACEMENT THERAPY

The following criteria apply to women age 18 and older.

Indicator	Quality of Evidence	Literature	Benefits	Comments
1. Women with intact uteri should not use unopposed estrogen unless both of the following are true: <ul style="list-style-type: none"> • The patient has been tried on cyclic or continuous estrogen plus progestin regimen; • Endometrial sampling is performed yearly. 	I II	Writing Group for PEPI Trial, 1996; Grady et al, 1995	Reduce risk of iatrogenic endometrial cancer.	The minimum frequency of endometrial sampling necessary has not been established.
2. Women with a new diagnosis of menopause ¹ should receive counseling about the risks and benefits of HRT.	II III	USPSTF, 1996.	Reduce morbidity and mortality from cardiovascular disease and osteoporosis. Relieve symptoms of menopause.	While the benefits of using HRT have been established, the benefits of counseling have not.

Definitions and Examples

¹ Women in whom menses have ceased, either naturally or due to surgical removal of the uterus and ovaries, and in whom no other reason for amenorrhea is documented.

Quality of Evidence Codes

- I RCT
- II-1 Nonrandomized controlled trials
- II-2 Cohort or case analysis
- II-3 Multiple time series
- III Opinions or descriptive studies