HRT:
To Prescribe or Not to Prescribe?

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Presented at the University of Calgary's Evening Course Program for Family Practitioners, 2003

There is presently a lot of controversy over the role of hormone replacement therapy (HRT). Extensive press coverage following the early stopping of one arm of the Women's Health Initiative (WHI) study has left many women confused and disillusioned. It may have raised more questions than answers, more debate than decree, but women need to be informed.

The philosophy behind HRT revolved around the fact that chronic disease usually appears in the 30 years following menopause. HRT could possibly delay or stop disease progression by delaying aging. Many observational studies supported these notions.

The choice to begin, continue, or discontinue HRT involves a complex decision-making process. The choice is based on a woman's attitude toward menopause, the beliefs of others (family, friends, and physician), and the expectations of risks and benefits.[1]

The bridge ladies

Darya, 50, Linda, 60, Josette, 69, and Jasmine, 55, were playing cards at their weekly bridge game.

Darya had a hot flush and complained of all the menopausal symptoms she was having. She was considering starting hormone replacement therapy (HRT).

Linda quickly added that hormones were bad for you; at least that's what she had been reading in the papers.

Josette had been on hormones since menopause and was wondering what she should do.

Jasmine stated she had not given hormones much thought and would see her physician to get all the facts.

For a followup on the ladies, go to page 82.

What are the menopausal symptoms?

There is a constellation of symptoms that have been attributed to menopause. These symptoms often include, among others: hot flushes, vaginal dryness, mood swings, sleep disturbance, and decreased libido. Approximately 75% of women suffer from hot flushes and night sweats during the perimenopausal and menopausal period, and 30% of these women find the symptoms to be significant.[2] HRT decreases the rate of hot flushes by 77% and significantly decreases their severity.[2] Venlafaxine extended-release (75 mg daily) can decrease flushing rate by

Table 1
Breast cancer risks

HRT use or risk factor	Risk of breast cancer/1,000	Extra cancer
No HRT	45	—
HRT users	—	—
5 years	47	2
10 years	51	6
15 years	57	12
Late menopause	58	13
Overweight by 20%	59	14
Alcohol (≥ 2 drinks)	72	27
Lack of exercise	72	27

HRT: Hormone replacement therapy

61%, as compared to 27% with placebo.[3] Vaginal dryness can be treated with local vaginal estrogens or moisturizers.

Most women who choose to start HRT want to control distressing menopausal symptoms. Alternative therapies have had limited effects on symptom control.[2]

What about the breast cancer risk?

Breast cancer is associated with levels of estrogen. It was initially felt that estrogen alone was a risk factor, and that the risk would be mitigated by progesterone. However, it appears that progesterone actually imparts an increased risk. Estrogen alone increases the relative risk (RR) to 1.2; the RR increases to 1.4 with progesterone.[4] The annual risk of estrogen replacement therapy (ERT) is 1.023 (confidence interval [CI]=95% [1.011-1.036]).[4] Table 1 clarifies how these numbers relate to cancer diagnosis. It is expected that 2/1,000 extra breast cancers will be diagnosed in HRT users after five years. The risk increases with duration of use and returns to baseline after cessation.

There appears to be a decrease in mortality in women who are diagnosed with breast cancer who are current HRT users, as compared to women who never used HRT.[4] The mortality decrease is approximately 50% for all stages of breast cancer. However, if there is disease found in the lymph nodes, this protection is no longer seen after four years. The decrease is not related to an earlier cancer detection in women taking HRT as previously argued.

In retrospective, case-controlled studies, there is no indication that breast cancer survivors have a worse prognosis if they initiate HRT.[4] Until randomized trails are available, caution should still be exercised in prescribing HRT in breast cancer patients.

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Table 2
Attributable risks from the WHI trial

	Continuous combined HRT	Placebo	HRT attributable cases per 10,000 years
Total women	8,506	8,102	—
Coronary heart disease	164	122	+7
Stroke	127	85	+8
VTE (1)	151	67	+18
Osteoporotic fractures	650	788	-5
Invasive breast cancer	166	124	+8
Colorectal cancer	45	67	-6
Endometrial cancer	22	25	0

HRT: Hormone replacement therapy WHI: Women's Health Initiative
VTE: Venous thromboembolism

What are the cardiovascular risk factors?

HRT was touted as decreasing cardiovascular disease (CVD) rates significantly. This was supported by large cohort studies and studies looking at surrogate markers. As CVD is the leading cause of death in women, this would have a significant health impact. Recently, all the protective effects of HRT have been questioned. There are two aspects of CVD that must be looked at: primary and secondary prevention.

Primary prevention was addressed with the WHI study.[5] The WHI study randomized healthy women to HRT or placebo. The study included estrogen and progesterone, or estrogen alone (in the case of a previous hysterectomy) versus placebo. The estrogen and progesterone arm was stopped early because of unacceptable adverse events (Table 2). Most heart attacks (81%) occurred in the first year. These findings had been corroborated with a prior meta-analysis that showed no protective effect with the use of HRT.[6]

The Heart and Estrogen/progestin Replacement followup Study (HERS) was a randomized, controlled study looking at the secondary prevention of HRT after a myocardial infarction (MI).[7] The main outcome was fatal and nonfatal MI. After four years, there was no difference in outcomes. Interestingly, most events also occurred in the first year and then levelled off.

There has been extensive criticism of these trials. It appears that estrogen and progesterone do not have protective cardiovascular effects. Whether this is a class effect (all estrogens and progesterones) or only related to conjugated equine estrogen and medroxyprogesterone acetate is unknown. It is speculated that progesterones negate the effects of estrogens by down-regulating estrogen receptors.[7] Despite many uncertainties, presently HRT should not be prescribed for the primary or secondary prevention of CVD.

Take-home message

- The choice to begin, continue, or discontinue HRT involves a complex decision-making process based on a woman's attitude toward menopause, the beliefs of others, and the expectations of risks and benefits.
- The risk of breast cancer is associated to estrogen levels. The risk increases with duration of HRT use and returns to baseline after cessation.
- Estrogen and progesterone do not have protective cardiovascular effects.
- HRT is considered second-line therapy for treatment of osteoporosis.
- HRT does not maintain cognitive function for women with Alzheimer's dementia.
- Observational studies suggest a significant decrease in colorectal cancer in women who have taken HRT.

What did the bridge ladies do?

Darya decided to start HRT to manage her symptoms, then slowly withdraw.

Linda decided to stop her HRT, as she was concerned about breast cancer.

Josette decided she would continue taking HRT. She felt the studies had not addressed women who were presently on HRT.

Jasmine decided to wait until other studies are published and, in the meantime, manage her symptoms with other therapies.

What about osteoporosis?

HRT has long been advocated for the prevention of osteoporosis. This has been shown in studies that have looked at changes in bone densitometries (a surrogate marker for fracture risk).[8] Case-control studies found a 25% to 50% decrease in hip fracture rate, a 50% reduction in vertebral fractures,[8] and the WHI found a 24% decrease in all fractures.[4] Meta-analysis has shown that calcium and HRT show trends toward a decrease in vertebral fractures; alendronate, etidronate, risidronate, raloxifene, and calcitonin have demonstrated significant decreases. All of these elements show trends towards decrease in nonvertebral fractures.[8]

Presently, HRT, along with calcium, exercise, bisphosphonate, and selective estrogen receptor modulators, is advocated as a primary therapy for prevention of osteoporosis. However, HRT is considered second-line therapy for the treatment of osteoporosis.[8] This may not be related to a lack of efficacy, but more to a lack of clinical trials.

Is there a link with Alzheimer's dementia?

As estrogens have been shown to have several potentially beneficial effects on the central nervous system, it is biologically plausible that maintaining increased levels of estrogen could be protective against cognitive decline.

Observational studies suggested a decrease risk of Alzheimer's dementia, but women who chose to start HRT are generally more educated, healthier, and have healthier lifestyles.[9] There is little prospective evidence that overall cognitive function in healthy post-menopausal women is affected by ERT or HRT.[9] Beginning HRT in women with diagnosed Alzheimer's dementia does not maintain cognitive function.[10]

What about colon cancer?

Observational studies suggest a 20% reduction in the risk of colon cancer and a 19% decrease in the risk of rectal cancer in post-menopausal women

Net Readings

1. The North American Menopause Society
   www.menopause.org
2. Society of Obstetricians and Gynecologists of Canada
   www.sogc.org
3. National Women's Health Network
   www.nwhn.org
4. Women's Health Initiative
   www.whi.org

who had ever taken HRT, as compared to women who had never taken it.[11] This is more apparent in women presently taking HRT, who demonstrate a 34% reduction in such cancers.[11] Caution must be taken in interpreting observational studies and these findings need to be confirmed with randomized trials.

What do you do?

Many factors will influence a woman's decision to begin or decline HRT. The risks and benefits, real or perceived, must be weighed. By providing information and other management options, women will be in a better position to make a decision.

Some clarification of the role of HRT will be addressed after the completion of the Women's International Study of Long Duration Oestrogen after Menopause (WISDOM) trial, the WHI (estrogen arm), and the Women's Lipid Lowering Heart Atherosclerosis (WELL-HEART) trials. CME

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