HRT: What's the Right Answer?

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Darlene's Concerns

Darlene, 52, is the third of three sisters reaching menopause. While she doesn't have hot flashes, she does experience some discomfort during intercourse, which is relieved by Astroglide®.

She is concerned about her bones because her mother fractured her hip and both sisters were diagnosed with osteoporosis.

She asks about hormone replacement therapy (HRT) and you tell her you do not think it is necessary.

She returns two weeks later with her middle sister, asking why it is good for her siblings, but not for her. Conversely, her middle sister also wants to know if HRT is not good for Darlene, why have you not told her to stop treatment?

What would you tell your patients?

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Almost 40 years have passed since the release of Robert Wilson's book, *Feminine Forever*, in which he suggests ovarian hormone therapy, particularly estrogen, could counteract the effects of advancing age in women after menopause.

While few would now believe estrogen is a source of eternal youth, opinions about the therapeutic and preventive values of estrogen and hormone replacement therapy (ERT/HRT) vary. HRT has been subject to outrageous swings of popularity, ranging from comments that it would constitute malpractice not to offer ERT/HRT, to the recent Canadian Cancer Society pronouncement that the cancer-causing risks of HRT outweigh its benefits.

Why the change of heart on HRT?

Much of the recent swing away from ERT/HRT has come from a series of studies published by the Heart and Estrogen/progestin Replacement Study (HERS) and the Women's Health Initiative (WHI).

Based on HERS and WHI, several organizations, including the Society of Obstetricians and Gynaecologists of Canada and the North American Menopause Society, have issued recommendations about the role of HRT in post-menopause. These recommendations generally agree that HRT should:

- be restricted to symptomatic women and
- not be used for disease prevention in asymptomatic women.

While perhaps there should also be agreement that safer alternatives be used when available, few drugs have undergone the same extensive scrutiny as estrogen; some have been adapted without any appropriate investigation.

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ERT/HRT is effective in controlling moderate to severe hot flashes in a majority of women. In these cases, the patient may agree the benefits outweigh the risks. While alternatives do exist, evidence of efficacy is poor, at best.[1]

Randomized controlled trials (RCTs) of non-prescription remedies have been disappointing at best.

Clonidine and methyldopa have been reported to be effective, but with significant adverse effects. Antidepressants (venlafaxine, paroxetine, fluoxetine) and the anticonvulsant gabapentin are non-hormonal agents with demonstrated efficacy reducing hot flashes with few adverse effects in small controlled and uncontrolled trials. While their efficacy in severe hot flashes is debatable, they can be considered a viable option in patients unwilling or unable to take hormonal therapies.

Progestational agents are effective, but their safety may not be more assured than estrogen alone. Randomized, controlled trials (RCTs) of non-prescription remedies (*i.e.*, soy, isoflavones, black cohosh, vitamin E, dong quai, evening primrose oil, magnet therapy, acupuncture, and licorice) have been disappointing, with clinically insignificant improvements.

Therapy is not indicated for mild hot flashes that have no impact. In these patients, it may be beneficial to;

- avoid triggers,
- layer clothes for easier shedding,
- practice relaxation techniques, and
- get regular physical activity.

Treating urogenital atrophy

Local and systemic estrogen therapy usually relieves symptoms of vaginal atrophy. Local therapy with the estradiol-releasing ring (Estring®) and vaginal estrogen tablets (Vagifem®) are effective without substantial systemic absorption. It is likely, but unproven in large-scale, long-term RCTs that such therapy will provide local relief without placing the patient at risk for complications of systemic therapy. While urinary frequency and irrita-

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Darlene's Followup

The dilemma of advising the three sisters about HRT is that recommendations have changed since the sisters have been going though the menopausal transition.

HRT is not indicated in the younger sister and use should be reviewed in the older sisters. Continuing use in the two older sisters should follow a review of the indications and anticipated benefits and risks.

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tion are improved by HRT, the benefit of such therapy on stress and urinary incontinence is of doubtful worth.[2,3]

Can HRT prevent disease?

It is clear that, despite preventive use of estrogen dating back 40 years, we still do not understand all the implications of preventive ERT/HRT. Evidence from the WHI and HERS suggest there may be a transient increased risk in women with existing cardiac disease or others at risk of an estrogen-induced thrombotic episode. Overall, the long-term benefits of ERT/HRT reported in the observational studies have not been proven in the HERS or WHI.

While the studies of continuous, combined estrogen-progestin therapy described the risks of coronary heart disease, stroke, venous thrombo-embolism, and breast cancer as increased, colorectal cancer and fracture risks were decreased. There was no significant change in mortality.

In the estrogen-only arm of the WHI, a number of results were somewhat contrary. The effects of estrogen on coronary heart disease was statistically neutral, while breast cancer risk narrowly escaped being improved by estrogen. Fracture rates were better, while venous thromboembolism and stroke risks were worse. Mortality was similiar between groups and few risks or benefits were substantial. An increase in breast cancer diagnoses/year of one in 1,000 must be weighed against a 50% reduction in mortality for women with estrogen-associated breast cancer, compared with those who had not taken estrogen.[4]

Following the WHI study, many organizations agreed that women taking long-term HRT should not panic, but rather discuss their current usage with their physician. Unfortunately, advice is lacking for the physician in these circumstances. Clearly, in the present circumstances, hormone therapy should not be started or continued for the primary or secondary prevention of heart disease. Furthermore, asymptomatic women should not take ERT/HRT as a preventive measure.

Where does this leave HRT?

Despite the adverse epidemiologic results with conjugated equine estrogens, the extensive biologic and metabolic evidence suggests there may be a formulation capable of improving the cardiovascular health of postmenopausal women.[5]

We also need to determine if the WHI study should be the final word on hormone replacement. This complex question involves looking at the methodology of the various studies and overall validity of the design of the WHI studies, and the conclusions drawn from them.

A recent meta-analysis of RCTs of hormone therapy shows an almost 40% reduction in mortality in younger women taking HRT.[6] Results in any of the studies may not relate to lower doses of drugs or other estrogens or progestins, or other formulations or routes of administration. In the absence of clinical trial data, one cannot assume greater safety of other estrogens and/or progestins. Post-WHI we still cannot definitively answer:

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- who benefits from HRT?
- what formulation and dose is best?
- how long should therapy continue? or
- what should one do about patients already taking HRT?

What role should HRT play?

There is no doubt that estrogen has a positive impact on the menopausal syndrome and urogenital atrophy. The WHI study seems to have dashed the hope that long-term HRT use might have greater benefit than harm on the three major causes of death in older women: cardiovascular disease, cancer, and osteoporosis.

Regardless of any optimism expressed, there is no good indication for giving HRT to asymptomatic women. Long-term HRT should not be continued, nor started in anticipation of improvement in heart disease. Long-term use may be appropriate to reduce fracture risk in symptomatic women, but probably not in asymptomatic women. The following alternative therapies should be considered in women at risk for osteoporosis and fragility fracture:

- bisphosphonates,
- selective estrogen receptor modulators,
- nasal calcitonin, and
- parathyroid hormone.

Any knee-jerk reaction of patients and physicians to simply stop HRT should be discouraged. We should be prepared for these recommendations to change and, therefore, should be looking for evidence without the sensationalism that surrounded the release of the WHI papers. CME

Take-home message

- Several organizations have recommended HRT should be restricted to symptomatic post-menopausal women.
- Knee-jerk reactions of patients and physicians to stop HRT should be discouraged.
- Alternative therapies should be considered in women at risk for osteoporosis and fragility fracture, including:
  - bisphosphonates,
  - selective estrogen receptor modulators,
  - nasal calcitonin, and
  - parathyroid hormone.

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