Hormone Therapy: The Changing Landscape

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The question of hormone replacement therapy (HRT) for menopausal women remains to be one of the most hotly debated questions in medicine today. This is partly due to a flurry of recently published studies, many of which appear to be at odds with each other, as well as with our widely held impressions and beliefs about the subject.

With a woman's life expectancy now at approximately 83.5 years,[1] a full one-third of a woman's life may be post-menopausal. Maximizing quality of life and minimizing the development of chronic diseases is very important given these changing demographics.

The changing evidence

In recent years, our beliefs and expectations about HRT have shifted considerably. The release of the Women's Health Initiative (WHI) trial results in 2002[2] has shifted our attitudes and practices in women's midlife health more than any other single trial in history. Prior to the release of these results, it was widely believed that HRT helped to prevent cardiac disease, osteoporosis and other chronic diseases. Important trials in the late 1990s, such as the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial,[3] suggested that estrogen was beneficial to lipids, while progestins were more variable. The WHI trial led to the widespread use of progesterone to replace medroxyprogesterone in many of our formulations.[4] But the role of estrogen in mitigating against heart disease was still unquestioned at that time.[5]

Until the WHI trial, there were no large randomized studies that asked the following question directly: "if we control for other variables (such as age, exercise, diet, *etc.)*, how much will HRT affect outcomes (such as breast cancer, heart disease, *etc.*)?"

Certainly, there are concerns about the design of the WHI trial. It was the largest randomized trial ever undertaken to examine this issue. But it involved starting women on HRT, many of whom were in their sixties and seventies, something rarely done in Canadian practice.[6] It also involved the use of only one formulation of estrogen and progesterone, which is not used widely, largely because of the results of the PEPI trial.[7]

In all, the WHI trial showed us that estrogen did not have the protective effects that we had assumed[8] and did not help to solve the following questions:

- What can we do for a perimenopausal or early menopausal woman with significant symptoms affecting her quality of life?
- Can we safely treat these women hormonally, should their symptoms warrant it?
- If we do treat hormonally, do we increase or decrease their risk of cardiovascular disease (CVD)?

- Is it safe to use HRT for a short-term (up to five years) in women with moderate-to-severe menopausal flushes?

As the results of the WHI subanalyses are being released, we are finally getting some answers and the results are reassuring.

WHI subanalysis results

A study by Rossouw, *et al*,[9] released in April 2007, looked at the effect of time from menopause to the start of HRT on the development of CVD. It suggests that women who start hormones within 10 years of their natural menopause may be less likely to develop CVD than women in older age groups. However, it does not suggest a protective role for estrogen and further cautions that the risk of stroke does not seem to be age-related. Another subanalysis suggests that breast cancers are also less common in those < 60-years-of-age than in older women.[10]

What we now know suggests that HRT may be relatively safe for women in their early menopause years.[11] Over the coming months we will see further studies being published which analyze this data in a number of different ways and we will continue to refine our understanding of this complex area.

The clinical picture: Optimizing treatment

Despite all of the available epidemiology on the subject, the fact remains that many of our patients suffer significant side-effects of menopause.[12] The task of those clinicians involved in the care of perimenopausal women is to balance the risks of HRT with the possible advantages for each woman. Generally speaking, this will mean using the lowest dose for the shortest possible time needed to control symptoms. The 2006 Society of Obstetrician-Gynaecologists of Canada's (SOGC) update supports this approach as the safest with regard to both short-term and long-term outcomes.[13]

Preventing chronic disease

The greatest changes in the recommended use of HRT come in the area of prevention of chronic diseases. For example, while there is evidence that estrogen will help to prevent bone loss, there are other treatment modalities that will have equal effects with less associated risk.[14] While there is evidence that endogenous estrogen has a role in the apparent protection of perimenopausal women from CVD, it now seems clear that we are unable to mimic that effect by giving exogenous estrogens to post-menopausal women.[15] Therefore, the use of estrogen in the prevention of chronic disease should be abandoned and its use restricted to short-term symptomatic treatment.[16]

Menopausal symptoms and HRT

As a result of changes that have taken place since 2002, there is no longer a place for treating menopause *per se*. Our goal should be to treat specific symptoms, understanding (of course) that there will be systemic effects to anything that is prescribed. Therefore, the first step is to decide exactly what you are treating. A detailed history and physical exam, together with an accurate description of the symptom complex, will help you decide on the best approach and rule out those women with contraindications to HRT (such as abnormal bleeding, hypercoagulability and liver disease).[17]

Distinguishing individual symptom profiles will help to direct treatment. The following is a short summary of considerations for prescribing HRT for specific menopausal symptoms.[18]

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Vasomotor symptoms

Most women will go through menopause without any major concerns, though the majority will have some hot flashes.[19] Unless these hot flashes are really disabling, reassurance may be the only treatment required. If symptomatic support is needed, often conservative measures and lifestyle modifications will do the trick.[20] Many women will also opt for evidence-supported alternative therapies (*e.g.*, herbs, vitamins, *etc.*). Black cohosh and red clover have both been found to decrease hot flashes, though not to the extent of estrogen-containing preparations.[21] Studies on other herbal therapies show only marginal effects, but many of these are very small trials and more information is needed.

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In about 10% of cases, symptoms will be severe enough to warrant HRT. Since 2002, many women have been undertreated and may have suffered unnecessarily. In many trials, estrogen has been shown to be highly effective in relieving hot flashes.[22] A smaller number of trials have also shown positive effects for progesterone.[23]

Urogenital symptoms (vaginal dryness)

Physiologic changes in the vagina are universal with increasing age. Up to 60% of women will have symptoms severe enough to report to their physician. Many more will have some discomfort with intercourse and never report it. When a lack of lubrication is the main problem, correcting this may be all that is necessary.

Many women will benefit from the use of vaginal estrogens,[24] which are available in several different forms (*i.e.*, estrogen cream, estradiol delivered via a sylastic ring and estradiol tablets).

Sleep disturbance

Sleep disturbance may underpin many of the other reported symptoms common during menopause. If it is associated with severe flushing, estrogen may be the best treatment.[25] However, if not, it may not respond to estrogen therapy.[26]

Correctly characterizing and diagnosing the pattern of sleep disturbance is a necessary first step to intervening successfully.

Mood disturbance

Mood disorders presenting at perimenopause or menopause can be complex and difficult to sort out. Rarely will changes in estrogen levels themselves be sufficient to cause severe depression or other significant mental health problems.[27]

The sleeplessness associated with menopause may be largely responsible for the irritability and loss of concentration that is so often reported. Likewise, forgetfulness may be largely the result of sleep deprivation.[28] Prior to any trial of HRT for mood instability, an accurate diagnosis should be obtained. If a true depression is found, evidence suggests that specific antidepressant therapy will be more effective.[29]

In women with underlying or previously diagnosed depression, symptoms may worsen during menopause. If they do, the use of adjuvant HRT along with an antidepressant, may be helpful.[30]

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Other menopausal issues

Many other physiologic changes that occur with passing time certainly have an estrogen-related component to them. Some of these include changes in:[31]

- Skin
- Hair
- Gums
- Weight
- Muscle tone
- Voice

This does not necessarily mean that we can or should try to reverse these changes with the use of exogenous hormones. Optimal health in menopausal years requires a holistic approach, including healthy diet, exercise and stress management.

Choosing a treatment regimen

Estrogens

Estrogens available for human use can be either semi-synthetic, made from plant or animal sources, or fully synthetic. The three main human estrogens are:

- estrone,
- estradiol and
- estriol.

Estradiol is by far the most potent for symptom control. However, in their natural state, estrogens are rapidly broken down in the GI tract and must be modified to assure bioavailability. This can be done by conjugating, micronizing, or stabilizing it with another molecule. Transdermal preparations circumvent this problem and allow estradiol to be delivered directly, bypassing the GI tract and liver.[32]

The route of estrogen administration is a personal choice for most women. However, there is evidence that a transdermal approach (bypassing the liver) is advantageous in many circumstances. For example, women with high triglycerides should benefit from transdermal therapy as the potentially negative effects of oral estrogen on lipids will be avoided. Similarly, smokers may benefit from transdermal therapy for the same reason.[32] Transdermal estrogen can be delivered by a patch, a gel, or a cream.

Vaginal estrogens are clearly preferable for localized symptoms of vaginal dryness or dyspareunia.[34] In fact, it may be necessary to use directed vaginal therapy to treat vaginal symptoms even in women who are taking systemic HRT.[35]

Remember that the smallest dose possible to control symptoms is the goal, even with localized therapy. Vaginal estrogens can contribute to endometrial hyperplasia, though most vaginal symptoms can be treated without reaching these levels.

Progesterones

Even for short-term use, endometrial hyperplasia remains a real concern, so adjuvant progesterone should be used only if the patient has had a hysterectomy. There are a variety of ways to achieve this effect. Oral progesterones are used most commonly, medroxyprogesterone acetate and micronized progesterone being the most common.[36] At present, studies suggest that transdermal progesterone may not reach high enough levels to protect the endometrium, so progesterone creams are not recommended for the prevention of endometrial hyperplasia and associated malignancy.[37]

The use of a progesterone-containing IUD is another viable treatment option for endometrial protection, with studies showing negligible endometrial thickening during its use.[38]

Cyclical vs. continuous approach

The choice of a cyclical vs. continuous approach depends on several factors. In women who are perimenopausal, or still having periods, continuous therapy is likely to result in irregular bleeding. For this reason, cyclical therapy, traditionally using estrogen from day one to 25 and adding progestin from day 11 to 25, is often the preferred approach.[38] In women who are no longer menstruating, continuous therapy using both estrogen and a progestin on a daily basis may be more convenient.

In my experience, it seems that women more than a year past their last period are not likely to experience ongoing irregular bleeding on continuous therapy, though they may have some spotting in the first month or two of treatment.

Stopping hormone therapy

There is very little information available to help us answer the question "what is the best way to stop hormone therapy?" The main goal is to stop therapy with as little chance of having symptoms recur as possible. I think a gradual reduction in dose, at a time of minimal stress, will be most successful. However, some women will do just fine with an abrupt cessation, so individual choice and motivation are really the main variables to consider.

Summary

Optimal health will always be the goal of treatment. Our goal to practice evidence-based medicine will always be hampered by the fact that we will never have all the information we need and that the evidence itself will always be flawed. Our job as clincians is to weigh the available evidence and to consider it in the complex equation of our patients' lives.

Sometimes, depending on the symptoms, women will truly benefit from HRT in the short-term. Our goal should always be to balance the risks and benefits while optimizing the chance of good health throughout the life span. Dx

For references, please contact **diagnosis@sta.ca.**