DRUG REVIEW

Menopause and Hormone Replacement Therapy What is The Future ?

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Introduction

Until recently, hormone replacement therapy (HRT) was quite straightforward. Oestrogen prevented the symptoms of the climacteric, particularly flushes, sweats, vaginal dryness, depression, loss of energy and loss of libido. Cyclical or continuous progesterone, protects endometrium. There were also long term benefits of protection from osteoporosis reduction in colon cancer and both primary and secondary prevention of heart attacks.

Release of data to the media from various trials of HRT has resulted in tremendous fear and anxiety for women and has put HRT in an extremely negative light. The principal concern here is that the data have not been interpreted correctly (1).

In the 1990s, when observational data were considered to be so consistent in showing a protective effect of HRT against coronary heart disease (CHD), various RCTS (Randomized Clinical trials) (2) were designed to prove this association because it would be faster to obtain data from a secondary prevention trial (treating women with established disease).

Between 1993 and 1998 (3), 27000 women were recruited by investigators of WHI (Women's Health Initiative) and were randomized to receive CEE (Conjugated equine estrogen) 0.625mg + MPA2.5mg (Medroxy progesterone Acetate) or placebo.

Accumulating evidences suggest that initiating HRT (at standard doses) in women with CHD (proven or silent) induces coronary events, but not in young healthy women at the onset of menopause.

The HERS study first challenged the optimism that oestrogen exerted a protective effect in women with coronary artery disease and more recently the paper from WHI study and the Million Women Study (MWS) have caused enormous alarm by reporting that heart attacks, strokes, venous thrombo-embolism and breast cancer are more common in women who are receiving treatment (4). In December 2003 the UK CSM following the lead of EMAS advised that HRT Should no longer be the first choice for the prevention and treatment of osteoporosis. A subsequent paper from WHI study indicated no improvement in quality of life with HRT. As a result there has been a 50% reduction of HRT taking in the US and a significant, but rather less, reduction in Europe.

To add further to the confusion, the oestrogen only arm of the WHI study has been stopped because the increase in stroke has been confirmed after 7 years with an extra 8 more strokes per year for every 10,000 women than on placebo. But there is no increase in breast cancer or heart attack (5).

Data from 10 studies now points to a greater risk of breast cancer in women receiving progesterone with estrogen (6). The risk with oestrogen alone, although not trivial, appears to be much lower, and this risk disappears after cessation of use. In the estrogen only trial of WHI (April 2004) there was no increase observed over 7 year of use (7). To put the breast cancer findings into perspective, if there is an increased relative risk, the absolute increase in risk is extremely small (less than 1%) particularly in women using lower doses; although in some studies, no dose effect was evident. The majority of papers looking at mortality from breast cancer in women taking HRT have found this to be greatly reduced by as much as 30% of what physicians anticipate for the future.

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Preventive measures at an early age for osteoporosis

If maximum peak bone mass is achieved by the third decade in young women, their risk of developing osteoporosis will be less. Public health awarness to ensure adequate calcium intake, nutrition and exercise, beginning in childhood should be an achievable goal.

Heart disease

Cardiovascular disease remains the leading killer of women, particularly older women. Data from the women's Health initiative (WHI) trial and various secondary prevention trials have proved the lack of cardiovascular benefit of estrogen and estrogen plus progesterone in older women who have established diseases. The current focus of prevention of CVD in women is directed at (1) awareness (2) education (3) lifestyle modification and (4) use of established therapies (8).

Future Hopes for Cancers

Breast Cancers

Early detection remains the key. Screening for genetic susceptibility is likely to be more successful in the future. Digital imaging ultrasound and MRI are likely to become more precise and will be ways to counteract specific technical problems, such as increased tissue density as seen on mammography in some women using HRT.

Strategies for chemoprevention beyond the use of tamoxifen are being explored at present. Other SERMS in development may also be in use in the future, as will aromatase inhibitors, which have been shown to be extremely effective in patients who have breast cancer (9). Most recently, aspirin use also has been shown to exert a protective effect as has been shown in colon cancer.

Cervix and uterus

Detection of precancerous lesions using papanicolaou smears and human papilloma virus DNA technology will continue to reduce the cancer rate.

Uterine cancer may be reduced by continued vigilance in treating anovulation and targeting high risk individuals (e.g. those with obesity hypertension or diabetes mellitus) women who have polycystic ovary syndrome in particular would benefit from the use of oral contraceptives, which can reduce the risk by 50%.

Colon Cancer

This cancer can largely be eradicated by early detection of polyps. In the future the use of less invasive radiological evaluation is likely to be applied clinically but is still not recommended at present.

Lung Cancer

In women this cancer can be significantly reduced by smoking cessation programs.

Ovarian Cancer

Surveillance and early detection is a major inititiative at the National Cancer Institute and among most oncology groups. Hopes lies in genetic screening, proteomics and high resolutions scans for early detection. The ovarian pap smear has been suggested but may be too invasive for routine use Among Cancer screening tests, although there has been some success with current markers available (CA 125, inhibin), the use of proteomics has resulted in screening tests that are close to being available and should in the future, offer a new dimension of hope.

Future Advice for HRT

- Oestrogen treatment should be used for the treatment of specific symptoms and low bone density. Other drugs instead of oestrogen should be tried first, if possible.
- Although estrogens appear to have no place for the secondary prevention of cardiovascular disease, it is still indicated in the early menopausal women for protection against CHD and strokes and Alzheimer's disease. There is window of opportunity in 45-60 year old symptomatic women who may show long term cardiovascular and neurological benefits from early estrogen therapy.
- Oestrogens commenced in older women of 60-79 years may do early harm in the form of heart attacks, strokes and vascular dementia before any benefit is achieved.
- The dose and route will depend upon symptoms, and the age of the parient. Peri and postmenopausal patients with vasomotor symptoms should be given either oral or transdermal oestradiol with cyclical progesteron for endometrial protection.

- Proven benefits of HRT confirmed in randomised trials are an improvement of symptoms such as hot flushes, night sweats, insomnia, vaginal dryness and peri menopausal depression and also a decrease in colon cancer, vertebral and hip fractures.
- Major side effects of HRT are VTE (venous thromboembolism), breast cancer (perhaps only with estrogen/progestogen preparations) and strokes and heart attacks in older high-risk women receiving premarin.
- The usual duration of progestogen is 14 days, however, if the extra risk to the breast from progestogen is confirmed, it would be sensible to reduce the duration to 7 days. This shortened course is useful in women with progestogen intolerance.
- Patients may wish to avoid bleeding by using low dose oestrogen and progestogen or have insertion of a Mirena IUS or use Tibolone.
- Patients with hormone responsive mood disorders should have a higher dose of transdermal estrogens either by patch, gel or implant. As these are often progestogen-intolerant, 7 day cycles of progestogen are permissible.
- If loss of libido and loss of energy remain a problem, the addition of testosterone should be considered.
- The lowest effective dose should be used remembering that the dose for the elimination of vasomotor symptoms will be less than the dose required for mood disorders or low bone density.
- The indication and the need for HRT should be reviewed each year with discussion of current views on risk.
- A 5 years duration has been recommended but in reality women remain on HRT if they are feeling well with relief of symptoms. It is difficult to persuade these women to stop even after 10 or more years.
- A mammogram should be performed each year and breast examination every 6 months.

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