Managing menopause

after the Women's Health Initiative study

The findings of the Women's Health Initiative study profoundly affected patient and clinician perceptions of the role of hormone therapy in the management of menopause. This article reviews the options for women with menopausal symptoms.

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In 1966 Dr Robert Wilson's *Feminine forever* was published.[1] He wrote of the wonders of hormonal therapy:

'When you see a woman of 50 looking like 30, or a woman of 60 looking and acting like 40, chances are that she is one of the lucky ones who have benefited from the new techniques of menopause prevention – at 50 such women still look attractive in tennis shorts or sleeveless dresses'.

And so began 30 years in which hormone therapy was widely promoted to menopausal women and their physicians.

Initially hormone therapy was seen as a means of relieving menopausal symptoms and preserving youth and vitality. In the 1980s there was a shift in emphasis to the perceived long term health benefits, particularly regarding the prevention of bone loss and cardiac disease.

By the 1990s, however, there was growing disquiet among a number of researchers about whether the health benefits claimed for women using hormone therapy might be counterbalanced by a number of possible risks.

Challenging the paradigm

In 1995 the Nurses Health Study suggested an increased risk of breast cancer (relative risk: 1.35) in women using hormone therapy,[2] and in 1997 a collaborative meta-analysis of data from 51 previous studies indicated a similar risk (relative risk: 1.3).[3]

Doubts were also emerging around the cardioprotective effects of hormone therapy. The Heart and Estrogen/Progestin Replacement Study (HERS), published in 1998, examined the use of hormone therapy in women who had already suffered a cardiac event.[4] It not only showed an increased rate of thromboembolism in those using hormone therapy but, more alarmingly, an increased rate of deaths in women in the treatment arm during their first year of treatment. By the late 1990s most clinicians had incorporated these

IN SUMMARY

- **The promotion of a healthy lifestyle and reduction of risk factors for heart disease and osteoporosis form an integral part of an overall approach to menopause management.**
- **Hormone therapy remains the most effective way of managing vasomotor symptoms such as hot flushes, and there is no evidence that the use of combined hormone therapy for less than five years is associated with an increased risk of breast cancer.**
- **There are few risks associated with the use of topical vaginal oestrogen, and its more widespread use has the potential to reduce many of the urogenital symptoms common in older women.**
- **There is now a range of therapies available for the management of osteoporosis; these should be tailored to the particular needs of the woman seeking treatment.**
- **Although many women regard complementary therapies as safer alternatives to conventional medical treatments, there is conflicting evidence for their effectiveness and long term safety.**

Table 1. The Women's Health Initiative study: key findings[5,6]

Combined hormone therapy

The Women's Health Initiative (WHI) study was a randomised, placebo-controlled trial, with 16,608 women enrolled in the arm of the trial comparing combined continuous hormone therapy (conjugated equine oestrogens, 0.625 mg/day, and medroxyprogesterone acetate, 2.5 mg/day) with placebo.[5] This arm of the trial was ceased prematurely after 5.2 years because the preset limits on breast cancer incidence were reached. Compared with those on placebo, for every 10,000 women on combined hormone therapy per year there were:

- eight more cerebrovascular accidents
- eight more cases of pulmonary embolism
- eight more cases of breast cancer
- seven more coronary heart disease events
- six fewer cases of colon cancer
- five fewer cases of hip fracture (similar for spinal fracture)
- a statistically nonsignificant reduction in uterine cancer

Unopposed oestrogen therapy

A further 10,739 women were enrolled in the arm of the trial comparing conjugated oestrogen alone with placebo. This arm was ceased in 2004.[6] Compared with those on placebo, for every 10,000 women on this regimen per year there were:

- 12 more cases of cerebrovascular accidents
- no significant change in cases of pulmonary embolism
- no significant change in cases of breast cancer
- no significant change in cases of coronary artery disease
- six fewer cases of hip fracture (similar for spinal fracture)

DAVID OLIVER, TAXI

Figure 1. For 30 years, hormone therapy was widely promoted to menopausal women and their physicians. In 1966, Dr R. Wilson wrote of its wonders, stating 'When you see a woman of 60 looking and acting like 40, chances are that she is one of the lucky ones who have benefited from the new techniques o f menopause prevention'.[1]

findings into their practice when counselling women regarding the risks and benefits of hormone therapy. But few were prepared for the impact created by the publication of the Women's Health Initiative (WHI) study in July 2002,[5] when headlines urged women to cease hormone therapy immediately.

The WHI study has been criticised on the basis that it examined only one therapeutic regimen, and that it was not truly a primary prevention study due to the age and pre-existing medical conditions of many of those enrolled. Some statisticians have also suggested that, because of the number of variables examined, the study required a different statistical analysis from the one used by the researchers. However, despite these limitations the WHI study was a very large, randomised, controlled trial, providing high level medical evidence, and there is no doubt that its findings have profoundly influenced medical practice. The key findings of the study are summarised in Table 1.[5,6]

The more recently published Million Women Study also showed an increased risk of breast cancer in women using a variety of hormone therapy regimens and delivery systems.[7] The design of this study meant that it carries less evidentiary weight than the WHI study, and the validity of the statistical analysis used in this study has been widely questioned.

With the passing of some time since the publication of both these study findings, we may now be in a better position to assess more accurately the role of hormone therapy in the management of menopause. To this end, a consensus statement by Australian experts was developed in August 2004, but only the broadest of principles were articulated. Based on the recommendations

of these experts and those of various specialist menopause clinics, a suggested approach, more clinical in its emphasis, is proposed in the box on this page.

General advice for menopausal women

Hormone therapy is merely one component of effective menopause management, and an explanation of the expected symptoms and physiological changes is an integral part of therapy. For some women avoidance of known vasomotor triggers, such as hot drinks and spicy foods, may be all that is required. Also important is advice on the benefits of exercise in maintaining bone strength and cardiovascular fitness.

Menopausal women should be advised to control their intake of fats and simple carbohydrates since weight gain is an issue for many. Alcohol intake of more than two standard drinks per day is an independent risk for breast cancer and is also a factor in weight gain. Menopausal women should have the equivalent of three to four serves of calcium rich foods per day or use calcium supplements to make up their intake to the recommended 1000 to 1500 mg daily.

Exposure of the face and arms to the sun for 30 minutes a day will provide enough vitamin D to maintain bone strength. Vitamin D deficiency is not uncommon in older age groups and may be associated with loss of muscle tone and balance as well as bone strength. One study has suggested that adequate vitamin D supplementation has the potential to reduce fracture risk in the general community by up to 30%.[8]

It is claimed that menopausal symptoms are less troublesome in societies where there is a high intake of plant-derived phyto-oestrogens such as soy, and a number of women have sought to increase their intake of these at menopause. Although some studies do indicate a reduction in blood pressure and an improvement in the HDL/LDL ratio in those on a diet high in soy products,[9] most studies have been less convincing in demonstrating any long term improvement in menopausal symptoms. It is also questionable whether adopting such a diet in one's fifties rather than it being a lifelong habit is likely to offer the same therapeutic benefits.

Managing menopause: clinical guidelines*

- The control of menopausal symptoms remains the best indication for the use of hormone therapy.
- Short term use (less than five years) of combined therapy does not appear to increase the risk of breast cancer and there is no evidence that oestrogen-only therapy does so even with longer term use.
- It is advisable for a woman to have a breast examination and mammogram before commencing hormone therapy, and to consider annual mammography while using it.
- After four to five years of hormone therapy the risks and benefits of the treatment should be reviewed. At this time, it is reasonable to try reducing the dose gradually with a view to withdrawing therapy. If symptoms persist, therapy could be recommenced with the lowest dose that controls symptoms. Although not evidence-based, some authorities are recommending the use of a levonorgestrel IUD as the progestogen component of hormone therapy in the hope that such a regimen may reflect the risks of oestrogen-alone rather than those of combined hormonal therapy.
- In younger women who have undergone an early menopause, reassessment of the risks and benefits of treatment should be made four to five years after the average age of menopause in Australia, which is 51 years. Despite a lack of direct evidence, it is assumed that in these women the benefits of the earlier hormone therapy are greater and the risks smaller than those shown in the WHI study, since treatment before the average age of menopause brings their hormone exposure levels only to those of the general female population.
- At present, osteoporosis remains an indication for hormone therapy, particularly in symptomatic women. However, its long term use is more controversial. After five years' use other treatments for osteoporosis should be considered.
- There is at present no convincing evidence for or against the use of complementary or natural hormone therapies for menopausal symptoms.

* Adapted with kind permission of Professor Rod Baber of the Menopause Unit at Royal North Shore Hospital, Sydney, from the clinical guidelines he developed following the publication of the findings of the Women's Health Initiative study in 2002.

Managing vasomotor symptoms

It is estimated that up to 80% of women experience vasomotor symptoms such as hot flushes and night sweats around the time of menopause, with about one-third of these rating their symptoms as impacting significantly on their lives. For most women these symptoms improve over the first few years, but 25% of women will still be experiencing vasomotor symptoms into their sixties, and in 10% they will persist into their seventies.

A large number of randomised controlled trials have demonstrated the effectiveness of oestrogen therapy in alleviating vasomotor symptoms, and this is undoubtedly the best indication for hormone therapy. However, it should always be undertaken in conjunction with the general lifestyle advice described above.

There are also some women who are unsuitable for hormone therapy. Contraindications to the use of hormone therapy are listed in Table 2.[10,11]

Tailoring hormone therapy

When the decision is made to commence hormone therapy, the approach to treatment will be influenced by whether the woman has had a hysterectomy. Oestrogen therapy is usually all that is required for women who have had a hysterectomy since progestogens are added primarily to reduce the risk of endometrial hyperplasia and carcinoma.

Therapy is also influenced by the stage at which the woman presents. Symptomatic perimenopausal women are often best managed on a low dose combined oral contraceptive pill, provided that there are no contraindications to its use. These women continue to experience irregular ovulatory cycles and the pill usually provides better cycle control than does hormone therapy. However, they may require additional oestrogen supplementation during the placebo week to prevent vasomotor symptoms at this time. This is probably achieved most easily by the use of a seven-day oestrogen patch.

If the last menstrual period occurred less than 12 months previously, cyclical hormone therapy is indicated. This induces regular withdrawal bleeding. After 12 to 18 months the development of a more atrophic endometrium allows for continuous hormone therapy use. This has the advantage of avoiding the withdrawal bleeds induced by cyclical therapy and is generally preferred by most women. Similarly, tibolone (Livial) should also be avoided in the first 12 months since there is a high incidence of irregular bleeding if it is started before the endometrium is adequately atrophic.

A brief list and commentary on the hormone therapy preparations used in Australia and the alternative delivery systems is given in Table 3. It should be noted that the PBS generally requires that oral preparations should be used as first line therapy before benefits will be considered for alternatives such as patches or nasal sprays.

Other medical therapies for vasomotor symptoms

In women in whom hormone therapy is contraindicated, or who choose not to use it, selective serotonin re-uptake inhibitors (SSRIs) such as fluoxetine and venlafaxine (Efexor) have been shown in trials to reduce the number and severity of hot flushes by up to 60%.[12] (SSRIs are not available on the PBS for this indication.) Clonidine (Catapres) and high dose progestogens also seem to be effective at reducing troublesome vasomotor symptoms in some women, but side effects tend to limit their widespread use.

Urogenital symptoms

Four to five years after menopause, vasomotor symptoms settle for most women but urogenital symptoms such as vaginitis, dyspareunia, cystitis and incontinence may emerge as a problem. Pooled data from six randomised controlled trials have shown that oestrogen improves urogenital symptoms regardless of the route of administration or whether systemic or local therapy was used.[13]

Local vaginal oestrogen therapy, in the usual regimen of two to three times weekly, is not absorbed in significant quantities to cause the endometrial hyperplasia associated with unopposed systemic oestrogen and, therefore, additional progestogen is not required. There are minimal risks associated with its use, and it is the treatment of choice in all women whose primary symptoms are urogenital. As a therapeutic option it remains very much underused in Australia, particularly in older women troubled by recurrent urinary tract infections and incontinence. Its routine use should also be considered before cervical screening in all postmenopausal women not using systemic hormone therapy because it greatly reduces the incidence of atypical and unsatisfactory smears.

Preparations containing oestradiol are more potent and, therefore, will provide a more rapid clinical effect. Vaginal tablets tend to be better tolerated than pessaries and creams since they result in less vaginal discharge after use.

Table 2. Contraindications to hormone therapy

Absolute contraindications

- Previous oestrogen-dependent neoplasms: endometrial, ovarian and breast. It should be noted that the effect of hormone therapy use in women who have recovered from breast cancer remains controversial, with some studies indicating an increased risk of recurrence but others failing to demonstrate this.[10,11]
- Serious liver disease
- Ischaemic heart disease

Relative contraindications

These factors necessitate individualised decision-making and closer patient supervision:

- Diabetes
- Hypertension
- Risk factors for ischaemic heart disease
- Past history of thromboembolism
- Significant uterine fibroids

Osteopenia and osteoporosis

There is a sharp acceleration in bone loss in the first five years after menopause and adequate vitamin D and calcium levels and exercise are obviously integral in an overall approach to the management of bone loss. The WHI study provided the first solid evidence that hormone therapy actually reduces the risk of hip and spine fractures. At present, osteoporosis remains an indication for hormone therapy provided the woman has no other medical condition or family history that would make this an unacceptable risk. Oestrogen therapy is also the only treatment for osteoporosis subsidised by the PBS unless the woman has had a documented prior fracture.

In those women who have had a previous fracture, the bisphosphonates should be considered first-line therapy. Alendronate sodium (Fosamax) is the most extensively studied of this group and the most widely used in this country. These drugs are potent inhibitors of bone resorption, and treatment has been shown to reduce the rate of a subsequent spinal fracture by 50%.[14] Gastrointestinal disturbance is the most common side effect seen in those using bisphosphonates. This is no more of a problem with the use of the single weekly dose now advocated than with the daily doses used in the past.

Raloxifene (Evista), a selective oestrogen receptor modulator, is another treatment option for women who have, or who are at risk of, osteoporosis; however, this is available only on private prescription. It reduces the risk of spinal fracture by 65% but not the risk of fracture at other sites.[15] Unlike conventional hormone therapy, it has been shown to reduce the risk of breast cancer in users, but it has the same risk of thrombosis

Table 3. Hormone therapy preparations available in Australia

Oestrogens

Oral

- Piperazine oestrone sulfate (Genoral, Ogen)
- Oestradiol (Zumenon), oestradiol hemihydrate (Estrofem) and oestradiol valerate (Progynova). Oestradiol is also available in combination with norethisterone acetate (Kliogest, Kliovance, Trisequens) or dydrogesterone (Femoston). Oestradiol valerate is also available in combination with cyproterone acetate (Climen).
- Oestriol (Ovestin)

The above preparations vary in potency and potential side effects.

- Conjugated equine oestrogens (Premarin). This preparation, derived from the urine of pregnant mares, contains several oestrogenic compounds and has a long half-life. It may be useful in women whose symptoms are resistant to other forms of oestrogen therapy. It is also available in combination with medroxyprogesterone acetate (Premia, Provelle 28).

Subcutaneous

- Oestradiol implants (Oestradiol Implants). Long acting oestrogen therapy used mainly in women who have had a hysterectomy; women with an intact uterus are required to use progestogen therapy for many months after the implant has ceased to be effective for symptom relief because of continuing effects on the endometrium.

Transdermal

- Oestradiol gel (Sandrena), cream (Natragen Cream, available only in Western Australia) and patches (oestradiol alone: Climara, Dermestril, Estraderm, Femtran, Menorest; or combined with norethisterone acetate: Estalis, Estracombi). More constant absorption may mean fewer side effects than with oral medication. May be a safer option than oral oestrogens in women with a past history of thrombosis.

Intranasal

- Oestradiol hemihydrate (Aerodiol). Claimed to be less likely to cause mastalgia than oral medications.

Vaginal

- Oestradiol tablet (Vagifem)
- Oestriol pessaries and cream (Ovestin).

Progestogens

Oral

- Medroxyprogesterone acetate (Medroxyhexal, Provera, Ralovera). Has relatively poor endometrial suppression, requiring higher doses for good cycle control. This may lead to higher incidence of progestogenic side effects and be associated with a less favourable lipid profile. As mentioned above, is available in combination with conjugated equine oestrogens (Premia, Provelle 28).
- Dydrogesterone (Duphaston). Also available in combination with oestradiol (Femoston).
- Norethisterone acetate. More favorable effect on lipid profile. Available in combination with oestradiol (Kliogest, Kliovance, Trisequens).
- Cyproterone acetate (Androcur). Antiandrogenic effects useful in the management of menopausal hirsutism and alopecia. Also available in combination with oestradiol (Climen).

Patches

- Norethisterone acetate. Available in combination with oestradiol (Estalis, Estracombi).

Intrauterine

- Levonorgestrel-bearing IUD (Mirena). Local delivery of progestogen means maximal endometrial protection with minimal systemic side effects. Theoretically the use of such a device as the progestogen component of hormone therapy may mimic the benefits of oestrogen-only hormone therapy. This device is not PBS listed for this indication.

Tibolone

- Tibolone (Livial) metabolises to compounds with oestrogenic, progestogenic and androgenic effects. Reduced local effect on breast tissue usually results in less mastalgia. The androgenic component may lead to favourable effects on libido and sense of wellbeing.

and is completely ineffective against vasomotor symptoms.[16]

Androgens in menopause

Androgen levels have been shown to decline in women once they reach the mid-thirties and can lead to symptoms such as decreased libido and a lack of energy. An increasing number of women have been prescribed androgens as a means of combating these symptoms, but since these therapies do have potential side effects they should never be used indiscriminately.

One problem is that the assays used to determine normal androgen levels in women are not particularly accurate or sensitive. Another is that only 1% of circulating androgens are not bound to serum proteins, such as sex hormone binding globulin (SHBG), and are therefore free to act at the androgen receptor. It is important, therefore, to assay not only testosterone level, but also the free androgen index, which measures the amount of unbound active androgens circulating. Both the combined oral contraceptive pill and the oestrogens used in hormone therapy increase SHBG levels and, therefore, can make androgen deficiency symptoms worse.

Some experts suggest that if a woman has symptoms of androgen deficiency and androgen levels in the lower third of the normal female range, it may be worth considering androgen therapy. There are currently no such preparations licensed for use in women throughout Australia, although a 1% testosterone cream (Andro-Feme Cream) is available in Western Australia. Professional singers should be advised never to use these preparations since they can permanently affect the voice timbre.

Conventionally, androgens have only been used in women who are also using progestogen therapy since there have been concerns that testosterone, like oestrogen, may have the potential to induce endometrial hyperplasia. This is by no means certain, however, and several studies are investigating this further.

Alternative and complimentary therapies

Although widely used, there is no convincing evidence for the effectiveness of red clover extract over placebo for the management of hot flushes.[17,18] While evidence for the effectiveness of black cohosh is more convincing, this therapy should be used in double the dose usually recommended to achieve a significant improvement in the number and severity of flushes.[19] Transdermal progesterone cream has been recommended as a menopause treatment, but a small randomised controlled trial has shown no improvement in vasomotor symptoms, mood, libido or lipid levels.[20]

The use of 'bio-identical' hormone therapy has also been widely promoted in Australia. It is claimed that the active ingredients for these preparations are produced only from natural ingredients such as wild yam. It is worth noting that all conventional hormone therapies, except conjugated equine oestrogens, were originally derived from natural ingredients. The prescribed amount of active ingredient is generally combined with a flavoured delivery system, or troche, which is dissolved in the mouth. Alternatively, it can be made into a cream so that a measured amount is rubbed into the skin. The oestrogens used in these preparations include oestriol, oestradiol and oestrone. Proponents claim to be able to titrate the preparation to the woman's own individual hormonal needs, usually guided by salivary or blood estimations of the hormone being considered for supplementation. Oestrone predominance is often promoted as a benefit of such preparations since this is the oestrogen produced naturally in the highest amounts in the postmenopausal woman.

There are two main problems with such treatment protocols. Firstly, salivary levels of the hormones assayed are extremely variable and may not accurately reflect serum levels.[21] Secondly, enzymes exist in most steroid responsive organs that are capable of converting one form of oestrogen to another. This means that the eventual tissue levels achieved may not in fact reflect the initial proportions given in the prescribed preparation. Other hormones such as progesterone, testosterone, and DHEA may be added to the mix to achieve the desired therapeutic effect. These therapies are often promoted as a safer alternative to conventional hormone therapy. Although there is no doubt that many women obtain relief of menopausal symptoms while using them, limited evidence is available for the efficacy of these preparations and even less for their long term safety. There is also no evidence at the present time that bio-identical hormone therapy has the ability to prevent the development of osteoporosis.

Conclusion

The findings of the WHI study have underlined the need to regard every menopausal woman considering hormone therapy as an individual, with her own unique set of needs, desires and potential risks and benefits. It has also emphasised the need to involve the woman herself in the discussion and decision making around hormone therapy. But then hasn't the astute clinician always recognised the value of such an approach? MT

A list of references is available on request to the editorial office.

DECLARATION OF INTEREST: Dr Foran has been involved in developing and delivering educational programs and consumer product information for various pharmaceutical companies, including Wyeth, Schering, Organon and Pfizer, and has on occasions accepted sponsorship from such companies to attend or present at clinical meetings. She has also been a named investigator on several clinical trials on contraceptive and hormonal therapy preparations sponsored by Organon.

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