REVIEW

Hormone replacement therapy: the way forward

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Introduction

Over the last few years, health professionals and their patients have been inundated with information regarding the potential benefits and risks of hormone replacement therapy (HRT). Much information is available from a variety of sources; some, such as peer-reviewed journals and the British Menopause Society, are more reliable than others, for example, the popular press and the Internet. The press often sensationalises the risks of HRT and ignores the benefits. This has left the average health professional in a very difficult position as to what to advise their patients and has left patients bemused as to where they should turn in order to obtain reliable advice. This review attempts to clarify the decision-making process at a time of controversy.

Hot off the press

Breast

Recent prospective randomised data from the USA Women's Health Initiative (WHI) combined HRT study[1] have confirmed the previous observational data from the Imperial Cancer Research Fund[2] (now Cancer Research UK) regarding the risks of breast cancer with HRT. The WHI study was stopped prematurely by the study regulatory board after running a mean of 5.2 rather than 8.5 years. This was because it was deemed that the risk versus benefit statistic was exceeded due to an excess of breast cancer and coronary heart disease (CHD) cases in the treatment arm (continuous combined conjugated equine oestrogens 0.625 mg and medroxyprogesterone acetate 2.5 mg). The data from the WHI study suggested an excess risk of breast cancer with combined hormone therapy of 5, 8 and 13 cases per 10 000 women per year for the 50–59, 60–69 and 70–79 years age groups, respectively. A further analysis of the data this year detected a hazard ratio for breast cancer of 1.24 ($p>0.001$) for an average of 5.6 years exposure to HRT.[3]

This was followed by further bad news from the Million Women Study (MWS),[4] a questionnaire survey by Cancer Research UK of women attending the National Health Service breast screening programme. This study reported, in a blaze of publicity, an increased risk of breast cancer diagnosis with all HRT regimens [relative risk (RR) 1.66; 95% CI 1.58–1.75]; there was a statistically significantly higher risk with oestrogen/progestogen HRT (RR 2.00; 95% CI 1.91–2.09) than that seen with oestrogen alone (RR 1.30; 95% CI 1.22–1.38]) or tibolone (RR 1.45; 95% CI 1.25–1.67). This was reported by the press as a doubling of risk of breast cancer with HRT, failing to mention the absolute risk in terms of actual numbers of cases. For oestrogen-only therapy it represented an additional 1.5 per 1000 cases after 5 years of use, and for oestrogen/progestogen therapy an additional 6 per 1000 cases after 5 years of HRT use. In women aged 50–64 years, whose baseline risk is 32 in 1000, this translated to 33.5 per 1000 and 38 per 1000 cases, respectively.

The higher risk estimates from the MWS compared to the WHI were probably due to the observational nature of the MWS. This is likely to have underestimated duration of usage of HRT, as it did not count years of HRT exposure from baseline (filling in of the questionnaire) to breast cancer reporting on the UK cancer registry. Also, bearing in mind the natural biology of breast cancer development, it is unlikely that the cancers diagnosed after 1 year had developed de novo – it is more likely that these cancers were missed by mammography at baseline and that HRT had acted as a promoter rather than an initiator. Although the MWS reported an increase in breast cancer mortality, this was of borderline significance (RR 1.22; 95% CI 1.00–1.48; $p = 0.05$); the absence of tumour pathology details also made it difficult to draw any definitive conclusions on this issue. Numerous authors have expressed their reservations regarding the limitations of both the MWS and WHI data.[5–9]

Cardiovascular (CHD and stroke)

Initial cardiovascular data from observational studies suggested a 50% reduction in risk of CHD in HRT users. The HERS[10] secondary prevention study, however, did not confirm these data in women started on HRT for secondary prevention of CHD and the WHI did not show any benefit in a primary prevention setting. In fact, WHI suggested that after a mean usage of 5 years there was an excess of heart disease cases in the active treatment arm of the study compared to placebo. The study also showed an excess of stroke cases.

As is the situation with breast cancer, the cardiovascular risks in WHI were small, equating to an extra 7–8 cases per 10 000 women per year. These were largely accounted for by an excess of cases in the first couple of years of use, probably due to an initial prothrombotic effect of the preparation used. Sadly, the press presented the data as percentage increases in risk, which sounded far more dramatic than the absolute numbers (e.g. a 29% increase in risk of heart disease). The increase in risk for stroke was clearly age-related (i.e. age 50–59 years, 4 cases; 60–69 years, 9 cases; and 70–79 years, 13 cases per 10 000 women per year).

In view of the data from HERS and WHI, the guidelines from the American Heart Association,[11] the US Food and Drug Administration and the Medicines and Healthcare products Regulatory Authority (MHRA) were that HRT should not be used for primary or secondary prevention of CHD.

Alzheimer's disease

Observational and case-control data suggested a protective effect of oestrogen for the prevention of Alzheimer's disease. These data have not been supported by the recent randomised controlled data from the WHI, which showed that there was a two-fold increase in risk of all-cause

dementia.[12] However, the WHI data were from a older age group of women (average age 63 years, 21% of women aged over 70 years) and it may be that the 'window' for Alzheimer's disease prevention is in a much younger age group. Also, it may be that the WHI data reflected cases of multi-infarct dementia rather than Alzheimer's dementia. This could have resulted from the known prothrombotic effect of oral HRT.

Endometrial cancer

Although unopposed and sequential combined HRT appear to increase endometrial cancer risk,[13] continuous combined HRT appears to confer a small protective effect as witnessed by the trend towards protection in the WHI (RR 0.83; 95% CI 0.47–1.47) and other studies.[1,14]

Venous thromboembolism

It is clear from studies including HERS and WHI that there is a 2–3-fold increase in risk of venous thromboembolism (VTE) with oral HRT, with the greatest risk occurring in the first year of use. However, recent data suggest that transdermal therapy may not increase the risk of VTE.[15] There is biological plausibility for this; avoidance of hepatic first-pass metabolism minimises adverse effects on clotting factors and the fibrinolytic system.

Encouraging findings

For many years, bone marker and bone density data suggested that HRT had a beneficial effect on the skeleton. The data from the WHI study finally provided strong (randomised placebo-controlled) evidence for the gold standard outcome measure, i.e. prevention of fractures of the hip and spine (5 fewer cases per 10 000 women per year). The WHI also provided data confirming the beneficial effect of HRT in reducing the incidence of colorectal cancer (6 fewer cases per 10 000 women per year). As yet, there is still uncertainty as to the mechanism of action of HRT in reducing the risk of colorectal cancer.

The WHI controversy

The WHI study raised a number of questions that may remain unanswered if funding is not found for further long-term, randomised prospective studies using different preparations in healthier populations. Sadly, the Medical Research Council's primary prevention trial (WISDOM), using the same preparation as WHI, was prematurely terminated after much effort and expenditure, when it was realised that no new answers would be provided by this trial.

A fundamental question raised by WHI is whether the effects seen are related to the specific type of HRT used (continuous combined conjugated oestrogens and medroxyprogesterone acetate) or whether they are true for all HRT. It is likely that the effect on breast cancer is a class effect for combined HRT but this may not be the case for cardiovascular risk.

A further question is whether the adverse effects seen are related to the fact that both the HERS and WHI studies were conducted in a population of women who were too old when they started treatment (average age 63 years, 21% of women aged over 70 years in the WHI study). Most women in the UK commence HRT in their 50s to treat symptoms, not in their 60s and 70s. The risks of stroke in the WHI study were clearly age-dependent, supporting the hypothesis that a study in a younger age group would give different results. As with Alzheimer's disease, it is possible that there is a window of opportunity for giving women HRT to reduce their risk of CHD. This is likely to occur at a much younger age than the women included in the WHI study. A recent paper suggested that cardiovascular risk may increase in women who are still menstruating regularly; women with an elevated follicular phase follicle-stimulating hormone (FSH) were found to have higher lipid and lipoprotein levels compared to women with normal FSH levels.[16]

Although the WHI was designed as a primary prevention study of 'healthy women', 30% had a body mass index of 30 or above and 7% had pre-existing heart disease. Interestingly, if one controls for the cases in WHI in which there were abnormal lipids and lipoproteins at baseline, the excess risk for CHD with HRT is removed.

In contrast to the WHI, recent randomised pilot data from the National Heart and Lung Institute in women commenced on an alternative form of HRT after myocardial infarction have suggested a reduction in risk in the active arm of the study. A larger study is planned as a result of these data.[17]

Another question is whether the adverse effects seen in the WHI study were due to the oestrogenic or progestogenic component of the HRT. There are more than 8000 hysterectomised patients continuing on unopposed oestrogen until 2005; this suggests that the risks are lower in this group of patients and therefore probably due to the progestogen rather the oestrogen, as suggested by the MWS.[18]

Finally, there was no difference in mortality between the two groups and in absolute numbers; the risks were very small, total major adverse events occurring in less than 1% of the treatment group.

The way forward

'Official' advice

How are health professionals supposed to react to these data and advise their patients? Guidance from the MHRA, the Committee on Safety of Medicines (CSM)[19,20] and the American Heart Association advises that HRT should not be recommended for primary or secondary prevention of heart disease. It is recommended that HRT be used only for symptom relief and alternatives should be considered in the long term for prevention of osteoporosis. Annual reappraisal of HRT use should be carried out, weighing up the pros and cons on an individual patient basis. The advice from the Royal College of Physicians of Edinburgh consensus statement is that the lowest effective dosage of HRT should be used. However, the British Menopause Society consensus statement[21] advises that prescribing habits need not be changed by the recent studies because HRT use in the UK was already primarily for symptom relief rather than primary or secondary prevention.

HRT preparations

There have been significant advances in HRT preparations in the last 30 years. It behoves us to keep up to speed with genuine advances in HRT technology so that we can provide the most cost-effective methods for our patients that, in accordance with the best evidence that we have, minimise the risks and maximise the benefits.

There is general agreement now that we should be starting with the minimum effective dosage of oestradiol and progestogen – typically 1 mg oestradiol orally, 50 µg transdermally or 25 mg implanted oestradiol. Exceptions to this 'low-dose rule' are women who suffer premature ovarian failure or who have severe osteoporosis.

There have been significant improvements in oral preparations, some of which now contain micronised 17β-oestradiol and more cardiovascular-friendly progestogens. The low-dose continuous combined preparations have been particularly useful in maximising efficacy of therapy and ensuring compliance by minimising side effects.

If we adhere to the principle that we should try to reproduce the most physiological state possible with a 2:1 oestradiol:oestrone ratio then we should avoid the oral route altogether. There are particularly useful 7-day transdermal systems containing both oestrogen and progestogen that can be used either sequentially or as continuous combined HRT. Oestradiol can also be given transnasally in a 'pulsed' fashion, which is thought to maintain the benefits whilst minimising the side effects of chronically elevated oestrogen (e.g. breast tenderness). It is also available as a transdermal gel and as a vaginal ring delivering oestradiol systemically for 3 months.

The MWS has shown clearly that there is an excess risk of breast cancer using oestrogen and progestogen HRT compared to oestrogen alone. It has therefore been suggested that even non-hysterectomised women should be treated with oestrogen-only preparations. After 10 years of oestrogen/progestogen HRT there would be an extra 19 per 1000 cases of breast cancer and no cases of endometrial cancer. After 10 years of oestrogen alone in non-hysterectomised women there would be an extra 5 cases per 1000 of breast cancer and 10 cases per 1000 of endometrial cancer (total 15 per 1000 cases). From this simplistic viewpoint it would seem reasonable that all women (even those with a uterus) should receive oestrogen alone. However, this does not take intro account the excess cases of endometrial hyperplasia and bleeding problems. These would generate excessive investigations such as endometrial sampling, hysteroscopies and even hysterectomies, which would not be without their own morbidity and mortality.

In view of this fact, there is a strong tide of opinion (with which the author concurs) that progestogenic opposition should continue to be used. However, it is imperative that we continue to seek improved ways of administering progestogen to protect the endometrium while avoiding progestogenic side effects and minimising effects on breast tissue. The use of vaginal and intrauterine progestogens and natural progesterone should be commonly used alternatives for the progestogen-intolerant woman.[22] However, we still lack data as to the risk of breast cancer in women using oestrogen with a levonorgestrel intrauterine system as progestogenic opposition.

Alternatives

Women are looking for alternatives to HRT but many are ineffective and, at worst, some are dangerous. Further data and stricter regulation are required for these preparations. Phytoestrogens, such as red clover, are producing encouraging results in some studies. However, even with the advent of selective oestrogen receptor modulators, we still do not have an agent that will treat symptoms as well as act as a primary and secondary prevention agent in the long term. Although the tissue-selective agent tibolone gives minimal stimulation of breast tissue, the MWS suggested a small excess risk of breast cancer with this preparation. It is possible this was due to prescribing bias (higher-risk women preferentially put on this preparation) so the results of long-term prospective randomised data, due to report in 2 to 3 years from now, are awaited to clarify the issue. In the future, targeted agents that are able to switch on receptors in tissues where this is desirable and avoid receptors in tissues such as the breast and endometrium will undoubtedly succeed traditional HRT.

Duration of therapy

According to WHI, the risk of breast cancer increases only after 4 years of use, but the MWS showed a significantly increased risk after only 1 year. As mentioned earlier, taking the natural biology of breast tumours into account, then the cancers appearing at 1 year in the MWS must have been present at baseline, with HRT acting as a promoter rather than an initiator.

The editorial in the *Lancet* that accompanied the MWS publication suggested that duration of therapy should be limited to 3–6 months.[23] However, menopausal symptoms often return when HRT is ceased, even after many years of use. If the underpinning principle of HRT is that it should be used to improve and maintain a good quality of life, it is difficult to argue that women should have imposed on them an arbitrary deadline to cease therapy and therefore its benefits. Duration of therapy requires careful judgement of benefits and risks on an individual basis.

Conclusions

It is difficult for the menopause specialist, let alone the average clinician, to keep up with the rapidly changing data regarding HRT. With every new study there appears to be a change in advice given by the regulatory agencies. In the author's opinion current best practice should involve the following:

1. Advising women that the main indication for use of HRT is for symptom relief rather than for prevention of long-term problems.
2. Individualisation of therapy with consideration given to the use of newer agents with the aim of minimising side effects whilst maintaining benefits.
3. Starting with low-dose HRT and increasing the dose if necessary to achieve symptom relief.
4. The avoidance of rigid cut-offs in duration of therapy but with regular reappraisal (at least annually) of the benefits and risks for each individual user of HRT.

We must not underestimate women's desire for a high quality of life during the menopause. Women will continue to demand HRT or an effective alternative for their symptoms. It is our duty to strive to provide the best therapy for women to achieve this goal.

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OVERVIEW

The laboratory diagnosis of common genital viral infections

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Background: epidemiology and clinical features

The incidence of viral genital infections has risen considerably in recent years. Genital warts, a clinical manifestation of genital human papilloma virus (HPV) infection, is the commonest sexually transmitted infection (STI) in the UK and comprised 10% of all diagnoses made in genitourinary medicine (GUM) clinics in 2002.[1] There are over 90 subtypes of HPV, some are 'high risk' with oncogenic potential, the most frequently occurring of these are types 16, 18 and 32. However, the subtypes that result in the vast majority of genital warts are the 'low risk' types 6 and 11. Subclinical infection is extremely common, with up to 46% of sexually active young women found to be positive for HPV by polymerase chain reaction (PCR) DNA amplification testing of cervical and vulval specimens.[2] In younger women most HPV infections are transient and resolve spontaneously, but in older women they may be more persistent.[3,4] Clinically apparent genital HPV infection most often appears as single or multiple warty lesions in the genital areas. Another common cause of small, fleshy growths in the genital area is molluscum contagiosum, a pox virus. These can have a similar appearance to warts but the lesions have a characteristic umbilicated centre. In genital areas they are usually sexually transmitted. However, in children they are commonly observed on non-genital sites such as the hands, where they are not sexually transmitted, and in immunosuppressed adults they may cause problematic facial lesions.

Herpes simplex virus (HSV) infection is the commonest ulcerative STI. In common with HPV infection, HSV infection is frequently subclinical, but when symptoms do occur they include painful blisters or ulcers in the genital area with or without regional lymphadenopathy and systemic symptoms. Subclinical shedding of the virus from genital skin occurs even in the absence of symptoms[5] and plays a major role in transmission of the virus. Genital herpes is the result of infection with HSV type 2 or, with increasing frequency, HSV type 1 (the usual cause of oral herpes, or cold sores), which now accounts for nearly 50% of all cases of genital HSV infection. Between 1972 and 2002, the number of genital HSV diagnoses made at GUM clinics increased two-fold in women and nine-fold in men, with the highest rates of infection observed in those aged 20–24 years.[1]

Diagnosis of genital HPV infection

Diagnosis of HPV infection is usually by clinical observation, but if in doubt a biopsy may be taken for histology. For the purposes of clinical research HPV identification may be undertaken, but this is not usually available or performed in routine clinical practice.

HPV cannot be grown in vitro and so is usually detected by nucleic acid amplification tests. As HPV is an intracellular organism cells may be exfoliated by brushing, or alternatively by biopsy and placed in transport medium. Dot blot assay is a simple method of detecting viral nucleic acid from cells with labelled probes binding to the DNA. Southern blot technique involves separation of HPV DNA fragments extracted from cells by gel electrophoresis followed by hybridisation with labelled probes on a nitrocellulose membrane. In situ hybridisation is usually performed on tissue sections using DNA probes for hybridisation. PCR and hybrid capture II are further methods of nucleic acid detection, and hybrid capture has been successfully used with urine specimens.[6] Serological tests have no value in clinical practice or screening.