Women's Health Concern

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HRT: What you should know about the benefits and risks

If you are thinking about taking Hormone Replacement Therapy (HRT) or wondering if you should be coming off it, or going back on to it, you will be aware that there continues to be debate about its safety.

Although there have been concerns raised about HRT and the potential risks to various aspects of women's health, more recently published findings show that although not entirely risk free, it remains the most effective solution for the relief of menopausal symptoms and is also effective for the prevention of osteoporosis. It may in certain age groups provide protection against heart disease.

This leaflet sets out the known facts about HRT. It summarises the results of studies regarding its safety and addresses the controversy that still surrounds it, together with current thinking about its suitability. It is free of medical jargon and written specifically for women wishing to know about HRT. It is also a helpful and balanced primer for GPs who do not specialise in menopause. Our medical advisory panel strongly recommends that you should discuss with your doctor both the benefits and the risks of HRT on an individual basis. We suggest that you take a copy of this leaflet with you – note that on page 5 of the printed leaflet there is a section for your questions or concerns. The types of HRT available are listed **below**.

Concerns over the safety of HRT – a history

HRT was first available in the 1940s but became more widely used in the 1960s, creating a revolution in the management of the menopause. HRT was prescribed commonly to menopausal women for the relief of their symptoms such as hot flushes, night sweats, sleep disturbances, psychological and genito-urinary problems – urinary frequency and vaginal dryness – and for the prevention of osteoporosis.

In the 1990s two of the largest studies of HRT users were undertaken, one clinical randomised trial in the USA [Women's Health Initiative (WHI)] and one observational questionnaire study in the UK [the Million Women Study (MWS)]. The published results of these two studies during 2002 and 2003 raised concerns regarding the safety of HRT. These safety concerns revolved around two main issues: 1) that the extended use of HRT may increase the risk of breast cancer and 2) that the use of HRT may increase the risk of heart disease.

The results of the studies received wide publicity, creating panic amongst some users and new guidance for doctors on prescribing.

After the results were published, the UK regulatory authorities issued an urgent safety restriction about HRT, recommending that doctors should prescribe the lowest effective dose for symptom relief, should use it only as a second line treatment for the prevention of osteoporosis, and advised against its use in asymptomatic postmenopausal women.

There remains widespread confusion and uncertainty amongst both doctors and HRT users. Many doctors stopped prescribing HRT and many women abandoned HRT immediately, with a return of their menopausal symptoms. The number of women taking HRT fell by 66%, which has not changed so that now after more than 10 years, there has been almost a generation of women who have mostly been denied the opportunity of improved quality of life during their menopausal years. The women studied in the WHI were North American women in their mid-sixties, often overweight and thus totally unrepresentative of women in the UK for whom HRT might be considered suitable. These would usually be around the age of the menopause, namely 45-55 years.

It should also be appreciated that, in a surprising turnabout, subsequent publication of the full WHI results showed the apparent increased risk for breast cancer was only found in those who had been on HRT before entering the study. In addition, whereas the authors claimed initially that there was no difference in effects with age, further analyses from both the combined HRT and oestrogen alone WHI studies have shown no increase in heart disease in women starting HRT within 10 years of the menopause. This about turn and retraction of some of the previous findings has received little publicity in the media. Furthermore, a large controlled trial from Denmark reported in 2012 has demonstrated that healthy women taking combined HRT for 10 years immediately after the menopause had a reduced risk of heart disease and of dying from heart disease. This report supports the concept of a 'window of opportunity' when HRT is started shortly after menopause, whereas the WHI study confirmed that starting HRT after the age of 60 years may increase the risk of heart disease.

Further information on the two studies (WHI and MWS) is given in a detailed summary **below**.

HRT today

The balance of benefit to harm always needs to be assessed but appears to have shifted favourably for HRT. Users can be assured provided:

- HRT is taken for the correct reasons, i.e. to alleviate the symptoms of the menopause. It has a role in the prevention of osteoporosis but long term use is often required.
- HRT is taken for only as long as necessary at the lowest effective dose
- HRT users are assessed by their GP at least once a year.

If women start HRT around the time of menopause the risk is very small, but there is only limited data for continued usage beyond the age of 60. It is not usually appropriate for women over 60 to be starting HRT, as the WHI study shows, the risks are increased, but this does not mean that women who started HRT earlier should have to stop it on reaching 60.

Many women seek advice on the effects of HRT on sexual activity and desire. Whilst there is no definitive answer, case studies indicate that the oestrogen in HRT can help maintain or return sex drive. But it will definitely help other menopausal symptoms such as vaginal dryness and pain with intercourse. If vaginal symptoms are the only problem, then the use of local vaginal oestrogen may be preferable. Separate factsheets on Sexual Health are available for download from the Women's Health Concern website.

Bio-identical hormones are hormone preparations which are identical molecules to those produced by the body. However, in practice the term is used for preparations made by compounding chemists which are claimed to be safer than "traditional" hormones used in hormone replacement therapy (HRT). In fact, some traditional HRT preparations are actually "bio-identical", using oestradiol 17-beta which is the natural human oestrogen, or using micronised progesterone capsules which is the natural human progesterone.

It should be obvious that any product which is a "bio-identical" hormone will carry the same benefits and risks as the HRT products produced by pharmaceutical companies and properly licensed for use, and there is absolutely no evidence that the bio-identical hormones are any safer than those used in traditional HRT. Indeed, they may be less safe – their production is not monitored by government drug regulatory authorities and thus their dosage may be inaccurate or inconsistent, their purity is certainly not guaranteed, and their safety is not tested as it is with approved HRT formulations.

The bio-identical hormones are often compounded following salivary hormone measurements and are therefore claimed to be "customised". The accuracy and usefulness of such tests are highly questionable. We would not recommend the use of bio-identical hormones that have not been licensed by the UK regulatory authorities, and indeed would strongly caution women against obtaining such products.

Types of HRT available

There are more than 50 types of HRT available: HRT can be given orally (tablets), transdermally (through the skin); subcutaneously (a long-lasting implant); or vaginally.

- Cyclical HRT mimics the normal menstrual cycle. Oestrogen is taken every day and progestogen for 12 to 14 days. At the end of each course of progestogen there is some bleeding as the body "withdraws" from the hormone and the womb lining (endometrium) is shed. Progestogen regulates bleeding and protects the endometrium from harmful pre-cancerous changes
- Oestrogen-alone HRT is normally prescribed to women who have had their womb removed (hysterectomy). The benefits of all HRTs are derived from oestrogen; progestogen is only necessary to protect the womb lining
- In continuous combined therapy HRT (CCT) combinations of an oestrogen and progestogen are prescribed continuously to achieve period-free HRT. Usually, women start on cyclical HRT and change to CCT later
- Tibolone is a synthetic form of period-free HRT which may have similar benefits to CCT. It is taken continuously in tablet form
- Long cycle HRT uses a formulation which causes withdrawal bleeds every three months instead of every month, and is most suited to women who suffer side effects when taking a progestogen. Its safety in long-term use with regard to the lining of the womb is questionable
- Local oestrogen, such as vaginal tablets, creams, pessaries or rings, is used for treating local uro-genital problems, such as dry vagina, irritations or infections. Progestogen can also be given locally to protect the lining of the womb.

In summary

Women wishing to start HRT should carefully discuss the benefits and risks of treatment with their doctor to see what is right for them, taking into account their age, medical history, risk factors and personal preferences.

For the majority of women who use HRT for the short-term treatment of symptoms of the menopause, the benefits of treatment are considered to outweigh the risks.

The lowest effective HRT dose should be taken, with duration of use depending on the clinical reasons for use.

HRT remains licensed for osteoporosis prevention and can be considered the treatment of choice for women starting treatment below age 60 years, and especially for those with a premature menopause.

Women on HRT should be re-assessed by their doctor at least annually. For some women, long-term use of HRT may be necessary for continued symptom relief and quality of life.

Many health centres and practices have a doctor with a special interest in postmenopausal health. These specialist GPs will know the up-to-date recommendations for prescribing HRT. They may also belong to the British Menopause Society, the professional partner to Women's Health Concern, and therefore have access to its latest literature, studies and training. However, if your family doctor does not have sufficient knowledge of the current situation concerning the benefits and risks of HRT and many have lost confidence in prescribing because of the recent scares, then it is your right to request advice from a local Menopause clinic or a specialist with known expertise in menopausal health.

HRT timeline

1965 HRT becomes available to women in the UK

1993 A clinical trial starts in the USA – the Women's Health Initiative – looking at the health effects on women taking either oestrogen-only HRT or combined HRT, compared to women taking an identical placebo

1996 A study starts in the UK, called the Million Women Study, collecting questionnaires on HRT use and its effects on certain issues of women's health

2002 WHI study stopped the combined (oestrogen and progestogen) HRT arm of the study prematurely in light of findings of safety issues with combined HRT – a small increased risk of breast cancer, heart disease, stroke and blood clots

2003 Million Women Study publishes findings

2003 Both doctors and HRT users are confused regarding safety issues. Many doctors advise their patients to come off HRT. Some women stop taking HRT immediately. Such actions were, and continue to be, unduly influenced by a high level of media interest which has tended to attract some health scare headlines

2004 WHI finishes the oestrogen-only arm of the HRT study, finding trends for beneficial effects on breast cancer and heart disease risk but a small increased risk of stroke

2003-2007 Amongst continuing health safety fears, HRT users fall from 2 million to less than 1 million in the UK

2004-2007 The investigators of WHI publish a further analysis of the trial which is an about turn on some of the findings published in 2002 and indicates that risks for certain safety aspects were over-estimated. These new findings also show the additional benefits of HRT use for those initiating HRT in the 50-59 age group, or for those less than 10 years past the menopause – trends to a lower risk from heart disease; a lower risk of death from any cause; no clear increased risk from stroke. They also show a general increased risk for those starting HRT after the age of 60, which is later than normal UK clinical practice

2012 Publication of Danish study of combined HRT use for 10 years in healthy women started shortly after menopause showing reduced heart disease and mortality

2012 Further report from MWS showing no increased risk of thrombosis (blood clots) with use of transdermal (skin patch or gel) oestrogen HRT

The two studies

The Women's Health Initiative (WHI) oestrogen plus progestogen trial

- From 1993 to 2002
- Studied over 16,600 women in the United States
- Participating women were aged 50-79, around 50% of whom were randomly chosen to take HRT and 50% to take a placebo (dummy)
- Looked at the effects that HRT had on heart disease and other aspects of women's health.

Publication of the preliminary findings 2002

Of those taking HRT there were:

- An increase in coronary events, stroke, breast cancer and vein blood clots, and a decrease in osteoporotic fractures and colon cancer
- The study was stopped three years early by the safety monitoring committee as a previously specified limit for breast cancer cases was exceeded and overall risks were thought to exceed benefits
- Subsequent publication of the full findings from the same WHI Study showed different effects. When the results were adjusted for other influencing factors, the apparent increased risk of breast cancer was only in those who had been on HRT before entering the study
- When the results were split down by age:
    - Those starting on HRT under age 60 may actually be protected by HRT in some health aspects

- Those starting on HRT over 70 don't accrue the same benefits and could be at certain increased risks.

The Women's Health Initiative (WHI) oestrogen alone trial

- From 1993 to 2004
- Studied over 10,700 hysterectomised women in the United States
- Participating women were aged 50-79, around 50% of whom were randomised to take oestrogen and 50% to take a placebo
- Looked at the effects that HRT had on heart disease and other aspects of women's health.

Publication of the preliminary findings 2004

Of those taking HRT there were:

- Increases in stroke and venous thrombosis (blood clots)
- No increase in coronary events
- No decrease in colon cancer, and a decrease in breast cancer and osteoporotic fractures
- The study was stopped just under two years early by the trial sponsor but not by the safety monitoring committee
- Publication of the full findings from the same WHI Study in 2007 again showed different effects when the results were split down by age:
- Those starting on HRT under age 60 may actually be protected by HRT in some health aspects
- Those starting on HRT over 70 don't accrue the same benefits and could be at certain increased risks
- In 2011 further evidence of reduced risk of breast cancer.

The Million Women Study (MWS)

- From 1996 to 2001
- One million women in the UK who were attending breast screening clinics as part of the NHS Breast Screening Programme were surveyed by questionnaire
- Participating women were over 50 years old
- Looked at the risks of breast cancer and other health issues in HRT users compared with non-users in a total of 828,923 women.

Published findings:

- Oestrogen-only HRT causes a small increase in the risk of breast cancer
- Oestrogen-only HRT causes a small increase in the risk of womb cancer
- Oestrogen-only HRT causes a small increase in the risk of ovarian cancer
- Combined HRT increases the risk of breast cancer more than oestrogen-only HRT
- Combined HRT reduces the risk of womb cancer
- The longer HRT is used, the higher the risk of breast cancer
- The risk of breast cancer disappears as soon as HRT is stopped

- No increased risk of venous thrombosis (blood clots) with transdermal oestrogen.

Shortcomings of the WHI and MWS studies and their findings

The publication of these results triggered an immediate response from experts through the British Menopause Society, the International Menopause Society and others, who considered that both the WHI and the MWS studies had shortcomings and so were flawed.

Issues with the studies:

- WHI looked at only one dose and type of combined HRT or oestrogen only HRT
- The dose used, whilst appropriate for younger menopausal women starting HRT, was considered by many experts as too high for older women
- The profile of the American women in the WHI study is very different from the women in the MWS. The American women tended to be much older (average age 63.2) than the women on HRT in the UK study, with two-thirds over the age of 60 and therefore would have a higher absolute risk of stroke, heart disease and breast cancer (which increases with age)
- The majority of the women in the study were overweight (average BMI of 28.5) and this is a recognised risk factor for heart disease and certain cancers, including breast cancer
- There were a substantial number of drop-outs from the study.
- MWS's methodology has been criticised. It was not a randomised controlled trial, where two groups of women are recruited and half given HRT and half a placebo. The women were self-selecting and self-reporting HRT users
- The MWS women were already having a mammogram so that may make them at higher risk for cancer (they may already suspect a lump, for instance) or more aware of potential cancer risks because they were taking HRT
- Follow-up was done by reports from national cancer registries, not by subsequent questionnaires, so changes in HRT use after initial registration were not recorded.

Women's Health Concern also expressed its concern at that time, wanting to ensure that decisions on HRT usage were based on fact. Today it is important that the medical profession and the media do not create the impression that these flawed studies should significantly influence a women's decision making about HRT – which they should not.

Latest analysis of the findings of the two studies

Heart disease risk/benefit:

Starting on HRT at age range 50-59 or within 10 years of menopause onset:

- The risks for heart disease with all HRT were not increased, and the trend was for a reduction
- The risks for stroke with all HRT were not increased.

Breast cancer risk:

- Increase in risk with combined HRT in WHI was much less than initially reported and now equates to 4 extra cases per 1000 women after five years [It should be noted that this risk is less than that caused by smoking 10 cigarettes/day, alcohol and obesity]. The risk was significantly reduced in women taking oestrogen alone who had never previously taken HRT. Breast cancer risks from MWS appear to be grossly overestimated in comparison to WHI.

Ovarian cancer risk:

- The Million Women Study reported that HRT carries an increased risk of ovarian cancer, but this is unclear since an increased risk was not seen in women taking combined HRT i.e. women who had not had a hysterectomy. WHI showed no significant increase in risk of ovarian cancer.

Endometrial (lining of womb) cancer risk:

- Slightly increased risk with oestrogen-only HRT in MWS, but this risk has been known for over 30 years, which is why this HRT should only be used by women who have had a hysterectomy. The addition of a progestogen every day reduces the risk of this cancer compared to non-users.

Risk of stroke:

- The risk for women starting HRT below age 60 years in the WHI oestrogen alone trial was no higher than for women below 60 years who were not on HRT
- The risk is increased in women who smoke and are overweight.

Risk of weight gain:

- It is thought that for the number of people that gain weight on HRT there is approximately an equal number who will lose weight taking HRT. It depends on the individual. Women tend to gain weight with age and also after the menopause there is a redistribution of fat towards the abdomen.

Use for osteoporosis:

- HRT is not at present recommended by regulatory authorities as the first treatment of choice to prevent brittle bones, although it is currently the only validated treatment for younger postmenopausal women.

HRT is not generally recommended for women with a history of:

- stroke or deep-vein thrombosis (blood clot)
- breast cancer or endometrial cancer
- severe liver disease.

Sources

Writing Group for the Women's Health Initiative Investigators
Risks and benefits of oestrogen plus progestin in healthy postmenopausal women.
Journal of the American Medical Association 2002; 288: 321-33

Million Women Study Collaborators
Breast cancer and hormone-replacement therapy in the Million Women Study.
Lancet 2003; 362: 419-27

Women's Health Initiative Steering Committee
Effects of conjugated equine oestrogen in postmenopausal women with hysterectomy.
Journal of the American Medical Association 2004; 291: 1701-12

Million Women Study Collaborators
Endometrial cancer and hormone-replacement therapy in the Million Women Study.
Lancet 2005; 365: 1543-51

Anderson GL, Chlebowski RT, Rossouw JE, et al.
Prior hormone therapy and breast cancer risk in the Women's Health Initiative randomized trial of oestrogen plus progestin.
Maturitas 2006; 55: 103-15

Stevenson JC on behalf of the International Consensus Group on HRT and Regulatory Issues
HRT, osteoporosis and regulatory authorities Quis custodiet ipsos custodes?
Hum Reprod 2006; 21: 1668-71

Rossouw JE, Prentice RL, Manson JE, et al.
Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause.
J AMA 2007; 297: 1465-77

Million Women Study Collaborators
Ovarian cancer and hormone replacement therapy in the Million Women Study.
Lancet 2007; 369: 1703-10

Stevenson JC, Hodis HN, Pickar JH, Lobo RA.
Coronary heart disease and menopause management: the swinging pendulum of HRT.
Atherosclerosis 2009; 207: 336-40

Margaret Rees, John Stevenson, Sally Hope, Serge Rozenberg, Santiago Palacos
Management of the Menopause 2009 edition 5.

National Osteoporosis Position Statement. HRT for the treatment and prevention of osteoporosis. Dec 2010.
Sturdee DW, Pines A. *Updated IMS recommendations on postmenopausal hormone therapy and preventive strategies for midlife health.*
Climacteric 2011; 14: 302-20

Shapiro S, Farmer RDT, Stevenson JC. et al.
Does hormone replacement therapy cause breast cancer? An application of causal principles to three studies.
J Fam Plann Reprod Health Care 2011; 37: 165-72

LaCroix AZ, Chlebowski RT, Manson JE et al.
Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy: a randomised controlled trial.
JAMA 2011; 305: 1305-14.

Anderson GL, Chlebowski RT, Aragaki AK, et al.
Conjugated equine estrogen and breast cancer incidence and mortality in postmenopausal women with hysterectomy: extended follow-up of the Women's Health Initiative randomised placebo-controlled trial.
Lancet Oncol 2012 online March 7th.doi:10.1016/S1470

Schierbeck LL, Rejnmark L, Tofteng CL et al.
Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomised trial.
BMJ 2012; 345:e6409 doi: 10.1136/bmj.e6409

Bluming AZ, Tavris C.
What are the real risks for breast cancer?
Climacteric 2012; 15: 133-8.

Medicines and Healthcare Products Regulatory Agency website: **www.mhra.gov.uk**

Menopause Matters website: **www.menopausematters.co.uk**

Note for health professionals

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Email: **admin@thebms.org.uk**

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This leaflet has been prepared by specialists from the medical advisory panel of Women's Health Concern. It provides factual guidelines on the use of HRT. It may be viewed on the Women's Health Concern website and downloaded.

Printed copies of this leaflet are available from Women's Health Concern. Note: a small donation may be requested to cover handling and postage.

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