

HRT

What You Should Know about the Risks and Benefits

If you are thinking about taking Hormone Replacement Therapy (HRT) or wondering if you should be coming off it, you will surely know that there has been much debate in the past five years 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 still remains the most effective solution for the relief of menopausal symptoms and prevention of osteoporosis, and may, in certain age groups, provide protection against heart disease.

This leaflet sets out the known facts about HRT, summarises the results of studies regarding its safety and addresses the controversy that still surrounds it and current thinking about its suitability.

We strongly recommend that you discuss with your doctor both the risks and benefits of HRT on an individual basis.

The types of HRT available are listed at the end of the leaflet.



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 or WHI) and one observational questionnaire study in the UK (the Million Women Study or 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 was wide-spread confusion 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%. It must be remembered that the WHI data on which the concerns were raised related to overweight North American women in their mid-sixties and not to the women that are treated in the United Kingdom, who have menopausal symptoms and are around the age of menopause, namely 45 - 55 years.



The Two Studies:

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

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
- Combined HRT increases the risk of breast cancer more than oestrogen-only HRT
- The longer HRT is used, the higher the risk of breast cancer
- The risk declines as soon as HRT is stopped

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

Published findings 2002. Of those taking HRT there were:

- 7 additional coronary events per 10,000 women
- 8 additional strokes per 10,000 women
- 8 additional breast cancer cases per 10,000 women
- 18 additional vein blood clots per 10,000 women
- HRT protected users against osteoporotic fractures with 44 fewer fractures per 10,000 women
- HRT reduced the risk of colon cancer with 6 fewer cancers per 10,000 women
- The study was stopped three years early by the safety monitoring committee as a previously agreed limit for breast cancer was exceeded and overall risks were thought to exceed benefits
- Newly published findings from the same WHI Study showed different effects when the results were split down by age:
 - Under 60s can actually be protected by HRT in some health aspects
 - Over 70s 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

Published findings 2004:

Of those taking HRT there were:

- 5 fewer coronary events per 10,000 women
- 12 additional strokes per 10,000 women
- 7 fewer breast cancers per 10,000 women
- 7 additional vein blood clots per 10,000 women (but none in women aged below 60 years who were not overweight)
- HRT protected users against osteoporosis with 56 fewer fractures per 10,000 women
- HRT did not reduce the risk of colon cancer with 1 additional case per 10,000 women
- The study was stopped just under two years early by the trial sponsor, but not by the safety monitoring committee
- Newly published findings from the same WHI Study in 2007 again showed different effects when the results were split down by age:
 - Under 60s can actually be protected by HRT in some health aspects
 - Over 70s don't accrue the same benefits and could be at certain increased risks



Shortcomings of the MWS and WHI 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 MWS and the WHI studies had shortcomings and so were flawed.

Issues with the Studies:

- 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.
- WHI looked at only one dose and type of combined HRT or oestrogen only HRT.
- 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 was a substantial number of drop-outs from the study.

Women's Health Concern also expressed its concern at that time, wanting to ensure that decisions on HRT usage were based on fact.



HRT Today

In 2007, a subsequent analysis from both the combined HRT and oestrogen alone WHI studies looked at whether the health effects varied with age. This analysis showed wide variances from the initial WHI publication in 2002, with an about turn on some of the previous findings for which the authors had claimed categorically that there was no difference in effect with age.

The balance of benefit to harm appears to have shifted favourably for HRT, and users can be reassured provided HRT is taken for the correct reasons, i.e. to alleviate the symptoms of the menopause or prevent osteoporosis, that it is taken for as short a period as is necessary at the lowest effective dose, and that HRT users are assessed 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 older women, for whom the risks are increased, to start HRT as the WHI study shows.

Latest Analysis of the Studies' findings:

Heart Disease Risk/Benefit:

Age range 50-59 or within 10 years of menopause onset:

- The risks for heart disease with all HRT were reduced
- The risks for stroke with all HRT were increased

Breast Cancer Risk:

- Increase in risk with combined HRT in WHI was no longer significant when other factors influencing breast cancer were taken into account. 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.

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 on the WHI oestrogen alone trial was no higher than for women below 60 years who were not on HRT.

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.

Use for osteoporosis:

- HRT is not recommended 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 who:

- have had a stroke or deep-vein blood clot
- have had breast cancer or endometrial cancer
- have severe liver disease



Timelines

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| 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. |
| 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 1 million in the UK. |
| 2004-2007 | The investigators of WHI publish a further analysis of the trial which is a turn-around 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 50-59 age group, or for those less than 10 years past the menopause - 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 in HRT after the age of 60, which is later than normal UK clinical practice. |

In Summary

Women wishing to start HRT should carefully discuss the risks and benefits 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, for the shortest possible time depending on the clinical reasons for use.

HRT remains licensed for osteoporosis prevention and should still remain the treatment of choice for women starting treatment below age 60 years.

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.

Possible questions for your doctor or our Nurse Advisers:

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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 endometrium.
- **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.



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Menopause Matters website: www.menopausematters.co.uk

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



