

# Hormone Replacement Therapy / Oestrogen Replacement Benefits and Risks

HRT, or Hormone Replacement Therapy, means replacement of the female hormone – oestrogen – in women with low levels. In recent years it has been the subject of a lot of controversy in the media, after publication of scientific trials. This information sheet tries to put the benefits and risks into context to allow you to make a sensible decision about whether or not you should be taking hormone replacement. I'm sorry it's complicated – but so are the issues!

HRT may be considered in 3 circumstances:

- After the natural menopause - which occurs around 50-55 years of age and which is due to failure of the function of the ovaries themselves, which can no longer produce oestrogen
- After ovarian failure occurring at a younger age than the normal menopause. This may be because the ovaries were never able to function normally (e.g. in Turner's syndrome), when previously normal ovaries stop functioning - known as 'Premature Ovarian Failure' or 'Premature Menopause', or when normal ovaries are removed surgically or damaged by radiotherapy or chemotherapy given for other reasons.
- In hypopituitarism when the pituitary control hormones LH and FSH are deficient and no longer stimulate the ovaries to produce oestrogen

## **What problems does oestrogen deficiency cause?**

Lack of oestrogen can cause a number of problems - some of which are immediately obvious to the woman and some of which are not ...

- Lack of periods - periods are caused by the rise and fall of oestrogen and other hormones from the ovaries, and if the ovaries are not functioning then periods stop. This will rarely be a worry for women of normal menopausal age, but can be distressing when ovaries or pituitary fail in younger people.
- Hot flushes associated with the menopause are well known to everyone and are caused by oestrogen deficiency. In some women they can be very severe and unbearable, in others mild and easily tolerated.
- Skin changes which occur after the menopause are also worsened by the lack of oestrogen, with thinning, wrinkling and general ageing of the skin.
- Mood, well-being, libido & vaginal dryness: around the time of menopause many women notice mood swings, depression and loss of sex drive (or libido) - some of which may be due to lack of oestrogen. Women also frequently notice vaginal dryness and soreness due to lack of the beneficial effect of oestrogen here.
- Osteoporosis: oestrogen helps maintain the strength of the normal skeleton, and when oestrogen is deficient then bone density falls and the risk of breaking a bone increases. In more severe cases this leads to osteoporosis (or brittle bones) with increased risk of fractures of the arm, hip, ribs and bones of the spine (vertebrae). Changes in the spine may lead to loss of height, severe back pains and a 'bent over' spine.
- ? Protecting the heart and blood vessels: women have less heart disease than men before the menopause, and after the menopause the rate of heart disease in women rises steadily. Some scientific experiments have suggested that oestrogen has a direct beneficial effect of blood vessels (but see possible bad effects below).

## **What good does HRT or oestrogen replacement do?**

- Improvement of symptoms: HRT is generally very good at treating and preventing hot flushes & vaginal dryness. Many women also describe great improvements in mood, sleep, irritability, sex drive and general energy and well-being - but this varies from person to person and is not always the case. For some post-menopausal women life is 'normal' on HRT and unbearable without – others notice little major change.
- Bone density and osteoporosis - HRT prevents the loss of bone caused by oestrogen deficiency and can increase the strength of bones in osteoporosis
- Bowel cancer - surprisingly HRT also *decreases* the risk of large bowel cancer
- Skin and ageing - many women report that taking HRT makes them 'look younger' and slows the appearance of ageing on the skin. This is hard to prove scientifically, and the importance of this is very much an individual's own opinion.

## **So what are the problems with HRT?**

Some side effects of HRT have been well known for some time, others have only been suspected recently

- Endometrial hyperplasia and cancers of the lining of the womb: If oestrogen alone is given to women who still have a womb (i.e. who have *not* had a hysterectomy) then build up of the lining of the womb occurs with time which may lead to abnormal bleeding and an increased risk of cancer of the lining of the womb. This risk is very much reduced by giving progesterone together with oestrogen (and this is the reason that combined HRT is used in everyone with a womb). Women who have had a hysterectomy are usually given oestrogen alone.
- Periods: traditional combined oestrogen/progesterone HRT causes periods, and these are frequently not welcome to women who are past normal menopausal age. 'Continuous combined' HRT attempts to prevent periods from happening - but is also more similar to the form of HRT used in the big USA studies which reported heart problems (see below) than the types of HRT which cause regular periods.

- **Breast cancer:** many studies, including the largest US studies, show a slight increase in the risk of breast cancer in women taking HRT. However, in spite of this, it is worth bearing in mind that there is no proof of any increase in the risk of *dying* from breast cancer, and several studies have now suggested that when breast cancer occurs in women taking HRT it may be of a type which is *easier* to detect and treat effectively. One recent study suggested that breast cancer survival is *better* in women on HRT.
- **Ovarian cancer:** although many risks of HRT seem to apply to combined oestrogen/progesterone HRT rather than oestrogen alone, recent studies have shown a small increase in the risk of ovarian cancer in women taking oestrogen alone after hysterectomy. This risk is not seen in combined HRT.
- **Blood clots:** oestrogen replacement causes a small increase in the risk of blood clots in the legs and elsewhere. These clots can occasionally pass to the lungs and cause serious problems. This risk is also seen in women who take the contraceptive pill at a younger age.
- **Heart disease and stroke:** until recently doctors had hoped (based on smaller earlier studies) that HRT would protect women from heart disease and stroke in the same way as they are protected before the menopause. Several studies have now shown a small increase in risk instead, although it remains unclear whether this applies to every woman on HRT or only those starting at a much later age. This risk is small (see below) but certainly means that we should not use HRT to try to prevent heart disease and stroke.

### **What are the overall rates of risk and benefit?**

The "Women's Health Initiative" (WHI) study in the USA - which hit the headlines in 2002 - studied over 16,600 women on HRT. Its results represent the 'worst case scenario' for what the bad effects of HRT might be:

For women taking a particular combined oestrogen and progesterone combination this study reported:

- 41% percent increase in strokes
- 29% percent increase in heart attacks
- A doubling of rates of venous thromboembolism (blood clots)
- 22% percent increase in total cardiovascular disease
- 26% percent increase in breast cancer
- 33% percent reduction in cases of colorectal (large bowel) cancer
- 33% percent reduction in hip fracture rates
- 24% percent reduction in total fractures
- No difference in total mortality (deaths from all causes)

To put this risk into real numbers, the paper calculated that for 10,000 women taking combined oestrogen progesterone HRT at normal menopausal age, every year there would be:

- 7 more coronary heart disease events,
- 8 more invasive breast cancers,
- 8 more strokes, and
- 8 more pulmonary emboli,

*but*

- 6 fewer colorectal cancers and
- 5 fewer hip fractures.

The effects of bone, bowel cancer, breast cancer and blood clots had been known before – but the effects on heart disease and stroke had not been previously suspected

*Overall this means that over 5 years of treatment – and extra 1 woman in every 100 women taking HRT would develop an illness than they would if they were not taking it.*

The risk of breast cancer has also been calculated from earlier studies by the UK Committee on Safety of Medicines: They estimate that about 45 in every 1000 women aged 50 years not using HRT will have breast cancer diagnosed over the next 20 years; in those using HRT for 5 years, this figure rises by about 2 extra cases in 1000, in those using HRT for 10 years about 6 extra cases in 1000 and in those using HRT for 15 years about 12 extra cases in 1000.

### **Criticisms and Uncertainties about the Women's Health Initiative Study**

In the 10 years since WHI, the study has come in for a lot of criticism, and newer analyses of the same data and from other trials have suggested that the risk of heart disease and stroke may not be as bad as WHI suggested:

- Most women who start HRT in normal clinical practice start HRT very soon after they develop menopausal symptoms. WHI in contrast studied women who were much older (average 64yr), a long time after the menopause (an average of 10 yr) and who mostly had no symptoms. So perhaps they "treated and studied the wrong people"
- An analysis of the subgroups in WHI who were aged <60yr and <10yr after menopause at the time HRT was started found no increase in heart disease and stroke (in fact they found a non-significant reduction in death due to heart disease)

- In 2012, a study of over 1000 Danish women treated at average age 50 years and <1yr after the onset of the menopause reported a significant reduction in heart disease and cardiac death in women on HRT after at least 11 years on treatment.
- Some have criticised WHI for using “conjugated equine oestrogens” for HRT rather than synthetic oestradiol (the human hormone) – so perhaps they “used the wrong sort of oestrogen”.
- The particular HRT combination used in WHI is not used in the UK but is similar to *Premique* and *Premique cycle*, and uses the same oestrogen as *Premarin* & *Prempak*, and the same progesterone as *Tridestra* and *Indivina*. In contrast the Danish study used oestradiol in a ‘triphasic’ preparation (which results in periods every 3 months). In theory skin-patch HRT may be less likely to cause blood clots. However, there is no hard evidence to show that the particular HRT ingredients cause the problems, and while we may choose to avoid the WHI-type preparations as a precaution, it remains wise to assume that the same risks apply to all forms of combined oestrogen/progesterone HRT until we prove otherwise.

### ***What about if I have had a hysterectomy and just take oestrogen?***

The “Women's Health Initiative” study also included a group of women who had had a hysterectomy and therefore took oestrogen alone as HRT. These patients did not show the same increase in cardiovascular disease, stroke or breast cancer

Another recent US study of over 40,000 women has recently suggested that the risk of ovarian cancer may be increased (by 60%) in women taking oestrogen only HRT, but not increased in women who have only ever taken oestrogen/progesterone combined HRT.

### ***What other things alter my risk of heart disease, stroke and breast cancer?***

Many other things alter your existing risk of the diseases which may be more frequent (and those which are less frequent) on HRT. The overall risk to you as an individual depends on what your personal risk would be without HRT – if you have a high risk of heart attack for other reasons then a 29% increase could be very significant, on the other hand if your existing risk was very low (for example if you were very young) then the actual increase in risk would be negligible.

Your risk of Heart disease and Stroke are increased if:

- You smoke (risk doubles)
- You have diabetes (risk doubles)
- You have a high cholesterol in the blood (risk depends on level of cholesterol)
- You are overweight or obese and/or take no regular exercise
- You have untreated or inadequately treated high blood pressure
- You have a strong history of heart attacks and strokes in the family

Your risk of Breast Cancer is increased if:

- You have several female relatives who have also suffered from breast cancer

Your risk of osteoporosis is increased if:

- You have a very early menopause, or many years without periods at a younger age
- You have relatives who suffer from osteoporosis
- If you don't take regular ‘weight bearing’ exercise – which builds up the strength of the bones

Risk of ovarian cancer is increased if you have never been pregnant, and decreased by pregnancy and being on the combined ‘Pill’ for contraception

*Therefore, if you don't smoke, don't have diabetes, keep fit with regular exercise and have normal weight, blood pressure and cholesterol with no family history of heart disease, stroke or breast cancer – then your background risk of these problems is low and the absolute increase in risk by taking HRT is smaller than someone who has all these risk factors.*

### ***What are the alternatives?***

‘The Pill’: For younger women with premature ovarian failure or pituitary gonadotrophin deficiency we often choose to use the combined oral contraceptive pill as a form of oestrogen replacement. This is because there is a very large amount of data about the effects of young women taking the Pill and overall the results are very reassuring about long-term safety. There is no evidence to suggest that the Pill is actually any more or any less safe than other ‘HRT’ preparations – but at least we have the data available.

‘Natural alternatives’: a variety of foods contain substances which can act like weak oestrogens in the body. Much has been written about these in the press, but there remains insufficient evidence to show that eating these foods can have the beneficial effects which we know for HRT, and no evidence at all about what the long-term risks of heart disease, stroke or breast cancer might be.

Flushes: other sorts of tablets can sometimes help improve the hot flushes of the menopause – for example a tablet called clonidine. You may wish to discuss this with your doctor – but nothing is quite as good as oestrogen!

Osteoporosis: A number of other treatments exist which can treat or help prevent osteoporosis. At the simplest level, making sure you get plenty of calcium and vitamin D in your diet – or even taking a *calcium and vitamin D tablet* can help. When women have established osteoporosis – or low bone density on a scan – then drugs called *bisphosphonates* are the most powerful drug currently available, and do not have any of the other HRT risks (or indeed benefits). Synthetic drugs related to oestrogen – such as *raloxifene* – act like oestrogen to improve the bone, but don't have the unwanted effects on the breast, or cause periods – but also don't help other symptoms.

### **So who should take HRT? Who should decide?**

Ultimately only one person can decide whether or not you should take oestrogen replacement – and that is you yourself, having weighed up the risks and benefits for you. Whether you base your decision on the worst case scenario of risk described by WHI or whether you base your assessment on more optimistic studies in younger people depends largely on your own attitude towards risk and whether you have any symptoms.

*However in my opinion, HRT is still very appropriate for the following groups of women:*

Younger women: Women with premature ovarian failure or pituitary gonadotrophin deficiency from an early age should certainly always be offered oestrogen replacement. Without oestrogen the risk of osteoporosis in later life is very high, and at a young age the risk of heart attacks, strokes and breast cancer is very low – and that's not to mention the effects of oestrogen deficiency on libido and general wellbeing. I would advise that if you are aged less than 50 and have oestrogen deficiency then the benefits of HRT probably outweigh the risks unless you have other important risk factors. If you are less than 40 then HRT almost certainly is causing much more benefit than harm.

Women with oestrogen deficiency symptoms: Nothing is quite as good at dealing with hot flushes, sleep disturbance and vaginal dryness as oestrogen, and many women also notice a great improvement in their general well-being, energy and drive with oestrogen. If you are getting these benefits and are (say) aged less than 60y then you will probably feel that these benefits outweigh a debatable slight increase in the risk of heart disease, stroke and breast cancer at this age. You may also be influenced by the effects of oestrogen on your general appearance, and by other beneficial effects in the studies. Conversely, if you have gone through the menopause, are aged over 50 years and don't have any menopausal symptoms, then there is now no medical reason to advise automatic HRT – and if you are at particular risk of osteoporosis then there are safer ways to treat it.

Women of any age who have weighed up the risks and benefits for themselves – and decided that the benefits they are getting outweigh the risks. I believe that if women of any age feel that the benefits of oestrogen are very important and know that their risks are lower than average then they may still choose to continue HRT.

Claire Rayner wrote a very interesting article about this in 2002, which you can currently still read online at: <http://www.guardian.co.uk/women/story/0,3604,752991,00.html>

### **Things which may help decide**

Bone density: we can arrange a bone density scan if appropriate in the clinic. Automatic screening is not currently recommended – but if you are at particular risk of osteoporosis then it may be justified

Cholesterol levels: if you are considering HRT and want to be more certain of your underlying background risk of heart disease and stroke then a cholesterol level can help estimate this. The higher the cholesterol, the higher your risk of heart disease.

Blood pressure: The higher your blood pressure the higher your risk of heart disease and stroke. Everyone from middle age onwards should have blood pressure measured from time to time.

Family history: If you have a strong family history of heart attacks, strokes, blood clots or breast cancer then your background risk of getting this conditions is likely to be higher than average, and therefore the small increase in risk on HRT will be more significant

Other risk factors: if you have any of the other risk factors listed above (smoking, diabetes, obesity) then this may also influence your decision – since all of these will increase your risk

### **Don't panic!**

Before you suddenly decide to stop your HRT as a result of possible adverse effects of treatment remember:

- The risk to you now of taking HRT is no greater than it was before - it's just that now we can say more precisely what the risk actually is.
- Most heart disease and stroke events in the WHI study happened in the first couple of years on treatment, so if you have been on HRT for longer the risk may be less.
- Ultimately – it's your choice whether or not you continue to take HRT!

### What is my background risk?

Lower Risk	Neutral	Higher Risk
<input type="checkbox"/> Non smoker		<input type="checkbox"/> Smoker
<input type="checkbox"/> No heart disease or stroke in family	<input type="checkbox"/> Heart disease or stroke in a few relatives at old age	<input type="checkbox"/> Many family members with heart disease or stroke at a young age
<input type="checkbox"/> Noone in family has breast cancer	<input type="checkbox"/> Cancers other than breast cancer in the family. One distant relative had breast cancer.	<input type="checkbox"/> Many women in the family had breast cancer
<input type="checkbox"/> Low normal blood pressure	<input type="checkbox"/> Normal BP or well treated BP	<input type="checkbox"/> Untreated High blood pressure
		<input type="checkbox"/> Diabetes
<input type="checkbox"/> Normal weight	<input type="checkbox"/> Slightly overweight	<input type="checkbox"/> Obesity
<input type="checkbox"/> Regular aerobic exercise	<input type="checkbox"/> Occasional exercise	<input type="checkbox"/> No exercise at all
<input type="checkbox"/> Low cholesterol		<input type="checkbox"/> High cholesterol

### Calculated Risk of Heart Disease and Stroke

We can calculate your approximate risk of heart disease or stroke in the next 10 years if we know your blood pressure, cholesterol and whether you smoke or have diabetes (This is a standard calculation based on a long-term study of a small town in the USA where people have been followed up for many years). *If it would help you to know then please ask:*

My total cholesterol is:	My HDL Cholesterol is:	My Blood pressure is: /
Smoker?:	Diabetes?:	
10yr risk of heart attack: %	10yr risk of any heart disease or stroke: %	