

## Menopause



The menopause has been in the headlines a lot in the last few years. And for good reason. Researchers found that commonly prescribed hormone therapy did not have the longterm benefits many experts previously thought it had. For women who struggle with severe menopausal symptoms, this disappointing news did not make life any easier.

That is why we set out to find what is known for sure about the benefits and harms of hormones and other options. While there are many alternatives offered to women with menopausal symptoms, most have not been proven to give relief. The most research has gone into oestrogen-based hormone therapy, including combined oestrogen-gestagen hormones. These can provide relief for many women who have severe symptoms. But the same thing is true for hormones as for all other drugs: if they are effective, they can also cause unwanted side effects.

## 1. The personal impact of the menopause

### Karin

I enjoyed not having periods any more. I always got them fairly late. I always got cramps, and my breasts ached. If the kids bumped against me or I had to climb stairs, it hurt. It was great when that didn't happen any more.

### Susanne

This was a turning point in my life. I found it a real burden. I also had these doubts: 'Am I still a woman? What makes you a woman?'

### Maria

I found it a great relief that I couldn't get pregnant any more.

Menopause does not have a very good image. Little wonder, when women have been confronted for decades with the message that they should worry about their health, as though menopause speeds up the ageing process. This turned menopause into a medical problem with a medical solution: treating it with hormones.

When women are asked, though, how they judge their own experience of the menopause, they often describe a very different and more comprehensive picture [3], [4], [1]. Women find their own way through the menopause. There is no one right way to handle it. Some women pay it very little attention. Others see it as an important phase in their life, with a generally positive perspective. Some take the opportunity to think about their life and ask themselves critical questions about what is important for them. The menopause signals a new orientation in life for about one in every two women [5], [2]. They change their lifestyle [5], their focus in life and/or they concentrate more on their own interests or future. Others start paying more attention to their friends and social circle [2].

Nevertheless, it is also normal for re-orientation in life to make women feel insecure or cause mixed feelings. Impressions of the menopause are about as varied as women are themselves: they range from "new freedom and energy" through "loss of energy" to "feeling old and useless" [2].

### Susan

I think the menopause is a real crisis, and you have to find yourself again. You can really compare it to puberty. You have to find your place again. A lot of questions come up, not from others, but for yourself.

I can't say whether or not I was aware of the menopause as a time of opportunity. I never looked at the menopause as an opportunity.

When I was around 50 I got calmer and more easy-going. I worked through insecurities and some issues. Until then I hadn't been aware that the menopause could also be an opportunity.

### Maria

I think I got more independent during the menopause. I went alone to talks and to the theatre. My first grandchild was born around the time. I could concentrate more on myself and my grandchild. Without being aware of it, I was trying to adapt to a new life situation.

Many women like to talk about their feelings with their friends, their mother or their partner [2]. But that is not always easy. Some women prefer to avoid the topic, or to talk to their doctor or another professional advisor.

### Karin

It wasn't an issue in the past. People didn't talk about it. At the most, I maybe saw my mother in a petticoat. It was another time... A lot has changed. I envy my daughters. I missed out on a lot.

Some women find that their partner is not interested in their experience of the menopause or show little understanding for what they are going through [2]. Perhaps one in four men know almost nothing about this phase of life for women [6], [7]. Or you could look at that another way: most men try to be supportive [7].

### Karin

When I told him it must be the menopause, my husband said, 'Nothing will change for us.' I didn't feel like he took me seriously (laughs). My husband wasn't very sympathetic.

Physical change is only one of many aspects of the menopause for many women, as long as they are not having very severe symptoms. They do not usually feel

less attractive or feminine because of the menopause [1], [2]. However physical changes can be unsettling for some women [2]. For many women it is important to feel good about their bodies.

**Karin**

Maybe some women think: "Now I will never be able to have a child". I never thought that way, but I can imagine it. I didn't feel that way about it.

**Maria**

I found the menopause irrelevant for me. I just thought, I need to get through this. I didn't find the menopause unpleasant, but it wasn't bad. It was fairly uncomplicated.

In this article we concentrate on the medical aspects of the menopause. But that doesn't mean that menopause is primarily a medical problem.

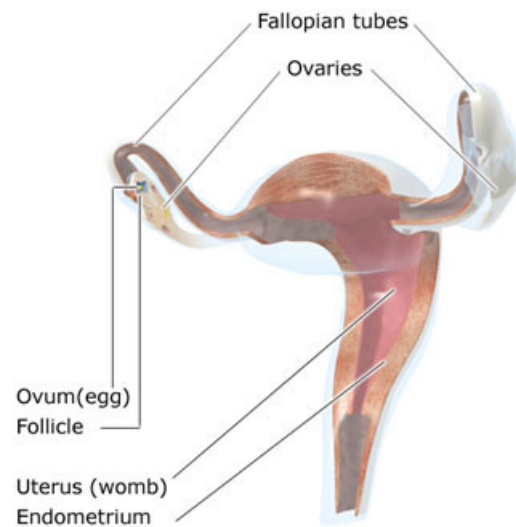
## 2. Background

### 2.1. About menopause

**Maria**

The gap between my periods kept getting bigger. But sometimes the gap was shorter. It was completely irregular. Over time the periods got lighter... I had my last period when I was 51.

Baby girls are born with all the eggs in their ovaries that they will have in their lifetime. These eggs are lying in little pockets called follicles. Once puberty starts, hormones ripen the first follicle so that it will release an egg (ovum). That is the beginning of fertility. From then on, hormones ripen a follicle every month. That follicle itself produces more hormones.



As part of the monthly menstrual cycle, the endometrium or lining of the womb prepares for the possibility that an egg might be fertilised. If the egg is not fertilised, it dies and the lining that has built up in the womb to receive an egg leaves the body. This is the monthly period or menstruation. As long as a woman is not pregnant and does not use hormonal contraceptive (like the Pill), the period is a sign that one menstrual cycle has finished and the next one has started.

Somewhere around 50 years of age women have their last period. Menopause is the medical term for this ending of the menstrual cycle [8]. A deciding factor for when the menopause will begin is the number of follicles remaining in the ovaries. From around the age of 40, the number of remaining follicles starts to drop. After that, the number drops quite quickly, until no more follicles ripen at all [8].

The gap between periods becomes irregular. Some periods might be heavier and others lighter. The start of this process can be so subtle that some women do not notice any change at all. For others though, there are very noticeable physical symptoms.

It is only in hindsight that it is possible to know which was the last period. Once there has been no period for 12 months, then a woman can be sure that she has reached the menopause.

The one or two years before the last period is called pre-menopause, and the time afterwards is called post-menopause [8]. During this time the body finds a new hormonal balance. For many women this time of

adjustment causes symptoms that will sometimes be very severe. The length of the process varies from woman to woman. For most women, the whole process will take a few years. This phase of life is sometimes called the climacteric. The word climacteric comes from Greek and means something like 'a critical point of life'.

## Karin

It started for me when I was 35. My periods were all over the place. In the beginning, my head would suddenly get hot while I was drinking coffee. It didn't occur to me, that this could be the menopause.

## Susanne

I noticed that my periods weren't as regular. At the time, I thought it was caused by stress or my new life circumstances. Before that I could fairly much count on how regular my cycle was, give or take three days.

## Induced menopause

For some women menopause is a side effect of treatment for an illness like cancer. Menopause occurs if both ovaries are surgically removed (ovarectomy). This is called induced menopause. Surgical removal of the uterus (hysterectomy) alone is not enough to cause the menopause if the ovaries are still there and functioning. Women who have induced menopause often experience the same symptoms as women having a natural menopause. But they might be a lot younger. Women having induced menopause have some different and specific questions, but this article deals mostly with natural menopause.

### 2.2. When the menopause starts

For most women the menopausal process starts somewhere between 40 and 58 years of age [9]. The average age is 51 years [10], [11]. If the menopause starts earlier than 40 it is called premature menopause.

## Maria

I could tell the menopause had started because my periods became more irregular. At that time I was about 45 years old.

There is some evidence that the age at which the menopause starts might be genetically determined [12]. This means that mothers, daughters and sisters might

experience menopause at about the same time of life.

## Susanne

I think that maybe it can run in the family. I remember that my mother used to complain about sweats. She was between 50 and 55 years old... When my periods finally stopped, I was at the beginning of my 50th year.

Some researchers suggest that there are other factors that might affect the timing of the menopause. These include the number of times women have given birth. A higher birthrate, for example, might be one of the reasons that women in some developing countries experience the menopause earlier [8].

It is also proposed that smokers might start menopause sooner, as well women who are over- or under-weight. The length of the woman's menstrual cycle is another suggestion [11]. But there is no conclusive evidence about these factors [11].

### 2.3. Hormone changes

## Karin

For the last years, my periods were very light, but they came more often. Sometimes they were longer, and sometimes they only went for two days.

The production of hormones is one part of the menstrual cycle. Until the release of the egg, the ripe follicle increases the amount of oestrogen. After the egg is released, the amount of progesterone climbs. Both of these hormones do not only prepare the uterus for a possible pregnancy. They also have an effect on the skin and mucus membranes for example [13].

During the menopause the overall level of oestrogen gradually reduces. This changes the balance between oestrogens and other hormones. The body reacts to the reduction in oestrogen by producing more of another type of hormone, called follicle-stimulating hormone (FSH) [14], [15].

Even though these changes are typical for the menopause, that does not mean that testing the hormone levels can provide information about how to handle the menopause. This is because hormone levels around the time of ending menstruation can swing about. Ovary function tests also cannot determine for certain whether or not the

menopause is underway [8].

#### **Susanne**

With these irregular periods at the beginning, it was clear to me how women could get pregnant at that age.

Even when periods are irregular or far apart, women can still get pregnant. Low or changing hormone levels do not protect against unwanted pregnancy [8], [10], [14]. Hormone therapy for menopausal symptoms also does not prevent pregnancy.

### 3. Menopausal symptoms and health

#### 3.1. Effects of the menopause on health

Hot flashes or flushes, outbreaks of sweating and vaginal dryness are common symptoms during the menopause [10], [11]. If hot flashes and sweats happen at night it can disturb sleep. But all physical and emotional changes that happen around this time are not caused by the menopause. Changes in mood, emotional wellbeing, concentration and cognitive ability, as well as physical problems like backache are not directly the result of menopause.

Some believe that menopause speeds up women's risk of a range of illnesses. One example is cardiovascular disease (heart and circulation problems). While it is true that women have a higher risk of cardiovascular disease after the menopause, this is solely because they have got older. The menopause itself does not influence the risk of heart disease [16], [17], [18]. The menopause could be a good motivator, though, to start thinking a bit more about how to stay healthy in older age.

#### 3.2. Hot flashes and sweats

Hot flashes and sweats are called "vasomotor symptoms". Hot flashes happen when the blood vessels just under the skin suddenly open up more widely. That means more blood can flow through and this feels like a surge of heat. This wave of heat hits very suddenly, usually starting from the chest, neck and face. The heat wave goes through the whole body, often in the direction of the head, arms or legs. Hot flashes can make the skin red, and can cause outbreaks of sweating that are sometimes major. Many women feel a strong racing of the heart at the same time. This is usually not a sign of heart problems. Some women also feel very unwell during a hot flash.

#### **Karin**

When it started it felt as though my head would explode and my heart pounded at the same time. Once when I was drinking coffee with some women, I really felt as though my heart was going to jump out of my chest. I didn't know what was happening. But before you could grasp what was happening, it was already over...

Sometimes I found it unpleasant, when I had to serve customers in summer. But it didn't smell at all. If I sweat when I'm being physically active, then it smells differently than having a hot flash.

Hot flashes last on average about three minutes. They can however last longer. For some women, this can be for up to an hour [8], [10]. After a hot flash a woman can sometimes have a short chill [10].

From a half to two-thirds of women will have hot flashes and sweats during the menopause [10], [11], [19]. But often the problem is only mild and does not cause much bother. But for some women hot flashes can become so severe that their daily activities, work or sleep are seriously disturbed.

#### **Maria**

I had hot flashes too, mostly in the night. But it wasn't very often. When I had them, I found it very unpleasant, especially at work. At first I would feel very warm, then hot and then I would break out in sweat.

#### **Susanne**

I thought to myself: "You won't be able to stand this for long." I was really worried that I would get sick. I had to work. If I had a hot flash during an interview, I wouldn't feel clean and I would lose confidence. It became clear to me that getting through the menopause naturally was going to be an unfulfilled dream for me.

Hot flashes come more often at the start of the menopause [11], but usually go away over time [9], [10], [11]. For most women, hot flashes will stop within one or two years all by themselves. For about one-third of women they last for up to five years, and for only a few women they will go on for longer than that [20].

#### **Karin**

In the beginning the hot flashes were dreadful. It is hard to explain. All at once, 20 minutes later, you get the next one. It is a bit like getting contractions when you are in labour.

It has been three years since I menstruated. But I still have the hot flashes. Sometimes there is a bigger gap, then they come again in short intervals. I don't have them every quarter hour, though, which is how it was in the first year.

### What causes hot flashes

Hot flashes are probably led by a centre in the brain that regulates body temperature. When the body temperature climbs too high, this centre can temporarily open the blood vessels under the skin more widely. This process is called vasodilation. It enables the body to get rid of heat and so help reduce body temperature. The skin experiences that as a wave of heat. Researchers suggest that the reduction in hormone production by the ovaries might somehow affect this temperature regulation system, but the precise cause of hot flashes is not really understood [8].

### 3.3. No major influence on sexuality

The impact of the menopause on sexuality varies from woman to woman. Some fear that they will enjoy sex less [21], while others are satisfied with their sex lives [22]. Some women experience less sexual arousal or less interest in sex [2], while others have an improved sex life [4].

These differences are already one sign that changes in sexuality in the middle years might not only be related to the menopause. There is no strong evidence that sexual response or desire is reduced by the menopause [11]. Psychological, social, cultural and individual factors are also involved.

One problem can be vaginal dryness. About 3 out of 10 women (30%) have problems with this from just before the menopause [11]. Vaginal dryness can cause some itchiness, and it can also make vaginal infections more frequent. It can also make sexual intercourse uncomfortable [10]. Vaginal dryness does not happen suddenly. Rather, it develops across the time of the menopause. Many women do not notice any change till after the menopause is over.

### Susanne

I didn't have a big problem with vaginal dryness. It took a bit longer, but it wasn't so bad that I needed to use a lubricant.

### 4. What a woman can try for menopausal symptoms

#### Karin

Getting through the menopause...I thought, there doesn't always have to be a treatment. Every day does not have to be great. Then I couldn't decide. Everybody has to find out for themselves, what is best for them.

There is a variety of options to try to help reduce menopausal symptoms. There possible benefits and unwanted side effects vary quite a bit. Even without any treatment hot flashes and sweats ease off for most women with time, and then go away completely by themselves. Menopause is not an illness. It is normal for hormone levels to lessen off with age. These hormones do not need to be replaced.

#### Susanne

I went to talks to learn more about how to go through the menopause without hormones. I was seriously determined to cope with the menopause naturally.

There are basically four options for handling hot flashes and sweats. Some women simply wait till the menopause passes. If that is not enough, you can consider changes in lifestyle, for example getting more exercise. Many women are interested in herbal options or other complementary or alternative remedies. For vaginal dryness, hormone-free lubricants and vaginal moisturisers are also options. Finally there is a range of hormone treatments.

Unfortunately, you cannot believe in all the promises that are made for different forms of advice and preparations. Some of these remedies do not seem to be as effective as is generally believed. Others have serious adverse effects that are sometimes under-estimated.

One reason for these misjudgments is that it is hard even for experts to keep fully up-to-date with all the research on the wide range of options. We have based our analysis on so-called systematic reviews, which helps us offer you as reliable an answer as possible to your questions.

There are many important questions in medicine where it is still not possible to give clear answers. We have chosen not to just speculate in those situations whether or not something is effective. But rather, we choose to be open in making clear that we do not know the answer. We would rather wait until new research evidence becomes

available to give us a clearer picture of the benefits and safety of an option. That means that we will be updating this article when there is new evidence.

#### 4.1. Diet

On the subject of diet, there are two types of advice: some experts recommend eating more of particular foods, while others recommending avoiding some. In general, though, there is no conclusive evidence that any of these reduce menopausal symptoms. Nuts, nut oils and some other plant oils are recommended, but whether or not they can work has not been adequately studied. The same is true for herbal teas, wheat, hops, grapefruit and many other foods.

Just as often, avoiding strong coffee, tea, alcohol, chocolate, salt and spices like curry are recommended for reducing menopausal symptoms. Again, there is no proof to show whether or not this will help.

But the most common recommendation is about soya. Many experts recommend a diet rich in soy products such as those including soy flour or soy milk. Others recommend dietary supplements which include soya to help reduce symptoms. There are trials of soya, but they arrived at conflicting results [11], [23]. That means that we cannot be sure about whether or not soya will reduce hot flashes and other symptoms. More trials of soy-rich diets or soya products are already underway. You can read more about this below in the section on dietary supplements.

#### 4.2. Exercise and physical activity

There are also contradictory research findings about whether physical activity has an impact on menopause symptoms [11]. In one study extra exercise improved women's quality of life, and in another it did not. But even if exercise does not have much influence on symptoms of menopause, activities like extra walking and light muscle training can have a range of other effects [24]. Very overweight women who do medium exertion walking or running for about 30 minutes a day and do muscle training twice a week might be able to reduce their blood pressure, for example. This can also increase muscle strength and flexibility [24]. With some forms of sport or exercise there is some risk of injury, of course.

#### 4.3. Relaxation

There is not enough good evidence to let us know whether or not relaxation techniques, breathing training, meditation,

yoga and Tai Chi can help menopause symptoms [11].

#### Susanne

I started meditation at the beginning of the menopause. After that I didn't do any relaxation for a while. Later I tried another type of training, but it was a bit problematic. Then I started yoga, and I do that regularly.

#### 4.4. Complementary or alternative therapies

A large market has developed for complementary therapies for the menopause. There is a wide range of herbal medicines and dietary supplements that aim to relieve menopausal symptoms. Acupuncture, homeopathy, chiropractic and foot reflexology are also on the list. But the evidence that any of them are very effective and safe ways of relieving symptoms of the menopause is not convincing.

Complementary therapies for the menopause are very popular [25]. It has been estimated that from 20 to 50 out of every 100 women in the USA (20-50%) use complementary therapies. The majority of women rate them as helpful, because their symptoms reduced while they were using the product [25], [26]. But from a scientific point of view, that is not proof that they work. That is because menopausal symptoms would have gone away for many women even without any treatment at all.

There are so many pieces of advice to women about how they should manage the menopause that we cannot list them all here. Many of these are completely speculative and they have not been systematically studied. We have concentrated here on describing complementary therapies that have been studied in at least one trial so that they have been covered by systematic reviews.

#### Susanne

I can't give other women much advice, because there are many things on the market I haven't tried. But I know, that what works for one woman does not necessarily have the same effect on someone else.

#### 4.5. Herbal remedies and dietary supplements

Some plants include substances that might work in the body in a similar way to oestrogen [27], [28], [29]. These are called phyto-oestrogens. This group includes, for example, soya and red clover (*trifolium pratense*). Dietary

supplements manufactured out of these plants are often recommended to women for symptoms of the menopause. If you are taking a herbal medicine, it is important for your doctor to know so that he or she can explain if there are possible contraindications or a drug interaction problem with something else you are using.

## **Soya - Isoflavone**

Soya-based products are the best studied herbal medicine for menopausal symptoms. They include so-called isoflavones, and they belong to the phyto-oestrogen group. But the results of over 20 trials testing soya preparations and a soya-rich diet are contradictory [11], [23]. Women's hot flashes improved in some of the trials, but not in others.

Taking these products for longer and at higher doses means that adverse effects need to be taken into account. Some women who took high-dose soya-isoflavone for five years in a study developed a condition called endometrial hyperplasia [11]. Women who have this condition are at higher risk of developing endometrial cancer. However, taking isoflavones for a short time is not believed to cause health problems [30].

## **Red clover**

The evidence base on red clover (*trifolium pratense*) is patchy. Red clover has isoflavones, but they are different to the kind in soya. This means the evidence about soya does not necessarily apply to red clover. There is no conclusive evidence that red clover products can help with menopause symptoms like hot flashes [11], [23], [31]. There has also not been enough study on whether or not red clover has adverse effects.

## **Black cohosh**

Some herbal medicines containing black cohosh (*cimicifuga racemosa* or *actaea racemosa*) are licensed for use in Germany. However there is no strong evidence that black cohosh can relieve menopausal symptoms [11],[31]. About 5 out of 100 women (5%) of women who take black cohosh report adverse effects [32], such as stomach or gut problems, headaches, dizziness, nausea and allergies [31]. These usually go away when the medicine is no longer used.

Some people have experienced serious liver damage after using black cohosh. The European drug authority therefore recommends that people stop taking these preparations if

they develop signs of possible liver damage such as tiredness, loss of appetite, yellowing of the skin or eyes, darker urine or severe upper stomach pain with nausea and vomiting [33].

## **Other herbal options**

A variety of other herbal substances are used to try to relieve the symptoms of the menopause, including rhubarb (*rheum raphaniticum*), ginseng, dong quai (*angelica sinensis*), evening primrose oil (*oenothera biennis*), monk's pepper (*vitex agnes castus*) and kava (*piper methysticum*). There is not good evidence that any of these can relieve symptoms like hot flashes [11], [31]. Some of these preparations can have adverse effects, or they cause problems if they are taken with other medicines. For example it is possible that taking ginseng at the same time as an anti-clotting drug (like heparin or ASA - acetyl salicylic acid), or evening primrose oil, could cause bleeding. It is not possible, though, to give accurate and reliable information about how often adverse effects might happen with these products.

In Germany and several other countries, products containing kava have been taken off the market for safety reasons. Kava can cause allergic reactions and skin problems. Liver damage or an impact on the nervous system might be possible [31]. Again, there is not enough research to show how likely or common this might be.

## **Other complementary therapies**

Acupuncture is a part of traditional Chinese medical treatment. It is based on the theory of life energy circulating through the body, with imbalances leading to illness or pain. This energy is sometimes thought of as a kind of electricity in the body. Needles inserted at specific points of the body aim to affect this flow of energy.

There have been some trials of acupuncture to try to relieve menopausal symptoms, but this is really in the early stages and the quality of the research is not high [11]. It is therefore not possible to say whether or not acupuncture can help reduce hot flashes or other problems.

Chiropractic is a form of manual therapy that seeks to adjust imbalances in the spine and neck. This is thought to reduce stresses on the nerves and other problems than can lead to pain or ill health. There is not enough evidence to enable a judgment to be made on whether or

not it can help with menopausal symptoms, and the adverse effects are not well studied either [11].

#### 4.6. Medications other than hormone therapy

A range of drugs other than oestrogen-based hormones are also tried for the symptoms of the menopause. These include DHEA as well as some antidepressants. None of these have been shown conclusively to work in trials against hot flashes and other symptoms of the menopause [11], [34]. All of these drugs have adverse effects. Most of them have not been licensed for menopausal symptoms in Germany.

#### 5. Hormone therapy

##### 5.1. Weighing up the pros and cons

Hormone therapy (HT) often used to be called 'hormone replacement therapy' (HRT). Behind this name lay the idea that during and after the menopause, women needed to have oestrogen in particular 'replaced' or else they would have, in effect, an oestrogen deficiency. The term also gave the impression that a woman did not have to worry about adverse effects, because it was only giving back something that was always there naturally.

But this idea has been shown to be misleading. Using hormones for the menopause is not just a 'natural' replacement of hormones, but rather a drug treatment that, like all others, might have benefits which need to be weighed against potential harms. That is why we no longer use the term 'hormone replacement therapy'. That term is also not appropriate for treatments with so-called 'natural' or 'bio-identical' hormones, that are supposed to be identical to the body's own hormones.

Hormone treatments are drugs that need to be prescribed by a doctor. The aim is to relieve symptoms caused by the menopause. During the 1980s, it was proposed that HT could protect women against some illnesses that become more common as we age, such as heart disease. This belief led to more and more women taking hormones for longer and longer, even when there were no menopausal symptoms.

However trials have shown that longterm use of HT does not have the health benefits it was thought to have. For example, trials showed that a particular combined HT if anything increases the risk of heart attack and breast cancer [35]. Some of the side effects of HT happen straight away,

while others slowly increase with use over years. These adverse effects are an important element in making a decision for or against HT. You can read more about this below.

HT has risks and does not overall offer protection against illnesses in older age. However oestrogen-based HT is the most effective treatment for hot flashes and sweats. And for women who are having particularly severe symptoms, this might be the only option that really helps.

#### Susanne

I advise every woman to be more informed than I was, so that they can find out what will be best for them. I wouldn't necessarily rule hormones out if the symptoms are so strong and you cannot manage them with natural remedies.

A woman should be able to decide for or against HT without pressure from others. The arguments for and against also depend on the type of hormones and how long they are taken.

#### Karin

How did women manage before? Without drugs. I don't want to talk anyone out of hormone patches. It is alright if someone takes hormones. It just wasn't right for me.

#### Maria

I got more informed and went to talks. Then there was that trial from America, and taking hormones was no longer a question for me. I didn't take any drugs.

#### Hormones

There are now several varieties of hormone treatment (HT). The central option is a combination of oestrogen with a progesterone. Both of these types of hormone were produced by the ovaries before the menopause, but the production drops a lot during menopause. Small amounts continue to be produced by the body after the menopause though, for example by fatty tissues.

However oestrogen has been shown to cause changes to the endometrium (lining of the uterus) that can increase the chances of cancer of the endometrium or uterus. The chances of this are reduced if a progesterone is added to the oestrogen.

That is why there are two main types of oestrogen therapy. For women who have had their uterus removed by a hysterectomy, there are preparations that include only oestrogen. This is called monotherapy or unopposed oestrogen. For women with a uterus, the option is combined oestrogen therapy, which includes one of the progestones. The progestones have additional adverse effects, which we will explain below.

There are three other options types of hormone therapy that are available in some countries and are sometimes used. These are testosterone, tibolone and so-called 'bio-identical hormones'. More research is needed on all of these treatments [11]. Testosterone is not licensed for use for the menopause in Germany, and tibolone is not often used.

Tibolone is a synthetic hormone that works in a similar way to oestrogen and progesterone. There is some evidence that tibolone might be able to relieve hot flashes and other symptoms, but this has not been as well-established as oestrogen-based treatment [11]. Taking tibolone can cause vaginal bleeding or spotting, as well as weight gain and headaches [11]. European drug regulatory agencies have expressed a suspicion that longterm use of tibolone might increase the risk of breast and uterine cancer [36],[37], [38], [39], [40].

### **Oestrogen and progesterone**

There are now dozens of different hormone preparations for menopausal symptoms. The choice begins with the question of whether or not a woman has a uterus. Progesterone is added to protect the uterus from cancer, but it is not needed if the woman has had a hysterectomy. They would usually then use oestrogen alone.

These hormones are available in the following forms:

- Oral - tablets or capsules to swallow
- Nasal - a spray for the nose
- Patches or gels - applied to the skin
- Injection
- Vaginal - creams or gels inserted with an applicator, tablets or rings made out of soft plastic to insert in the vagina

The different types of HT also need to be used at different times. For example, oral tablets are usually taken every day, while a new patch will need to be applied once or

twice a week. A vaginal ring needs to be replaced about every three months [41].

### **Susanne**

I got a hormone patch, at first with a 25µg dose, but later increased to 50µg. After a few years, when the hot flashes weren't so strong any more, I went back to a 25µg dose.

For combined HT, there is also another variation. With continuous HT, the woman takes both hormones every day. With cyclic HT, the usual monthly cycle is followed more closely. This means that particular hormones will only be used some days of the month. It could mean that there is still a treatment for every day, but the contents might be different.

### **Vaginal treatments**

Using HT in the vagina is also called local treatment. This is primarily aimed at relieving vaginal dryness. Creams and other preparations can help relieve this symptom [11]. Even with local treatment, though, some of the hormone spreads through the body. This is why women with a uterus will use a preparation with progesterone as well as oestrogen. Vaginal treatments can cause some of the same side effects as oral therapy [13]. This includes:

- Vaginal bleeding that is similar to a light period
- Breast soreness or tenderness

Below we list the most important possible benefits and harms from HT. These depend a lot on how long the treatment is used. Short-term therapy is usually enough to handle symptoms of the menopause.

### **5.2. Effectiveness of short-term use**

#### **Hot flashes and sweats**

Oestrogen-based HT can reduce hot flashes and sweats quite a lot for many women [11]. But even for HT, there is no guarantee that they will go away completely. However, hot flashes if they continue are generally less severe [42],[43].


This effect on symptoms comes mostly from trials that lasted between three and six months. Women were taking oral HT, but patches might be just as effective [42].


When the results of these trials are looked at together, it shows that out of 10 women with hot flashes who take oestrogen-based therapy, after three to six months:


- About 2 of the women will still have hot flashes (15%)
- About 8 of the women will no longer have hot flashes (85%)

But a large part of this reduction is not because of the hormones. The trials show that for about 5 out of 10 women who did not take HT, the hot flashes went away by themselves:



 Women whose hot flashes would have stopped anyway

 Women whose hot flashes stop because of HT

 Women who still have hot flashes despite taking HT

Combined oestrogen therapy often cause vaginal bleeding or spotting, a bit like light periods. Some women find this bleeding so annoying that they stop taking HT because of that. HT can also cause breast tenderness or soreness [42],[44].

### Other symptoms

The question of whether or not HT can relieve other menopausal symptoms than hot flashes and sweats has not been so well studied. Researchers do not agree on whether HT can improve sex lives and influence incontinence (inability to control urine) or overall quality of life. [11],[45]. It is possible that women who are being woken at night by hot flashes get more sleep thanks to HT. That might improve quality of life.

### Body weight

Women gain a bit of weight as they get older. Studies show that weight increases whether or not women use HT [46]. The drugs do not cause weight gain, but they also cannot stop it.

### 5.3. Effectiveness of longterm use

#### Broken bones and osteoporosis

Longterm HT reduces the risk that women will break bones, such as having a hip fracture. It does not matter whether it is oestrogen alone or combined oestrogen-progesterone. This is because oestrogen slows down the loss of bone that happens after the menopause, and this might delay the start of osteoporosis for some women.

#### Bowel or colorectal cancer

The impact of HT on bowel cancer is more complicated. Therapy with oestrogen alone does not reduce the risk of bowel cancer [35]. But women who take combined HT for more than five years during and after the menopause get bowel cancer a little less often [35]. But when bowel cancer was detected in women who have been taking combined HT, it was more advanced. That makes it more difficult to treat.

### 5.4. Risks of hormone therapy

Assessing the risks of HT is not simple. This is because there are so many variations on the market, used in different combinations and forms. The longterm use of two particular forms of oestrogen-based therapy is the best studied. One includes so-called conjugated oestrogen (0.625 mg daily) and the other combines the same dose of oestrogen with the progesterone called medroxyprogesterone (2.5 mg daily). These treatments were tested in the USA in around 27,000 for six years. Both of these treatments are commonly prescribed in other countries, including Germany.

Because there have not been direct comparisons between all the different forms of HT, it is not clear whether the harms that happened in this big trial are the same or worse for other forms of HT. So experts have different opinions, in the absence of a clear answer. Internationally, drug regulatory authorities have decided that women would be more protected if it was assumed that all hormone treatments have the same risk of causing harm [36],[47]. One thing is clear though: the potential

harms of combined HT are different to those of taking oestrogen alone.

## Heart attack and stroke

Many people used to think that HT could protect women from heart attacks. But this hope has faced a strong setback in recent years [35],[44],[48]. There is no known impact on heart attacks for women without a uterus who take oestrogen alone [35]. But women who are taking combined oestrogen therapy have a slightly increased risk of having a heart attack, particularly in the first year they are taking the drugs [35].

If a women has already been taking HT for years without having a heart attack, then her risk is no longer any higher than that of women who did not take HT. The question of whether or not HT might be able to reduce the risk of heart attack in younger women - those around 50 - is still unanswered. However this would not be likely to be a big difference, because heart attacks in healthy women around 50 are uncommon.

The risk of stroke also increases for women who take hormones for the menopause. That is true for both oestrogen alone and combined oestrogen therapy [35].

The numbers of women who have these adverse effects is shown in the table at the end of this article.

## Thromboembolism

A serious illness that needs to be taken into account with HT is thromboembolism. This happens when a blood clot gets stuck in a blood vessel, for example in the leg or in the lungs [35]. Here again there are differences between oestrogen alone and combined therapy: women taking oestrogen alone do not have a higher risk of thromboembolism [35]. But for women taking combination HT, the risk starts to increase from the start of treatment and keeps increasing. You can see more in the table on adverse effects at the end of this article.

## Breast cancer

Breast cancer is the potential complication from HT that has received the most attention. And again, there are differences depending on whether the treatment is monotherapy or combined oestrogen therapy. For women who take combined therapy for longer than five years, the risk of breast cancer noticeably rises [35]. But for women

who are only taking oestrogen because they do not need progesterone to protect their uterus, the picture is not so clear. According to the results of the major trial, there was no increased risk of breast cancer [35]. But international drug regulatory agencies have nevertheless considered that longterm treatment with oestrogen alone might also increase the risk of breast cancer. [36], [37],[38],[39],[40].

Some analysis has suggested that the risk of breast cancer from HT might be higher for European women than it was for the American women in the major trial [49]. One of the reasons for this might be because European doctors prescribe different hormones than their colleagues from the USA, at least in part.

You can read more about the risks of breast cancer in the table at the end of this article.

## Other adverse effects

Both forms of oestrogen-based therapy taken for five to seven years increase the risk of gallbladder disease serious enough to need an operation [35]. You can see how often this happens in the table at the end of this article.

The trial also had disappointing results about dementia: HT did not protect women against cognitive impairment or dementia. In fact, if anything, HT might be more likely to have a negative impact on cognitive ability in women older than 65 [35].

## 5.5. What happens when you stop taking hormones

Hormone therapy only helps relieve symptoms of the menopause while the hormones are being taken regularly. So an important question for women is what happens if a woman stops taking the hormones, after six months or a year, for example? Unfortunately there is no clear answer. There are two possibilities. One possibility is that the phase with symptoms is already over, so that stopping causes no problems. The other possibility is that the symptoms will return once the hormones are stopped.

The best evidence at the moment comes from a trial with about 16,000 women in the USA [50]. The women in this study were taking hormones for six years on average. After they stopped, they were asked how it was going for them. The answer was that the symptoms came back for more than half the women. That raised the possibility that by taking HT, women might have delayed the time when

they would need to cope with hot flashes and sweats but not avoided it completely.

**Susanne**

They never went away completely. But they were not as bad. They came much less often... I had the feeling; now I can cope with this.

It is possible to have lower doses of HT so that the woman still has the symptoms, but they are not a major burden. That gives women the chance to notice themselves when the symptoms are going away.

An important question too is what happens about the health risks: Does the higher risk of breast cancer with combined therapy stay if women stop taking the drugs or does the woman's risk go back to the usual risk? Unfortunately there is no reliable answer to this question. Some early study results suggest that it might be possible that the risk reduces over time.

5.6. Table: Benefits and harms of hormone therapy

**Impact of daily combined oestrogen-progesterone therapy on healthy women**

*The estimation of risks of hormone therapy depends on the length of treatment. Women who want to use hormones to relieve menopausal symptoms can usually get by with short-term treatment. The following numbers come from the results of the Women's Health Initiative Study. The numbers are averages that aim to provide an idea of how often things might happen. A woman's actual risk depends on her individual situation, and it might be higher or lower than the figures in this table.*

Illness or event	Impact of combined oestrogen therapy within the first 12 months compared with women taking no HT	Impact of combined oestrogen therapy for up to five years compared with women taking no HT
Heart attack	Increased risk: an extra 2 heart attacks for every 1,000 women	Not clear

Thromboembolism (blood clot)	Increased risk: an extra 4 clots for every 1,000 women	Increased risk: an extra 11 clots for every 1,000 women
Stroke	No noticeable change	Increased risk: an extra 5 strokes for every 1,000 women
Breast cancer	No noticeable change	Increased risk: an extra 4 breast cancers for every 1,000 women
Gallbladder disease requiring operation	No noticeable change	Increased risk: an extra 11 operations for every 1,000 women
Bowel (colorectal) cancer	No noticeable change	Reduced risk: 3 fewer bowel cancers for every 1,000 women
Hip fracture	No noticeable change	Reduced risk: 3 fewer hip fractures for every 1,000 women

**The impact of daily oestrogen therapy on healthy women (without a uterus)**

*The estimation of risks of hormone therapy depends on the length of treatment. Women who want to use hormones to relieve menopausal symptoms can usually get by with short-term treatment. The following numbers come from the results of the Women's Health Initiative Study. The numbers are averages that aim to provide an idea of how often things might happen. A woman's actual risk depends on her individual situation, and it might be higher or lower than the figures in this table.*

Illness or condition	Impact of oestrogen-only therapy within the first 12 months compared with women taking no HT	Impact of oestrogen-only therapy for up to five years compared with women taking no HT

Stroke	No noticeable change	Increased risk: an extra 8 strokes for every 1,000 women
Gallbladder disease requiring an operation	No noticeable change	Increased risk: an extra 21 operations for every 1,000 women
Hip fracture	No noticeable change	Reduced risk: 4-5 fewer hip fractures for every 1,000 women

## Glossary

### colorectal cancer

Colorectal cancer is cancer in the large bowel (including the colon) and/or the rectum. “Colo” stands for the colon, and “rectal” for the rectum. Colorectal cancer is one of the most common forms of cancer.

### hormones

“Hormones” is the collective term for different types of messenger substances in the body. They are produced in different organs or tissues and released into the blood or the lymphatic system to be distributed throughout the body. Hormones only have an effect on those parts of the organism that have a corresponding docking site. This is how hormones can have such specific effects. Insulin, estrogens, vasopressin and thyroxine are some well-known hormones. Many medical ingredients imitate the effect of hormones.

### evidence

Evidence is what we call scientific proof from well-conducted, good-quality scientific trials that have been carefully designed to answer specific questions. Depending on the types of questions, different scientific research methods (types of study) are most appropriate to find reliable answers to these questions. Randomized controlled trials (RCTs), for example, are the best way to get reliable evidence on the effectiveness of medical treatments (interventions). This type of study, however, is not the best form of evidence for all possible questions, and does not provide the best answers to all kinds of questions, either. Epidemiological studies, for example, are very suitable for establishing well-founded proof for the spreading of a disease in the population.

### systematic review

Systematic reviews pull together the evidence on a specific question. A systematic review sets out to find all the trials that have put that particular question to the test. The quality of the trials are then evaluated and then results analyzed and explained. Often, the results of trials can then be summarized together through a statistical method called meta-analysis.

### acupuncture

Acupuncture is a complementary form of therapy used in traditional Chinese medicine. A doctor inserts thin needles at precisely defined points on the body. This is supposed to loosen what are thought to be blockages in the body or to stimulate or calm different organs.

### dietary supplement

Dietary supplements (also known as food supplements or nutritional supplements) are concentrated vitamins, minerals, trace elements, fibers and/or other substances that are intended to supplement the diet. Advocates of dietary supplements claim that they have a certain, often preventive or strengthening effect on the body. They are available as capsules, pills, powder or ampules, for example. From a legal point of view, dietary supplements rank among foods and therefore – as opposed to medications – do not need official approval. More information is available on the website of the German Federal Institute for Risk Assessment (Bundesinstitut für Risikobewertung, BfR): To the BfR website (in English)

## Sources

- [1] Schultz-Zehden B. Körpererleben im Klimakterium. *Journal für Menopause* 1998; 5: 10-17.
- [2] Walter CA. The psychosocial meaning of menopause: women's experiences. *J Women Aging* 2000; 12: 117-131.
- [3] Avis NE, McKinlay SM. The Massachusetts Women's Health Study: an epidemiologic investigation of the menopause. *J Am Med Womens Assoc* 1995; 50: 45-49.
- [4] Hvas L. Positive aspects of menopause: a qualitative study. *Maturitas* 2001; 39: 11-17.
- [5] Utian WH, Boggs PP. The North American Menopause Society 1998 Menopause Survey. Part I: postmenopausal women's perceptions about menopause and midlife. *Menopause* 1999; 6: 122-128.
- [6] Papini DR, Intrieri RC, Goodwin PE. Attitude toward menopause among married middle-aged adults. *Women Health* 2002; 36: 55-68.
- [7] Mansfield PK, Koch PB, Gierach G. Husbands' support of their perimenopausal wives. *Women Health* 2003; 38: 97-112.
- [8] World Health Organization (WHO). *Research on the menopause in the 1990s: WHO Technical Report Series*. Genf: World Health Organization; 1996.
- [9] Morris E, Rymer J. Menopausal symptoms. *Clin Evid* 2003; : 2138-2150.
- [10] Greendale GA, Lee NP, Arriola ER. The menopause. *Lancet* 1999; 353: 571-580.
- [11] Nelson HD, Haney E, Humphrey L, Miller J, Nedrow A, et al.. *Management of menopause-related symptoms. Evidence Report / Technology Assessment No. 120*. Rockville: Agency of Healthcare Research and Quality (AHRQ). 2005.
- [12] Melby MK, Lock M, Kaufert P. Culture and symptom reporting at menopause. *Hum Reprod Update* 2005; 11: 495-512.
- [13] Suckling J, Lethaby A, Kennedy R. *Local oestrogen for vaginal atrophy in postmenopausal women*. 2003.  
( <http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD001500/frame.html>)
- [14] Frackiewicz EJ, Cutler NR. Women's health care during the perimenopause. *J Am Pharm Assoc* 2000; 40: 800-811.
- [15] Soares CN, Cohen LS. The perimenopause, depressive disorders, and hormonal variability. *Sao Paulo Med J* 2001; 119: 78-83.
- [16] Tunstall-Pedoe H. Myth and paradox of coronary risk and the menopause. *Lancet* 1998; 351: 1425-1427.
- [17] Barrett-Connor E. Sex differences in coronary heart disease. Why are women so superior? The 1995 Ancel Keys Lecture. *Circulation* 1997; 95: 252-264.  
( <http://circ.ahajournals.org/cgi/content/full/95/1/252>)
- [18] Lawlor DA, Ebrahim S, Davey Smith G. Role of endogenous oestrogen in aetiology of coronary heart disease: analysis of age related trends in coronary heart disease and breast cancer in England and Wales and Japan. *BMJ* 2002; 325: 311-312.
- [19] McKinlay SM, Brambilla DJ, Posner JG. The normal menopause transition. *Maturitas* 1992; 14: 103-115.
- [20] Hickey M, Davis SR, Sturdee DW. Treatment of menopausal symptoms: what shall we do now?. *Lancet* 2005; 366:

409-421.

- [21] Bertero C. What do women think about menopause? A qualitative study of women's expectations, apprehensions and knowledge about the climacteric period. *Int Nurs Rev* 2003; 50: 109-118.
- [22] Avis NE, Stellato R, Crawford S, Johannes C, Longcope C. Is there an association between menopause status and sexual functioning?. *Menopause* 2000; 7: 297-309.
- [23] Krebs EE, Ensrud KE, MacDonald R, Wilt TJ. Phytoestrogens for treatment of menopausal symptoms: a systematic review. *Obstet Gynecol* 2004; 104: 824-836.
- [24] Asikainen TM, Kukkonen-Harjula K, Miilunpalo S. Exercise for health for early postmenopausal women: a systematic review of randomised controlled trials. *Sports Med* 2004; 34: 753-778.
- [25] Kessel B, Kroneneberg F. The role of complementary and alternative medicine in management of menopausal symptoms. *Endocrinol Metab Clin N Am* 2004; 33: 717-739.
- [26] Newton KM, Buist DS, Keenan NL, Anderson LA, LaCroix AZ. Use of alternative therapies for menopause symptoms: results of a population-based survey. *Obstet Gynecol* 2002; 100: 18-25.
- [27] Cornwell T, Cohick W, Raskin I. Dietary phytoestrogens and health. *Phytochemistry* 2004; 65: 995-1016.
- [28] Keller C, Fullerton J, Mobley C. Supplemental and complementary alternatives to hormone replacement therapy. *J Am Acad Nurse Pract* 1999; 11: 187-198.
- [29] Murkies AL, Wilcox G, Davis SR. Clinical review 92: Phytoestrogens. *J Clin Endocrinol Metab* 1998; 83: 297-303.
- [30] Huntley AL, Ernst E. Soy for the treatment of perimenopausal symptoms - a systematic review. *Maturitas* 2004; 47: 1-9.
- [31] Huntley AL, Ernst E. A systematic review of herbal medicinal products for the treatment of menopausal symptoms. *Menopause* 2003; 10: 465-476.
- [32] Dog LT, Powell KL, Weisman SM. Critical evaluation of the safety of *Climicifuga racemosa* in menopause symptom relief. *Menopause* 2003; 10: 299-313.
- [33] EMEA Committee on Herbal Medicinal Products. Annex 1: Assessment of case reports connected to herbal medicinal products containing *cimicifugae racemosae rhizoma* (black cohosh, root). London: EMEA. 8 May 2007.  
<http://www.emea.europa.eu/pdfs/human/hmpc/26925806en.pdf> Accessed 2007- 5- 8
- [34] Somboonporn W, Davis S, Bell R, Seif MW. *Testosterone for peri- and postmenopausal women*. 2005.  
( <http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD004509/frame.html>)
- [35] Farquhar CM, Marjoribanks J, Lethaby A. *Long term hormone therapy for perimenopausal and postmenopausal women*. 2005.  
( <http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD004143/frame.html>)
- [36] Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM). *Änderung der Zulassung für die Arzneimittel: Estrogen- und Estrogen- Gestagen-haltige Arzneimittel zur Hormonsubstitution*. 0.  
( <http://www.bfarm.de/de/vigilanz/stufenpl/anschraugx.pdf>)
- [37] Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM). *BfArM informiert über neue Ergebnisse zur*

*Hormontherapie mit Tibolon nach den Wechseljahren.* 0.

( [http://www.bfarm.de/de/vigilanz/am\\_sicher\\_akt/index.php?more=tibolon.php](http://www.bfarm.de/de/vigilanz/am_sicher_akt/index.php?more=tibolon.php))

[38] Medicines and Healthcare products Regulatory Agency (MHRA). *Latest data on HRT from the UK Million Women Study.* 2005.

( [http://www.mhra.gov.uk/home/idcplg?IdcService=SS\\_GET\\_PAGE&useSecondary=true&ssDocName=CON2014999&ssTargetNodeId](http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&useSecondary=true&ssDocName=CON2014999&ssTargetNodeId))

[39] Medicines and Healthcare products Regulatory Agency (MHRA). *Questions and answers related to hormone replacement therapy and endometrial cancer.* 0.

( <http://www.mhra.gov.uk/home/groups/pl-p/documents/drugsafetymessage/con019452.pdf>)

[40] Medicines and Healthcare products Regulatory Agency (MHRA). *Safety of HRT.* 0.

( <http://www.mhra.gov.uk/home/groups/pl-p/documents/drugsafetymessage/con019453.pdf>)

[41] Bundesverband der Pharmazeutischen Industrie (BPI), Verband Forschender Arzneimittelhersteller (VFA), Bundesfachverband der Arzneimittel-Hersteller (BAH), Deutscher Generikaverband. *Arzneimittelverzeichnis für Deutschland (einschließlich EU-Zulassungen und bestimmter Medizinprodukte).* Frankfurt/ Main: Rote Liste Service. 2004.

[42] MacLennan AH, Broadbent JL, Lester S, Moore V. *Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flushes.* 2004.

( <http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD002978/frame.html>)

[43] Nelson HD. Commonly used types of postmenopausal estrogen for treatment of hot flashes: scientific review. *JAMA* 2004; 291: 1610-1620.

[44] Gabriel-Sanchez R, Carmona L, Roque M, Sanchez-Gomez LM, Bonfill X. *Hormone replacement therapy for preventing cardiovascular disease in post-menopausal women.* 2005.

( <http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD002229/frame.html>)

[45] Moehrer B, Hextall A, Jackson S. *Oestrogens for urinary incontinence in women.* 2003.

( <http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD001405/frame.html>)

[46] Norman RJ, Flight IHK, Rees MCP. *Oestrogen and progestogen hormone replacement therapy for peri-menopausal and post-menopausal women: weight and body fat distribution.* 1999.

( <http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD001018/frame.html>)

[47] Food and Drug Administration (FDA). *Estrogen and estrogen with progestin therapies for postmenopausal women.* 0.

( [http://www.fda.gov/cder/drug/infopage/estrogens\\_progestins/](http://www.fda.gov/cder/drug/infopage/estrogens_progestins/))

[48] Magliano DJ, Rogers SL, Abramson MJ, Tonkin AM. Hormone therapy and cardiovascular disease: a systematic review and meta-analysis. *BJOG* 2006; 113: 5-14.

[49] Lee SA, Ross RK, Pike MC. An overview of menopausal oestrogen-progestin hormone therapy and breast cancer risk. *Br J Cancer* 2005; 92: 2049-2058.

[50] Ockene JK, Barad DH, Cochrane BB, Larson JC, Gass M et al.. Symptom experience after discontinuing use of estrogen plus progestin. *JAMA* 2005; 294: 183-193.

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