
Biological changes during the menopause

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This chapter focuses on the biological changes that occur prior to, during and after the menopause. To help understand these changes the structure of the female reproductive organs and the process of normal menstruation is firstly outlined.

The female reproductive organs

The female reproductive system comprises the uterus (or womb), two ovaries connected to the uterus by fallopian tubes, and the vagina. Figure 1.1 shows the position of these organs.

The uterus is a muscular organ shaped like a pear. It is about $7\frac{1}{2}$ cm long and 5 cm wide, but is able to stretch during pregnancy as the baby grows. The lining of the uterus, called the endometrium, contains numerous blood vessels, which provide nourishment for the growing baby. When a woman is not pregnant, menstruation occurs as the endometrium is shed. The cervix is the lower part of the uterus and connects to the vagina.

The two tubes leaving the uterus are called the fallopian tubes, each being about 10 cm long. These tubes provide a connection between the ovaries and the uterus so that the egg (ovum) can be transported to the uterus for implantation. The ovaries are the female sex glands and sit on either side of the uterus. They contain millions of ovarian follicles and each month one of these follicles matures to produce an egg. The ovaries also produce the female hormones, oestrogen and progesterone, and the male hormones, testosterone and androstenedione.

The menstrual cycle

From puberty to the menopause, women experience a series of menstrual cycles, each occurring approximately every 28 days. During each cycle a sequence of bodily changes occur. The menstrual cycle is divided into three phases:

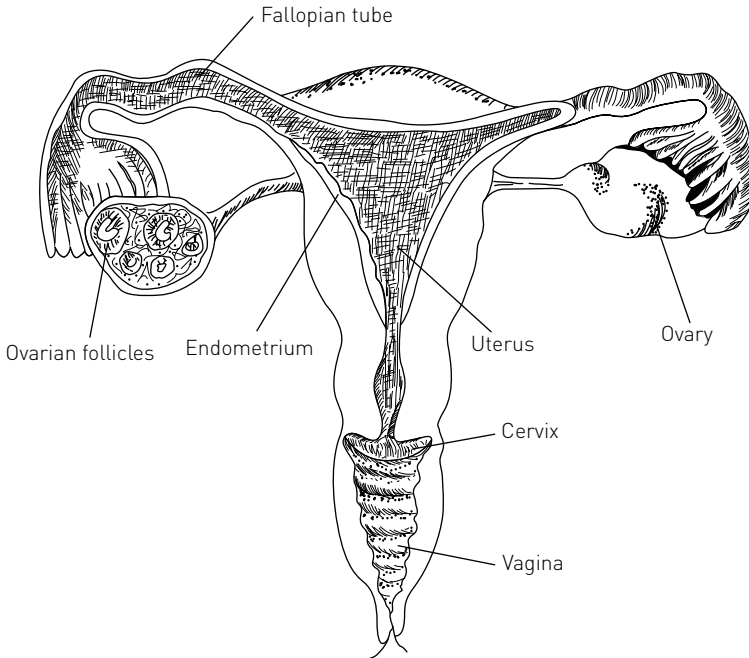


Figure 1.1. The female reproductive system.

- (1) The follicular phase – during this phase, follicle-stimulating hormone (FSH), which is produced by the pituitary gland (situated beneath the base of the brain) stimulates the growth of several ovarian follicles. Generally, just one follicle matures and contains an ovum (egg). As the follicle grows, it produces the hormone oestrogen, which stimulates the lining of the womb to thicken. Once the ovarian follicle has reached maturity, it ruptures (ovulation) and the ovum is released. The follicle then stops producing any more oestrogen and, in turn, the lining of the womb ceases to get any thicker.
- (2) The luteal phase – after ovulation what remains of the ovarian follicle is stimulated by a hormone called luteinising hormone to develop the corpus luteum. The corpus luteum then produces the hormones, progesterone and oestrogen, which stimulate the lining of the womb to produce a watery fluid that helps the sperm to swim towards the fallopian tubes for fertilisation. If fertilisation does not occur, the next phase of the cycle begins.
- (3) The menstrual phase – if fertilisation of the egg does not occur, the production of luteinising hormone ceases, and the corpus luteum breaks down. In turn, the production of progesterone and oestrogen decreases and the lining of the womb breaks down, leading to menstruation.

The ovarian hormones

The ovaries produce both female and male hormones. The main female hormones are oestrogen and progesterone and the main male hormones are testosterone and androstenedione.

Oestrogen

There are two types of oestrogen, oestradiol and oestrone. Oestradiol is the main source of oestrogen for women up until the time of the menopause, and is produced by the ovaries. From puberty to around the age of 30, the levels of oestradiol reach their highest (average blood levels of 450 to 550 pmol/l). After around the age of 30 years the production of oestradiol gradually lessens. A few years before the menopause, oestradiol blood levels are around 200–300 pmol/l. After the menopause, however, levels of oestradiol fall to around 80 pmol/l.

The other source of oestrogen (oestrone) comes from the adrenal glands, which sit on the top of each kidney. These glands produce a male hormone called androstenedione, which is converted in the fatty tissue to an oestrogen called oestrone. The average level of oestrone after the menopause is around 100 pmol/l. Since the conversion of androstenedione takes place in the fatty tissue, women with greater amounts of fatty tissue produce higher levels of oestrone.

The main functions of oestrogen are to:

- Help regulate menstruation.
- Help prepare the body for fertilisation.
- Stimulate the lining of the womb so that it thickens.
- Maintain lubrication of the vagina.
- Help maintain the acid level in the vagina, thereby protecting against infections.
- Work in conjunction with progesterone to help with the breakdown of the endometrium (lining of the womb) in the second stage of the menstrual cycle.
- Maintain a supply of calcium to the bones.
- Help maintain the health of blood vessel walls.
- Reduce the blood cholesterol level.
- Bring about the development of secondary sex characteristics, i.e. the breasts and nipples.
- Influence body shape at puberty, resulting in women having broader hips and narrower shoulders than men, and a tendency to deposit fat on the hips and thighs.

- Increase elasticity of the skin.
- Influence the growth of body hair, so that women have less body hair and more scalp hair than men.
- Stop the growth of the arm and leg bones, resulting in women being generally shorter than men.

Progesterone

The ovaries provide the only source of progesterone, where it is produced after ovulation.

The main functions of progesterone are to:

- Help prepare the body for fertilisation and maintain pregnancy.
- Work in conjunction with oestrogen, to help with the breakdown of the endometrium (lining of the womb) in the second stage of the menstrual cycle.
- Help regulate menstruation.
- Change the mucus produced by the glands in the cervix so that it becomes thick and acidic, thus protecting a potential pregnancy from infection.
- Aid development of the glands in the breast.
- Increase water and salt retention, which may lead to painful breasts and weight gain.
- Improve the immune system.
- Have a relaxant effect on some of the muscles in the body (i.e. stomach, uterus, and fallopian tubes).
- Increase production of sebum, leading to more oily skin and spots.

In addition, progesterone may have an impact on mood, leading to an increased irritability. Hence, women often report experiencing changes in mood prior to having a period when the levels of progesterone are at their highest.

Testosterone and androstenedione

Both female and male sex hormones are produced by men and women, but at different levels. Up until the menopause, women have about one-tenth of the amount of male sex hormones that are found in men.

Both testosterone and androstenedione are produced in the ovary, and after the menopause, these hormones go on being produced for a few years. In addition, androstenedione is produced by the adrenal glands (on top of each kidney). The amount of androstenedione produced by the adrenal glands is unchanged after the menopause, although after the menopause it is converted to a form of oestrogen (oestrone) in the fatty tissue.

The role of male hormones in women is not fully understood, although they have been shown to:

- Increase libido.
- Stimulate the growth of pubic, facial and underarm hair.
- Possibly enhance mood.
- Increase the density of specific bones (for example, the hip bone).

As can be seen from the above lists, both male and female hormones have a number of functions within the body. Although levels of these hormones change around the time of the menopause, this does not happen suddenly. Ovarian changes occur from around the age of 35 until around the age of 55 to 60 years.

Body changes leading to the menopause

A woman is born with around seven million ovarian follicles, containing egg cells. This number decreases from birth, until there are none remaining after the menopause. The reduction in the number of follicles is more rapid once women reach their mid-thirties and by the mid-forties, there are significantly reduced numbers of follicles. Over the next few years the body increases its efforts to stimulate the remaining follicles to produce egg cells. At this time, menstruation may become irregular or may change so that it is heavier or lighter than usual.

As women enter their forties, the ovarian follicles become less sensitive to stimulation by the hormone, follicle-stimulating hormone (FSH), which is produced by the pituitary gland beneath the base of the brain. Although the pituitary gland increases the production of FSH, ovulation does not always occur during each menstrual cycle.

During the years that women approach the menopause, the production of follicle-stimulating hormone can reach 10–15 times more than that which occurs at the time of the menopause. A blood test to measure the level of follicle-stimulating hormone may be carried out to determine whether a woman is approaching the menopause. However, since the levels of this hormone can fluctuate considerably, it is usually necessary to repeat the test over a period of time to be sure that ovulation has not recommenced. Many doctors feel that the reliability of this blood test is not good enough to make it of much value in determining whether or not a woman is approaching the menopause.

Although ovulation does not necessarily occur during each cycle prior to the menopause, women continue to menstruate since the ovary produces enough oestrogen to stimulate the growth of the lining of the womb. Bleeding occurs when

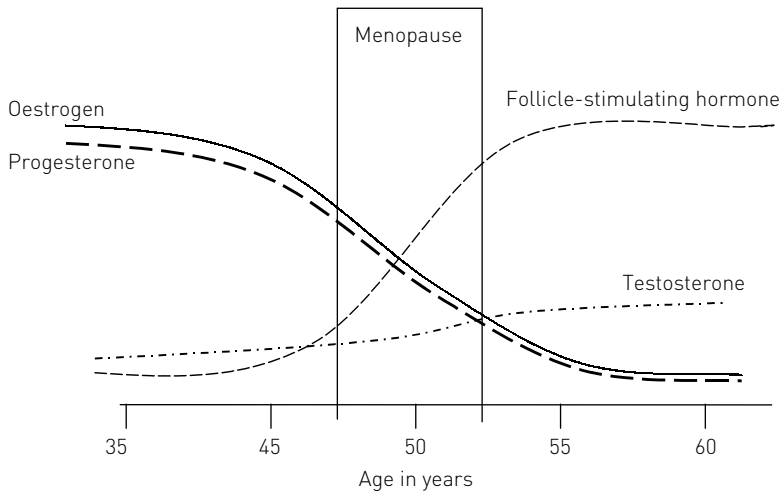


Figure 1.2. Changes in hormone levels over the years.

the oestrogen level falls. However, periods tend to be irregular, painless and heavy in cycles where ovulation does not occur.

Changes in the length of the menstrual cycle frequently occur in the time leading up to the menopause. Women sometimes notice that their cycle becomes shorter, often lasting for just 18–24 days. This is usually followed by a lengthening of the cycle duration, with occasional periods being missed. Eventually, as the menopause occurs, the periods stop altogether.

As can be seen in Figure 1.2, from around the age of 30 years, levels of oestrogen and consequently, progesterone, start to fall. Although initially there is quite a gradual decline in oestrogen production, the rate of decline speeds up around the menopause.

The term ‘menopause’ literally means the cessation of menstruation, and it occurs when the body has exhausted its supply of ovarian follicles containing eggs. Once the ovarian follicles cease to exist, the hormone oestrogen is no longer produced in the large quantities needed to stimulate growth of the lining of the womb (endometrium) in preparation for fertilisation. Thus, much smaller quantities of oestrogen are produced and menstruation ceases. Doctors tend to define women as menopausal once they have ceased to menstruate for 12 consecutive months.

When does the menopause occur?

The average age of the menopause in Britain is 51 years, with most women becoming menopausal between the ages of 45 and 55 years. Eighty per cent of

women will have reached the menopause by the age of 54 years. A number of factors have been found to contribute to the age of menopause:

- Smoking – women who smoke tend to experience the menopause on average, $1\frac{1}{2}$ to 2 years earlier than women who do not smoke.
- Weight – women with a greater body mass tend to have a later menopause than thinner women.
- Genetics – mothers and daughters tend to experience the menopause at a similar age.

In addition to factors contributing to the age of the menopause, a very small proportion of women experience what is called, 'premature menopause', where menstruation ceases before the age of 40 years.

Premature menopause

The cause of premature menopause is largely unknown, but it occurs when the ovaries fail to respond to stimulation by the pituitary gland. The pituitary gland produces the hormones, follicle-stimulating hormone and luteinising hormone, which are necessary for the production of the ovarian hormones oestrogen and progesterone. Thus, women experiencing a premature menopause will have high blood levels of follicle-stimulating hormone and luteinising hormone, but the ovaries do not produce ovarian follicles. Without ovarian follicles, oestrogen levels fall and progesterone is not produced.

Premature menopause can occur at any age before 40 years, and may even happen shortly after menstruation begins. Although very few women (just one per cent) experience premature menopause, those who do may suffer considerable distress. In addition to experiencing symptoms such as hot flushes, night sweats and vaginal dryness, women who experience a premature menopause are often concerned about their ability to have children. Although in the past, women were advised that they would not be able to conceive, advances in fertility technology mean that it may now be possible to achieve a pregnancy. In particular, treatment with a fertilised ovum from a donor may be possible. In addition, ovarian function has been shown to recommence in a few women, either spontaneously, or while taking hormone replacement therapy. Even so, the chances of becoming pregnant remain low.

The physical effects of reduced oestrogen levels

Many areas of the body are sensitive to oestrogen and therefore a reduction in oestrogen gives rise to a number of physical changes. The areas of the body sensitive to oestrogen include:

- Breasts.
- Blood vessels and the heart.
- Bones.
- Brain.
- Urinary organs (bladder and urethra).
- Genital organs (uterus, vagina and vulva).
- Skin.
- Hair.

Breasts

Before reaching the menopause, the breast tissue changes during each menstrual cycle and often results in women experiencing tender breasts during the days before a period starts. For some women, the breasts feel lumpy, especially near the armpits. After the menopause, these cyclical changes in breast tissue stop and the breasts feel soft, less firm and not lumpy.

The risk of breast cancer increases with age, and although all women are encouraged to carry out regular breast checks to look for changes, this becomes even more important as women get older. Although many breast changes are harmless and do not require further action, it is important to have any changes investigated, as there is a small chance that it could be the first signs of cancer. Any changes in the breasts, therefore, should be reported to the doctor as a matter of urgency. If there is a cancer present, treatment is more effective if started early.

Women should be aware of how their breasts normally look and feel, so that during everyday activities such as bathing, showering and dressing, they can detect any changes at an early stage. In 1998, the Department of Health issued a paper called *Be Breast Aware*, where a five-point code of breast awareness stated that women should:

- (1) Know what is normal for them.
- (2) Become familiar with the look and feel of their own breasts.
- (3) Know what changes to look for.
- (4) Report any changes without delay.
- (5) Attend three-yearly breast screening once they reach the age of 50 years.

In particular, changes that women should observe for are:

- Changes in the shape of the breast, especially when caused by arm movements or by lifting the breasts.
- Any puckering or dimpling in the skin.

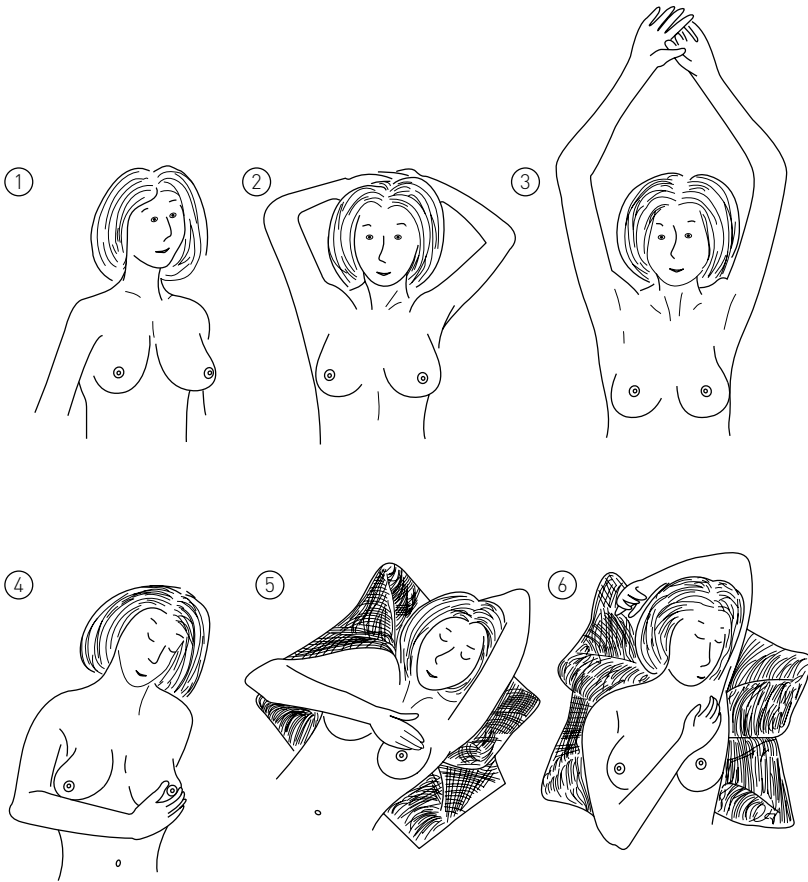


Figure 1.3. Carrying out self breast examination

Step one: Stand in front of the mirror with your hands by your sides or on your hips and look for any differences there may be between the two breasts. Then place your hands on your hips with your elbows pointing outwards and press inwards until your chest muscles tighten. Look carefully for any changes in the shape of your breasts, turning from side to side and leaning forward.

Step two: Raise your hands above your head and look for any changes in the appearance of your breasts.

Step three: Stretch your arms above your head, again looking for any changes in your breasts.

Step four: Check the nipples for any changes.

Step five: Many women find that the shower is a good place to carry out this and the next step. Some women, however, may find it easier lying down on the bed. Raise your left arm and use your fingers of your right hand to explore the left breast. Do not squeeze or prod the breast, but instead, keep your fingers together and use them flat to feel every part of the breast. Do the same with the other breast.

Step six: Again, using your fingers, feel between the breast and the armpit and then the area leading up to the collar bone.

- Any new discomfort or pain in one breast.
- Any lumps or bumpy areas in one breast or armpit, which appear different from the other breast or armpit.
- Discharge from the nipple.
- Bleeding or moist areas of the nipple that don't heal easily.
- Rashes on or around the nipple.
- Any change in nipple position, such as being pulled in, or pointing in a different direction.

Many women find it convenient to carry out self-checks of their breasts when preparing for a bath or a shower. Figure 1.3 may help to guide you through the steps of breast examination.

In addition to breast awareness, from the age of 50 years, women are advised to have a mammogram every three years. This is an X-ray procedure, which can detect any breast changes at an early stage. Because the breast tissue prior to the menopause is dense, it is difficult to accurately detect any breast changes, and therefore mammography is not routinely offered to women under the age of 50.

Blood vessels and the heart

Up until the menopause, heart disease is five times more common in men than it is in women. Following the menopause, however, there is a sharp increase in the incidence of heart disease amongst women. The mechanisms that increase women's risk of heart disease after the menopause are still not fully understood, and research is ongoing in this area. Studies suggest, however, that oestrogen affects the heart through its ability to influence the blood cholesterol level, the clotting mechanism, the blood vessel walls, and the production of insulin.

Research has shown that after the menopause, there is anything between a two and twenty per cent increase in blood cholesterol level, suggesting that oestrogen reduces the level of cholesterol in the blood. In addition, a further fat found in the blood (triglycerides) has been found to increase by between seven and thirty-five per cent after the menopause. The body's supply of oestrogen, therefore, appears to protect women against the development of atherosclerosis (where the blood vessels get 'furred up'). Furring up of the blood vessels, not only reduces the amount of blood that can get to important organs, such as the brain and the heart, but also increases the risk of a thrombosis (a blood clot) occurring in the blood vessels leading to these organs. Studies have also found that oestrogen acts directly on the blood vessel walls, causing dilation of the vessels,

and therefore improving the blood supply to vital organs such as the heart and the brain.

The clotting mechanism in the body is complex, with a number of different clotting factors acting in different ways to decrease and increase clotting as the need arises. Studies have shown that before the menopause women are less likely than men to experience arterial thrombosis (blood clots), and therefore, the body's oestrogen appears to be protective against this type of blood clot.

Older women have been shown to be less able to control the breakdown of carbohydrates, and consequently the body produces higher levels of insulin. Research has suggested that not only is this reduction in control over carbohydrates linked to low levels of oestrogen, but that it is an important mechanism in the development of heart disease.

See also Chapter 5 for other factors influencing heart disease and ways of minimising the risks, and Chapter 8 for the impact of HRT on heart disease.

Bones

Bone is a living tissue, and is constantly changing in structure. In adults, the entire skeleton is completely replaced every 7 to 10 years. There are two mechanisms within the body that maintain bone formation. Firstly, the bone is formed by *osteoblast* cells, using minerals such as calcium; and secondly, the bone is resorbed by *osteoclast* cells, which maintain the shape of the growing bone. These two mechanisms are kept in balance by hormones such as oestrogen, parathyroid and calcitonin.

In both men and women, bone mass rises from childhood, until it peaks around the late twenties. Over the following ten years or so, the balance between bone formation and bone breakdown stays stable. After this, from the age of around 40, both men and women gradually start to lose bone mass as part of the general ageing process. For women, however, bone loss is more rapid and accelerates in the years after the menopause. When oestrogen levels fall around the time of the menopause, the rate of bone resorption by osteoclast cells increases, but the rate of bone formation by osteoblast cells remains the same. Hence, there is a gradual loss in bone mass. For some women, the bone mass falls significantly and the bones become thin and vulnerable to being broken. This is termed 'osteoporosis' or 'brittle bone disease'. The rate of bone loss increases in the years immediately after the menopause, with up to 20 per cent of bone loss occurring in the first 10 years after menopause. The rate of bone loss slows thereafter.

Osteoporosis generally affects the spine first, with crush fractures resulting in a loss of height, curving of the spine and long-term backache. A woman's risk of developing osteoporosis, and consequent broken bones, depends on the peak bone mass (the peak bone density that is reached in the late twenties), and the rate of bone loss. Peak bone mass is increased by factors such as a diet rich in calcium

and weight-bearing exercise. The age and rate of bone loss is influenced by factors such as the menopause, family history, smoking, and excessive alcohol intake. A woman's chances of sustaining hip fracture doubles if her mother has a history of hip fracture.

See also Chapter 5 for further information about factors influencing osteoporosis and ways of reducing the chances of developing this disease.

Brain

Oestrogen has been found to be necessary for the maintenance of healthy tissue in a number of areas of the brain, in particular the area of the brain responsible for memory. This area of the brain is also the place that becomes diseased during Alzheimer's disease (see Chapter 5).

In addition to memory, a number of studies have shown that oestrogen improves mood. Progestogens, however, which are synthetic forms of progesterone, have been found to decrease some of the positive effects of oestrogen on mood. But it is important to note that low mood is very different from a clinically diagnosed depressive disorder: they arise from the alteration of different mechanisms within the brain. Indeed, studies have shown that women with clinical depression tend to get worse when taking oestrogen replacement therapy.

In much the same way that the body's oestrogen appears to be protective against heart disease, it also seems to offer some protection against strokes.

The urinary organs

The body's supply of oestrogen has been shown to influence many aspects of the urinary organs. It maintains the pliability and softness of the lining of the urethra (the tube from where urine is passed), it maintains the elasticity of the bladder, and it possibly decreases the irritability of the urethral and bladder muscle. After the menopause, therefore, women may experience problems with incontinence, frequency in passing urine and urgency in passing urine.

The genital organs

Oestrogen maintains the thickness and lubrication of the lining of the vagina and stimulates the production of useful vaginal bacteria, which help to prevent infection. In addition, oestrogen maintains the acid level in the vagina at a level where these useful vaginal bacteria can survive. After the menopause, therefore, women may experience an increase in vaginal infections. They may also experience vaginal dryness, making sexual intercourse uncomfortable or painful.

Skin and hair

Although women often report skin and hair changes when taking hormone replacement therapy, relatively few studies have been carried out to prove whether there is a link between oestrogen and the skin and hair. In addition, the few studies that have been carried out often report conflicting results. Nevertheless, the general findings are that oestrogen increases the collagen (elasticity) level in the skin and enhances the blood supply to the skin. It has also been suggested that oestrogen increases the lifespan of the hair follicle, which is presumably why women report thinning and drying of the hair after the menopause.

Summary

- The normal menstrual cycle is divided into three phases: the follicular, the luteal and the menstrual phase. During these phases varying amounts of the female hormones oestrogen and progesterone are produced.
- Women also produce the male hormones testosterone and androstenedione. The role of these hormones in women is unclear.
- Ovarian changes do not suddenly occur at the menopause, but start around the age of 35 and go on until age 55 to 60.
- In Britain, the average age of the menopause is 51 years, with most women having reached it by the age of 54 years.
- A small proportion of women will experience a premature menopause before the age of 40 years.
- Oestrogen and progesterone have many functions within the body. After the menopause, when significantly lower amounts of female hormones are produced, a number of body changes are experienced. Particular areas of the body that are sensitive to oestrogen are the breasts, blood vessels, heart, bones, brain, urinary organs, genital organs, skin and hair.

