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In this article...

- Age-related changes to the reproductive tracts
- Effects of reduced sex hormone secretion in men and women
- Symptoms of the perimenopause, menopause and andropause

Anatomy and physiology of ageing 8: the reproductive system

Key points

In middle and old age, there is a gradual loss of fertility and changes in the production of sex hormones

In the peri-menopause and menopause, women experience considerable fluctuations in the levels of oestrogen and progesterone

Perimenopause and menopause often cause burdensome symptoms such as hot flushes, vaginal dryness and mood changes

Men also undergo hormonal changes, but the symptoms of the andropause are less dramatic than those experienced by women

Hormone replacement therapy can relieve symptoms in both men and women, but has risks and side-effects

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Abstract In men and in women, middle age brings about changes to the reproductive system that eventually lead to infertility – although men stay fertile for longer. These changes are partly due to dramatic fluctuations in the production of sex hormones such as oestrogen, progesterone and testosterone. In the perimenopause and menopause, most women experience physical and psychological symptoms that can be extremely disruptive. Although less dramatic, the changes prompted in men by the andropause can lead to erectile dysfunction and a loss of libido. Article 8 in our series on the effects of ageing explores the changes occurring in the female and male reproductive systems, and the role of hormone replacement therapy.

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Throughout the fertile years, the male and female reproductive organs (testes and ovaries) produce gametes (sperm and ova) which, through sexual intercourse, may fuse to form an embryo. The production of gametes is orchestrated by a cascade of hormones and growth factors, many of which have complex effects on the body. In middle and old age, the reproductive systems undergo significant changes: a gradual decline in fertility and fluctuations in the production of sex hormones, the latter triggering anatomical and physiological changes in distant organs and tissues. This article examines these changes and explores some of the treatments available to alleviate their consequences.

Female reproductive system Ovaries

As women age, there is a progressive decline in the number of ovarian follicles, which gains speed in the fourth decade of life; the number and quality of ova

diminish and oestrogen production declines, which in most women triggers the menopause around the age of 51. The speed of ovarian ageing is determined primarily by genetics, although oxidative stress, apoptosis and environmental factors also play a role. Premature ovarian failure (POF) can be triggered by surgery, radio- or chemotherapy, autoimmune reactions, and infections caused, for example, by the mumps virus and cytomegalovirus (Amanvermez and Tosun, 2016; Broekmans et al, 2009).

The perimenopause

In women, the first episode of menstrual bleeding (menarche) marks the onset of puberty. The prime child-bearing years correspond to the period between menarche and perimenopause (Dutton and Rymer, 2015). Before the menopause, when menstruation ceases and women become infertile, the hormones that drive the menstrual cycle start to fluctuate. This perimenopausal phase, which can last 2-10

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years, is often accompanied by increasing irregularity of the menstrual cycle. Although perimenopausal women are still fertile, pregnancy becomes more difficult.

The symptoms of the perimenopause are similar to those of the menopause. Some women experience few symptoms, but for others the perimenopause can be extremely challenging, since fluctuating hormone levels can cause physical and psychological symptoms such as hot flushes, night sweats, mood swings and feelings of sadness (Wagner, 2016).

The menopause

The irregular menstrual cycles characteristic of the perimenopause eventually cease completely. Strictly speaking, the menopause is the cessation of periods for 12 months (Goodman et al, 2011). In most of the world it occurs in the early 50s, with some variation. Around 95% of women go through the menopause between 44 and 56 years, the average age being 50.7 (Freeman, 2015). Many factors that precipitate POF can also trigger early menopause (Dutton and Rymer, 2015). Since no more ova are being released, it is impossible for post-menopausal women to become pregnant without fertility treatment.

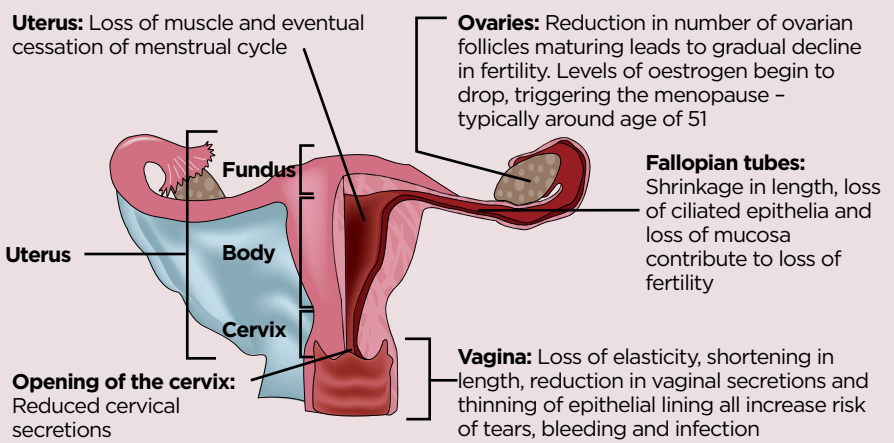
Hormonal changes

Follicle-stimulating hormone (FSH), secreted by the pituitary gland, drives the menstrual cycle. It stimulates the development of ovarian follicles, and as these enlarge they secrete the female sex hormone oestrogen. In perimenopausal and menopausal women, FSH levels remain high – or are higher than in premenopausal women – but FSH is unable to stimulate follicular development. Eventually, follicular activity ceases altogether, leading to a rapid decline in oestrogen secretion. Similarly, luteinising hormone, which triggers ovulation, is secreted at normal or higher than normal levels (Burger et al, 2007), but without mature follicles, no ova can be released so menopausal women become infertile.

Symptoms and clinical features

As during puberty and pregnancy, the transition to and through menopause is associated with dramatic fluctuations in the sex hormones oestrogen and progesterone. Symptoms are diverse and sometimes unique to the individual, but there are four that most women experience to varying degrees: hot flushes, vaginal dryness, mood changes and sleep disturbances (Santoro et al, 2015).

Fig 1. Ageing of the female reproductive tract



Hot flushes

Around three in four women experience hot flushes in the perimenopause and menopause (Bit.ly/NHSCHOicesHotFlushes). They are described as a rapid heat increase, particularly in the face, neck and chest, often with sweating and palpitations. The length of time women experience them varies between 4 and 10 years; most experience them every day and a third have more than 10 a day (Committee on Practice Bulletins – Gynecology, 2014).

Hot flushes appear to be related to increased levels of FSH and decreased levels of oestrogen. Decreased oestrogen seems to affect serotonin levels in the hypothalamus, causing fluctuations in the set point of the thermoregulatory centre; this leads to vasodilation and increased blood flow in the skin (Santoro et al, 2015).

Vaginal atrophy and dryness

The menopause is associated with a loss of elasticity and shrinkage in the length of the vagina. The epithelial lining becomes thinner and infiltrated by neutrophils, while the production of natural lubricating secretions slows down, increasing the risk of tears, bleeding and infection. In this changing environment, faecally derived species of bacteria may become dominant over the lactobacilli populations typically seen in premenopausal women. Lactobacilli produce lactic acid, so their depletion reduces the acidity of the vagina, resulting in a neutral or alkali pH that can encourage the growth of *Candida albicans* and other micro-organisms (Milsom, 2006). These vaginal changes can make sexual intercourse uncomfortable or painful (dyspareunia), and can reduce libido; 27-60% of menopausal women are affected by vaginal dryness and dyspareunia.

Menopausal women are also at risk of urinary incontinence: the bladder and urethra are sensitive to oestrogen (both have oestrogen receptors), so it seems likely that decreased oestrogen levels contribute to urethral shrinkage and urinary incontinence (Santoro et al, 2015). Breast tissue is also oestrogen sensitive and women often notice a loss of supporting connective tissue in the breasts (Chahal and Drake, 2007); age-related skin thinning and loss of skin elasticity can exacerbate this.

Mood changes and depression

Fluctuating concentrations of FSH, oestrogen and progesterone are often associated with mood changes. Despite inconsistencies in the literature, it is generally accepted that normal fluctuations in hormone levels – whether in the premenstrual stage of the menstrual cycle, during pregnancy or in the perimenopausal years – can be associated with negative psychological symptoms. The perimenopause is also associated with poor memory and concentration, problems with other people and low self-esteem. Other psychological symptoms are anxiety, irritability and rapid mood swings, but not necessarily low mood (Freeman, 2015; Cohen et al, 2005).

A previous history of depression or premenstrual syndrome is associated with an increased risk of clinical depression in the perimenopause and menopause. Women may also have pre-existing pathologies – such as metabolic syndrome, osteoporosis or cardiovascular disease – that are associated with depression and depressive symptoms. It is unclear if there is an increased risk of clinical depression in the perimenopause (Freeman, 2015), so clinical depression should not be regarded as a normal feature of either perimenopause or menopause.

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Sleep disturbances

Sleep problems become more common with age. In women, the risk of insomnia is 41% greater than in men. Around 25% of women aged 50-64 report sleep problems – rising to 50% in postmenopausal women (Santoro et al, 2015; Ameratunga et al, 2012). Many reasons for sleep disturbances during the menopause have been suggested: hot flushes and night sweats, anxiety, depressive symptoms and sexual dysfunction (Jehan et al, 2015). Not all studies agree that the menopause is directly linked to sleep problems. A recent study showed no statistically significant differences in sleep quality between premenopausal and menopausal women (Tao et al, 2016).

Decreased bone health

Reduced oestrogen levels can lead to a decrease in bone density and increased risk of fractures. Menopausal women lose up to 15% of their bone mass (Riggs and Melton, 1986). Significant losses in the spongy bone of the vertebrae contribute to the curvature of the spine often seen in postmenopausal women with osteoporosis.

Fallopian tubes

Shrinkage in the length of the Fallopian tubes, loss of ciliated epithelia and loss of mucosa have been reported (Hwang and Song, 2004). Since the Fallopian tubes are the site of fertilisation and are responsible for transporting the fertilised ovum to the uterus, these changes contribute to the age-related reduction in fertility, and may explain why older women are at increased risk of ectopic pregnancy (Bouyer et al, 2003).

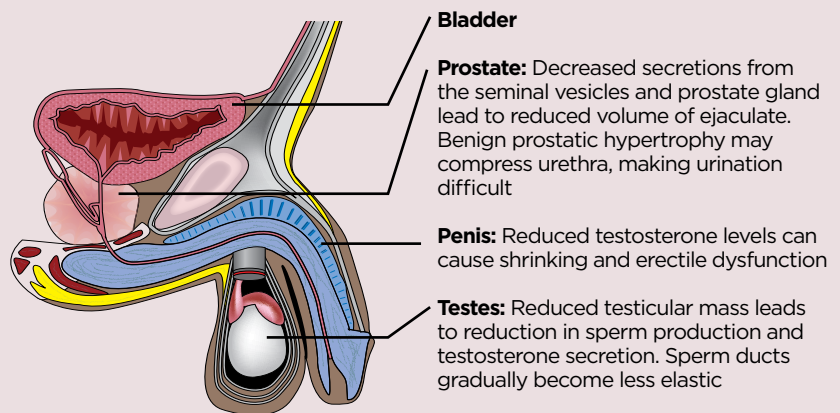
Uterus and cervix

The endometrium is the inner mucosal layer of the uterus that is shed during menstruation and then rebuilt under the influence of oestrogens. When oestrogen production decreases, this rebuilding is gradually compromised, until it becomes impossible and menstruation ceases.

The myometrium, the middle layer of the uterus, is composed almost entirely of smooth muscle fibres. In childbirth its contractions push the baby through the birth canal. In the menopause, it begins to shrink. Oestrogen helps to maintain the myometrium, so its reduction is thought to contribute to the loss of smooth muscle fibres – although the mechanisms of myometrial atrophy remain unclear (Mwampagatwa et al, 2013).

The perimetrium – the thin outer serous layer of the uterus – appears to change little with age.

Fig 2. Ageing of the male reproductive tract



The cervix (neck of the womb) consists of a smooth muscle layer overlaid by a mucus-producing cervical epithelium. Cervical mucus is essential to female fertility, aiding sperm to pass through the cervical aperture and enhancing sperm motility and maturation. The menopause is associated with a reduction in cervical secretions which contributes to reducing fertility (Gorodeski, 2000).

Male reproductive system

Testes and sperm ducts

Most men show an age-related reduction in testicular mass (Chahal and Drake, 2007) with an associated reduction in testosterone and sperm production. Since spermatozoa are produced in huge numbers, most men remain fertile until their 80s and 90s, although erectile dysfunction (ED) may be a problem. The sperm ducts, which carry sperm from the testes during ejaculation, gradually become less elastic because of an accumulation of collagen (sclerosis).

Prostate gland and seminal vesicles

The secretions from the seminal vesicles and prostate gland, which form the semen in which sperm swim, decrease with age, so the volume of ejaculate is reduced. Due to the parallel decrease in sperm numbers, sperm concentration remains fairly constant, which helps maintain male fertility. Secretions from the prostate contain antibacterial factors, so their decrease may increase the risk of urinary tract infection.

A common age-related problem is benign prostatic hypertrophy (BPH), a gradual, non-malignant increase in the size of the prostate contributing to age-related micturition difficulties. BPH may cause symptoms that are similar to those of prostate cancer, so investigations may be needed to rule out malignancy.

The andropause

Although most men do not experience the profound physiological and psychological changes that many women go through, they do undergo hormonal changes indicative of the so-called andropause – often inaccurately referred to as the male menopause (Chahal and Drake, 2007). In their 30s, men start to experience a decline in serum testosterone levels of around 1-1.4% per year. This is thought to be due to a reduction in the number of interstitial cells that synthesise testosterone and a reduced availability of free testosterone in the blood (Matsumoto, 2002).

Physiological and psychological symptoms

Compared with the literature on the perimenopause and menopause, there is little research on the andropause. Reduced testosterone levels are associated with various physiological and psychological changes:

- Increased body fat (usually visceral);
- Reduced muscle and bone mass;
- ED and reduced libido;
- Increased risk of anaemia;
- Memory problems;
- Sadness;
- Irritability;
- Loss of facial and pubic hair;
- Lethargy;
- Decreased endurance (Jakiel et al, 2015).

Penis and erectile dysfunction

Reduced testosterone levels can cause the penis to shrink, both in its flaccid and erect states. However, in most men, the earliest symptom of the andropause is a loss of libido, often accompanied with problems achieving an erection and maintaining it to the point of orgasm. The number of erections decreases and weaker erections become more common. Men who smoke

or have pre-existing pathologies such as diabetes, blood pressure problems or atherosclerotic occlusion are at higher risk of ED. Today, ED can be treated by techniques such as counselling and medications such as sildenafil (Viagra) (Bansal, 2013).

Hormone replacement therapy In women

Some effects of the perimenopause and menopause can be alleviated by hormone replacement therapy (HRT) – usually either oestrogen alone or oestrogen and progesterone given orally or transdermally. HRT has been reported to be effective in:

- Treating osteoporosis and reducing the risk of bone fractures;
- Improving muscle strength;
- Reducing vaginal dryness;
- Reducing hot flushes and night sweats;
- Improving sleep;
- Reducing headaches;
- Improving memory;
- Reducing panic attacks.

HRT carries certain risks and there is growing evidence that HRT (particularly oestrogen plus progesterone) increases the risk of breast cancer (Sood et al, 2014). Evidence of other risks of HRT is conflicting.

In men

There has been much research into the benefits and risks of HRT in women, but HRT in men going through the andropause has received less attention. Recent research has shown that testosterone replacement therapy (TRT) can have positive effects (Sofiajdpour et al, 2015).

However, increasing the level of circulating testosterone is associated with a variety of side-effects and risks including oily skin, acne, increased haematocrit count, gynaecomastia (breast tissue development) and increased risk of prostate cancer. The effect of TRT on cardiovascular health remains unclear (Nandy et al, 2008).

Modifiable risk factors

The ageing of the reproductive tracts, and the changes and symptoms brought about by the menopause and andropause, are inevitable. However, certain lifestyle changes may delay, or reduce the effects of the menopause or andropause – although some of the evidence is contradictory.

Smoking is the main modifiable risk factor. The inhalation of cigarette smoke increases the risk of infertility and early menopause in women, and the same risks exist for women exposed to second-hand smoking (Hyland et al, 2016). In men, smoking increases the risk of ED and lowers sperm count and quality (Sengupta and Nwagha, 2014).

A low body mass index (BMI) and being undernourished are both associated with an earlier menopausal onset. The effect of an increased BMI is less clear: some studies show that it is linked with a later menopausal onset (Akahoshi et al, 2002), others suggest no influence (Hardy et al 2008). A high BMI and obesity seem to be associated with more severe hot flushes and other perimenopausal symptoms (Saccomani et al, 2017). In men, a high BMI is associated with lower circulating testosterone levels, which can exacerbate the effects of the andropause (Bansal, 2013). **NT**

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