1 Physiology and definitions

At a glance

- The menopause is relevant to all populations.
- The number of older people is growing both in real and relative terms.
- There has been a 17.8% increase in people over 65 years in the UK in the last 10 years and a 31% increase in those over 85 years.
- Similar changes are occurring in most other industrialised countries and are starting to occur in developing countries.
- Worldwide, the population over 60 years is expected to double to over two billion by 2050.
- Menopausal age may be determined by both genetic and environmental factors.
- The main steroid hormones produced by the ovary are estradiol, progesterone and testosterone.
- Ovarian function is regulated by the gonadotrophins luteinising hormone and follicle-stimulating hormone produced by the pituitary gland.
- Over time, the ovary becomes less responsive to the gonadotrophins and estradiol levels start to fall.
- Reproductive ageing can be divided into various stages (Stages of Reproductive Aging Workshop+10).

Introduction

The menopause is defined as the cessation of the menstrual cycle. It is caused by ovarian failure. The term is derived from the Greek *menos*, meaning month, and *pausos*, meaning an ending. The median age at which the menopause occurs in the UK is approximately 51 years. Women who have been through their menopause are considered to be postmenopausal.

Increasing life expectancy and decreasing fertility rates mean that the number of older people is projected to grow considerably in absolute and relative terms. In 2015, there were more than twice as many children

under the age of 15 years in the world as there were people aged 60 years or above. By 2050, however, there will be almost complete global parity between the number of people aged 60 and above and the number of children under the age of 15. In Europe, 24% of the population is already aged 60 years or over and is projected to reach 34% in 2050 and 35% in 2100. Similar demographic changes are being seen in other areas of the world; for example, in Asia the population is expected to shift from 12% aged 60 or over to 25% by 2050. Even in Africa, which has the youngest age distribution of any major area, the proportion of over 60s is projected to rise from 5% in 2015 to 9% by 2050.[1]

The United Nations Population Division world population projections estimate that the number of people aged 60 and over will more than double by 2050 and more than triple by 2100, increasing from 901 million in 2015 to 2.1 billion in 2050 and 3.2 billion in 2100. Two-thirds of this increase between 2015 and 2050 will occur in Asia, 13% in Africa, 11% in Latin America and the Caribbean, and the remaining 10% in other areas.[1] Furthermore, the number of people aged 80 or over is projected to triple by 2050 and to increase more than seven-fold by 2100. Globally, the number of persons aged 80 or over will increase from 125 million in 2015 to 434 million in 2050, and 944 million in 2100. In 2015, 28% of all persons aged 80 and over lived in Europe, but that share is expected to decline to 16% by 2050 and 9% by 2100, as the populations of other major areas continue to increase in size and to grow older themselves.[2] Thus, the menopause must now be considered to be a truly midlife event that is relevant to all populations.

Definitions

Various definitions of the menopause are in use:

- **Menopause** is the permanent cessation of menstruation that results from loss of ovarian follicular activity. Natural menopause is recognised to have occurred after 12 consecutive months of amenorrhoea for which no other obvious pathological or physiological cause is present. Menopause occurs with the final menstrual period and thus is known with certainty only in retrospect one year after the event. No adequate biological marker exists.
- **Perimenopause** includes the period beginning with the first clinical, biological and endocrinological features of the approaching menopause, such as menopausal symptoms and menstrual irregularity, and ends 12 months after the last menstrual period. It is also sometimes called the 'menopause transition'.

- **Premenopause** is the whole of the reproductive period before the menopause, which encompasses the entire reproductive period from menarche to the final menstrual period. During this phase, the woman will continue to have her normal menstrual cycle, although for many women there may be gradual changes in their menstrual pattern over time.
- **Postmenopause** is the time from the final menstrual period, regardless of whether the menopause was induced or spontaneous. Surgical menopause is timed precisely but, as noted above, the time of natural menopause can only be determined retrospectively after a period of 12 months of spontaneous amenorrhoea.
- **Climacteric** is a term sometimes used to encompass the transition from the reproductive state to the non-reproductive state, the menopause itself being a specific event that occurs during the climacteric.
- **Climacteric syndrome** refers to the occurrence of symptoms during the climacteric. Both these terms are less commonly used now and the term 'menopause transition' is preferred.
- **Induced** or **iatrogenic menopause** is the cessation of menstruation that follows surgical removal of both ovaries or the ablation of ovarian function by chemotherapy, radiotherapy or treatment with gonadotrophin-releasing hormone analogues. In the absence of surgery, induced menopause may be permanent or temporary.
- **Premature ovarian insufficiency** (previously known as premature menopause or premature ovarian failure) is the occurrence of the menopause before the age of 40. This is discussed in detail in Chapter 12.
- **Early menopause** – a menopause that occurs between 40 and 45 years of age.

Determinants of menopausal age

The age at menopause may be determined by genetic and environmental factors. Growth restriction in late gestation, low weight gain in infancy and starvation in early childhood may be associated with an earlier menopause. Research from the InterLACE study has indicated that early puberty (less than 11 years) and childlessness increase the risk of premature ovarian insufficiency.[3] Early puberty can lead to an 80% increase in early menopause, which is further increased if the woman has no children. Childlessness on its own can double the risk of early menopause. Women from some developed countries have menopause on average 1–1.5 years earlier than those in developing countries and earlier menopause is also noted in women who smoke, those who live at high

altitude, those who have Down's syndrome or who are socially deprived. Conversely, being breastfed, higher childhood cognitive ability, and increasing parity are associated with later onset of menopause.

Ovarian function

The main steroid hormones produced by the ovary are estradiol, progesterone and testosterone. In premenopausal women, ovarian function is controlled by the two pituitary gonadotrophins: follicle-stimulating hormone (FSH) and luteinising hormone (LH). FSH itself is controlled primarily by the pulsatile secretion of hypothalamic gonadotrophin-releasing hormone (GnRH) and is modulated by the negative feedback of estradiol and progesterone and the ovarian peptide inhibin B. LH is under the principal control of GnRH, with negative feedback control from estradiol and progesterone for most of the cycle; positive estradiol feedback generates the mid-cycle surge in levels of LH that triggers ovulation (Figure 1.1).

Each ovary receives a finite endowment of oocytes, the numbers of which are maximal (5–6 million) at 20–28 weeks of intrauterine life. From mid-gestation onwards, a logarithmic reduction in these germ cells occurs over the next 50 years or so, with about 2 million oocytes remaining at birth, 400,000 around menarche and less than 1000 around the time of the menopause. The ovary gradually becomes less responsive to gonadotrophins several years before menstruation stops. This results in a reduction in production of estrogen and an increase in levels of gonadotrophins. There is thus a gradual increase in circulating levels of FSH, and later of LH, and a corresponding decrease in levels of estradiol and inhibin B. Levels of FSH fluctuate markedly from premenopausal to postmenopausal values on virtually a daily basis during the menopausal transition (Figure 1.2) and, as a result, their diagnostic use is severely limited (see Chapter 4). These changes in circulating levels of hormones frequently occur with ovulatory cycles. As ovarian unresponsiveness becomes more marked, cycles tend to become anovulatory and complete failure of follicular development eventually occurs. Production of estradiol is no longer sufficient to stimulate the endometrium, leading to amenorrhoea, with levels of FSH and LH now persistently elevated. Levels of FSH of greater than 30 iu/l are generally considered to be in the postmenopausal range.

Anti-müllerian hormone is a peptide growth factor produced by the granulosa cells in the ovary in the early stages of follicle development. Production starts around the time of birth and peaks in the mid 20s but is fairly constant throughout the menstrual cycle. Levels fall as ovarian function declines and cannot be measured by around five years before

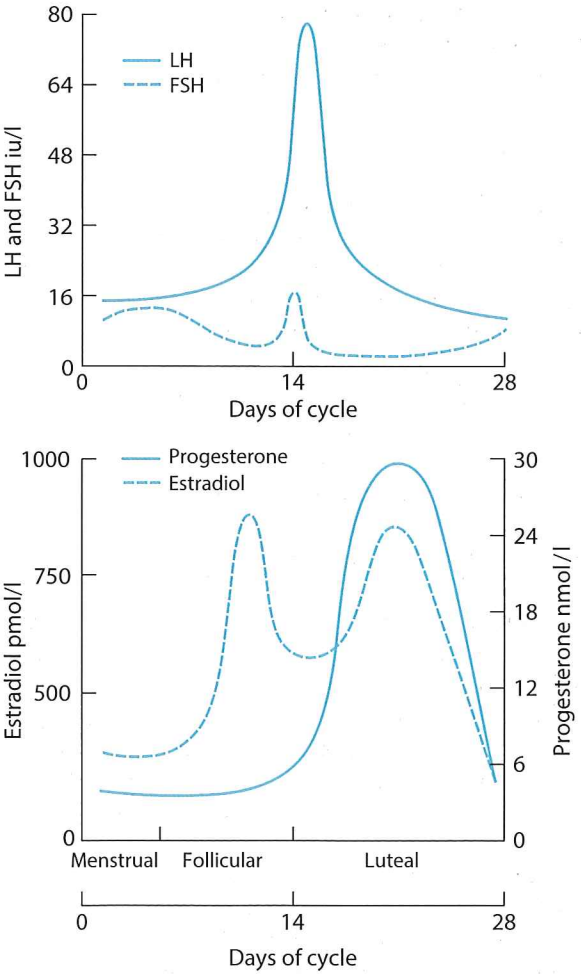


Figure 1.1 Levels of gonadotrophin, estradiol and progesterone during the menstrual cycle

menopause. A single measurement is not predictive of future fertility and its clinical usefulness at the moment is limited (see Chapter 12).

The ovaries are an important source of testosterone, which is hydroxylated to dihydrotestosterone. Testosterone also can be aromatised to estradiol. Precursor hormones, such as androstenedione and dehydroepiandrosterone (DHEA), are produced in the ovaries and the adrenals, and both possess a less potent androgenic effect than testosterone. By the time women reach their mid-40s, mean circulating

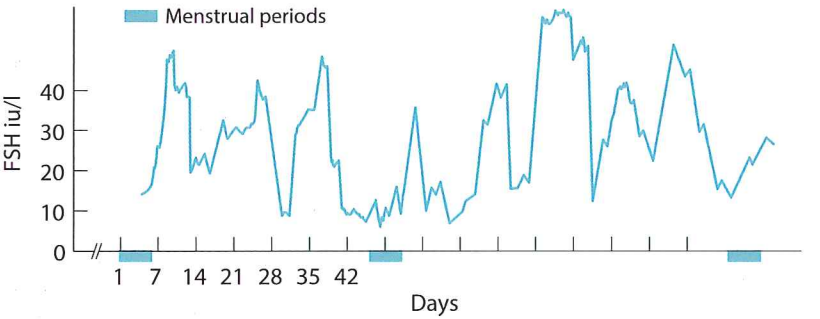


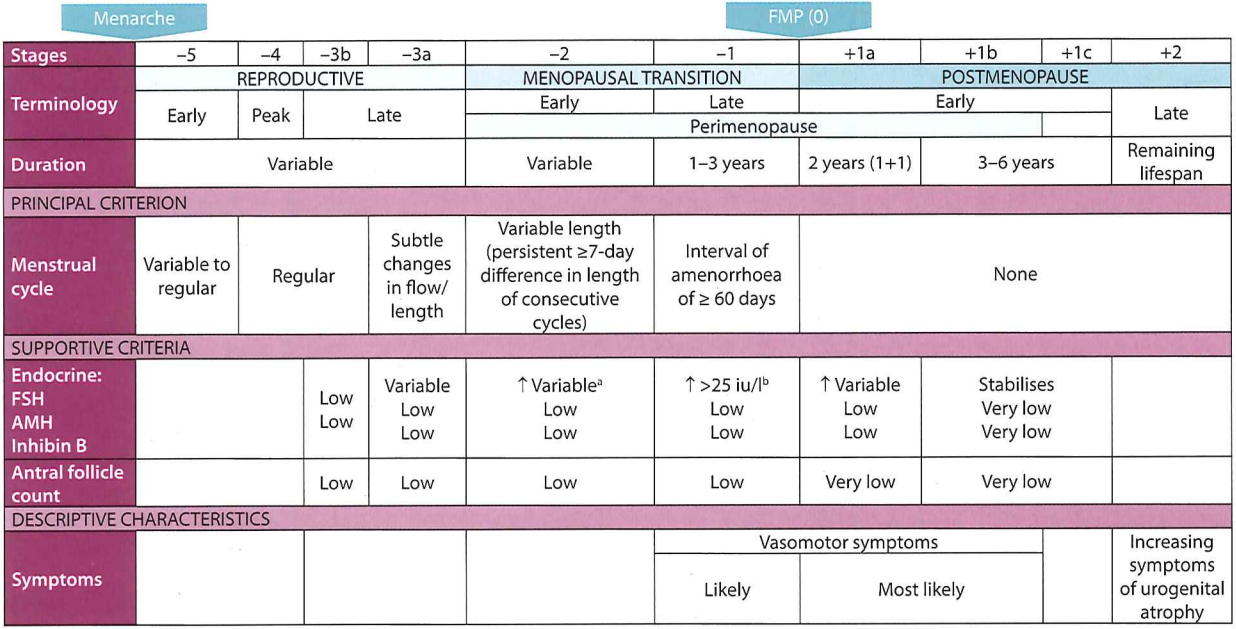
Figure 1.2 Levels of follicle-stimulating hormone during the menopause

levels of testosterone, androstenedione, DHEA and the sulphate product are approximately 50% of those of women in their 20s. However, menopausal status does not affect levels of androgens in women aged 45–54 years and the postmenopausal ovary continues to produce testosterone. Low circulating levels of androgens have been proposed to be associated with low sexual desire; however, there is no correlation between androgen levels and sexual desire or responsiveness in women.

Stages of reproductive ageing

The Stages of Reproductive Aging Workshop (STRAW) staging system is generally considered to be the gold standard for characterising reproductive ageing through the menopause. The STRAW staging system was originally described in 2001 and was updated in 2011 as the STRAW+10.[4] The system divides female reproductive ageing into three phases: reproductive, the menopausal transition and postmenopause using the final or last menstrual period as the main reference point. There are seven stages, five preceding and two following the final menstrual period. Stages –5 to –3 encompass the reproductive interval, stages –2 and –1 are the menopausal transition and stages 1 and 2 are the postmenopause (Figure 1.3).

After menarche (stage –5), it usually takes several years for regular menstrual cycles to become established. Menstrual periods should then occur every 21–35 days for a number of years (stages –4 and –3). The late reproductive phase (stage –3) is divided into: –3b, during which the menstrual cycle remains regular and FSH remains low, and –3a when the cycle starts to become irregular and FSH levels begins to fluctuate. In stage –2 (early menopausal transition) the menstrual cycle length becomes increasingly variable in length (over seven days from normal



[a] Blood drawn on cycle days 2–5
[b] Approximate expected level based on assays using current international pituitary standard
↑ = elevated; AMH = anti-müllerian hormone; FSH = follicle-stimulating hormone

Figure 1.3 The Stages of Reproductive Aging Workshop+10 staging system for reproductive ageing in women. FMP, final menstrual period; FSH, follicle-stimulating hormone; AMH, anti-müllerian hormone (reprinted from Harlow et al., Executive summary: Stages of Reproductive Aging Workshop +10: addressing the unfinished agenda of staging reproductive aging. *Climacteric*, 2012; 15: 105–14; *Fertil Steril*, 2012; 97: 843–51; *J Clin Endocrinol Metab*, 2012; 97: 1159–68; *Menopause*, 2012; 19: 387–95)

length) and persistently (twice or more within 10 cycles) accompanied by variable FSH levels. Stage –1 (late menopausal transition) is characterised by increasing variation of cycles and at least one episode of amenorrhoea for 60 days or more. FSH levels are often elevated but vary considerably. Early postmenopause (stage +1) is defined as five years since the final menstrual period and is divided into three. Stage +1a is the first 12 months of amenorrhoea (that is, the time required to confirm the diagnosis of the final menstrual period). Stage +1b is the next 12 months. FSH levels continue to rise during this time (and estradiol levels fall) and symptoms are most likely during this time. The 'perimenopause' is thus the time from stage –2 to end of stage +1a. Stage +1c lasts for three to six years, with stabilisation of high FSH and low estradiol levels. The late postmenopause (stage +2) is from this point onwards until death. This is characterised by more ageing changes and, typically, when the urogenital and other longer term consequences of the menopause become more apparent.

There are obvious limitations of this type of approach. It is not applicable to women who have had a hysterectomy, those with polycystic ovary syndrome, hypothalamic amenorrhoea or other conditions or treatments that affect ovarian function, such as chemotherapy. It does, however, provide a reproducible, evidence-based standardised classification system, which is useful in our understanding of the late reproductive stage and early menopause.

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