Chapter 1
An Overview of the Extent and Nature of Menopause and Its Physiological Basis

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Keypoints

- Menopause is defined as the permanent cessation of menstruation due to depletion of the follicle pool.
- The menstrual cycle and changes in the cyclic pattern until a complete stop are orchestrated by gonadotrophins, steroids, and inhibins.
- The median age at natural menopause is around 50–51, for centuries and across populations.
- Menopause is associated with vasomotor menopausal symptoms; of other symptoms such as incontinence, depressed feelings, and vaginal dryness it is not clear whether it is the menopause per se that causes these symptoms and complaints, or whether aging also plays a major role.
- Early menopause is associated with increased risk of cardiovascular disease and osteoporosis and a decreased risk of breast cancer.
- These effects are generally ascribed to estrogens, but for osteoporosis and breast cancer this is much more clear than for cardiovascular disease.

Keywords Menopause • Endocrinology • Epidemiology • Physiology • Vasomotor menopausal symptoms

Abbreviations

FMP	Final menstrual period
STRAW	Stages of reproductive aging workshop
LH	Luteinizing hormone
FSH	Follicle-stimulating hormone
GnRH	Gonadotrophin-releasing hormone
VMS	Vasomotor menopausal symptoms
CVD	Cardiovascular diseases
CHD	Coronary heart disease
HT	Hormone therapy
HERS	Heart and estrogen/progestin replacement study
WHI	Women's Health Initiative trial
BMD	Bone mineral density

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Introduction

The word "menopause" is derived from the Greek word παυσις (pausis, cessation) and the root μεν- (men-, month). Menopause is defined as the permanent cessation of menstruation [1]. Most animals do not have a post-reproductive life, and menopause has been considered as something unique to human [2]. There is a lively debate among evolutionary biologists and anthropologists why human females have menopause. The grandmother theory proposes that natural selection increased the length of the human postmenopausal period—and, thus, extended longevity—as a result of the inclusive fitness benefits of grandmothering [3]. The other theory, also known as the disposable soma theory, states that longevity requires investments in somatic maintenance that reduce the resources available for reproduction [4]. Recently it was shown that menopause is not unique for humans, but is also experienced by nonhuman primates [5, 6].

Menopause occurs with the final menstrual period (FMP), which is known with certainty only in retrospect after 12 consecutive months of amenorrhea. There is no biological marker of menopause [1]. Perimenopause is the time immediately before menopause, when the endocrinological, biological, and clinical features of approaching menopause commence, and the first year after menopause [1].

Treloar was among the first to observe a group of female students in Minnesota starting in 1934 until the 1960s of the previous century, in order to describe menstrual cyclicity during women's lives [7, 8]. The Stages of Reproductive Aging Workshop (STRAW) group have proposed definitions for staging female reproductive aging (Fig. 1.1) [9]. According to STRAW, the menopausal transition is

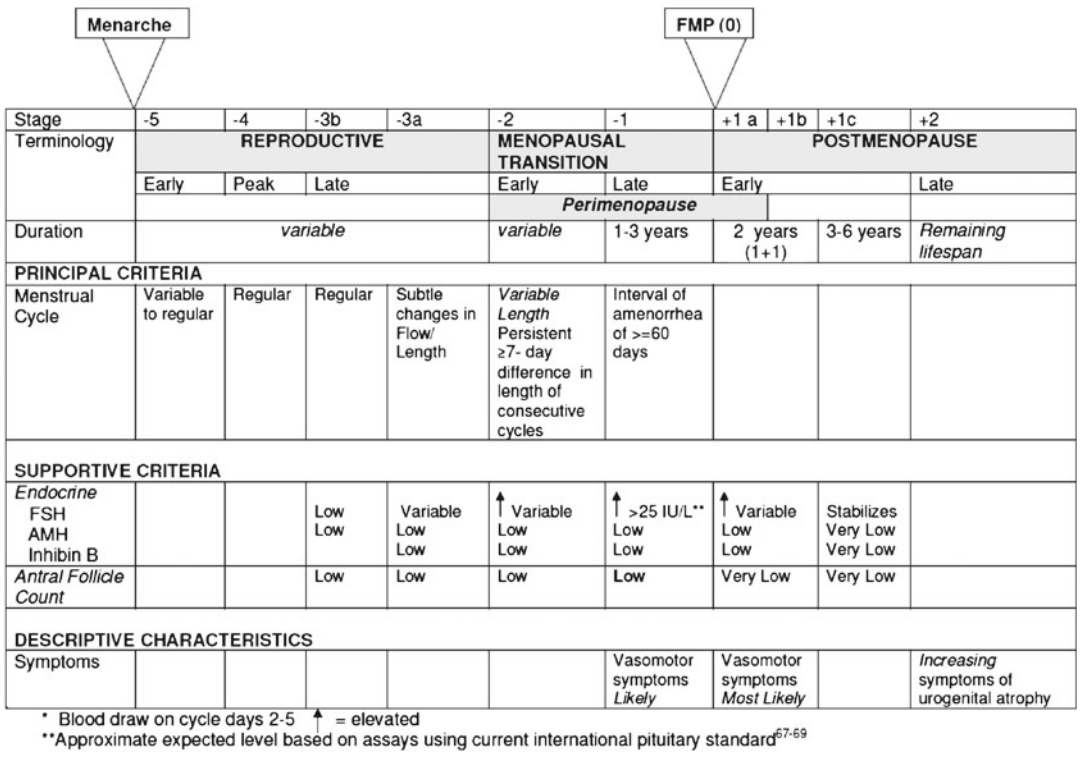

Fig. 1.1 The stages of reproductive aging workshop + 10 staging system (STRAW) for reproductive aging in women. Reproduced from [9] with permission from Wolters Kluwer Health

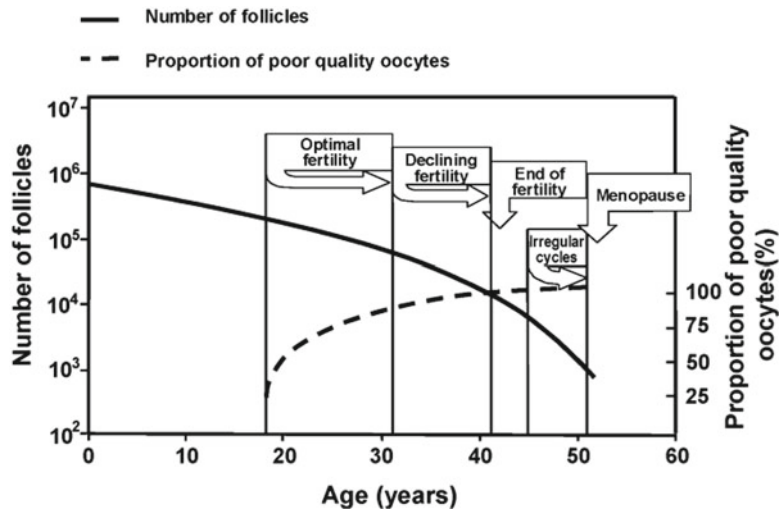

Fig. 1.2 The decline in follicle number and the increase in the proportion of poor-quality oocytes in relation to reproductive events with increasing female age. Redrawn after de Bruin JP 2004 and [106]. Reproduced from [107] with permission from Elsevier

the time before the FMP, when variability in the menstrual cycle is usually increased. It may be subdivided into the early transition, marked by a 7 or more days' persistent difference in cycle lengths from the woman's previous normal range, and late transition, marked by 60 or more days of amenorrhea, observed on at least one occasion.

Menopause is the ultimate result of ovarian aging and the consequence of a decrease in the number of remaining follicles with increasing female age. Women are born with the full stock of primordial follicles, containing six to seven millions [10], to serve the needs of reproduction for the rest of a woman's life. From birth onwards, the follicle pool decreases; a process called atresia makes the follicles deteriorate before or after they have initiated follicle growth [11]. At puberty, only ~300,000 follicles are left, and subsequently with every menstrual cycle hundreds vanish. This also occurs during periods when no ovulation takes place, such as pregnancy, breastfeeding, or oral contraceptive use. The rate of disappearance increases markedly from age 37 to 38 onwards. At 45–46 years, the stock has diminished to several thousands, a critical number, and menstrual bleeding starts to become irregular [12]. When reduced to a thousand or less, the number is too small to maintain the cyclic hormonal process needed for menstruation, and menopause occurs [13]. There is substantial interindividual variation in the onset of menopause, varying roughly between 40 and 60 years, with a mean age of 51 which is rather constant over time and populations worldwide [14]. In parallel to the *quantitative* decline in the number of oocytes also the *quality* of the oocytes held in the follicles declines with increasing female age. This results in a decrease in female fecundity after the age of 31, which may accelerate after age 37, leading to sterility at a mean age of 41 (Fig. 1.2) [15].

Endocrinology

The decrease of the follicle pool appears to be caused by endocrine changes [16]. Gonadotrophins, steroids, and inhibins play a crucial role in the endocrinology of the menopausal transition (Fig. 1.3) [16]. The pituitary is stimulated by gonadotrophin-releasing hormone (GnRH) from the hypothalamus

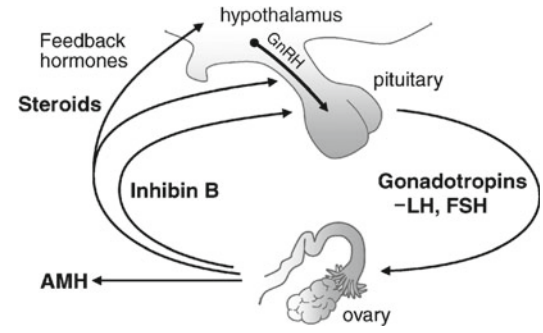

Fig. 1.3 Schematic of hypothalamopituitary-ovarian axis. Antimüllerian hormone (AMH) is also a product of antral follicles, but does not appear to participate in the closed-loop feedback system. Reprinted from [16] with permission from Wolters Kluwer Health

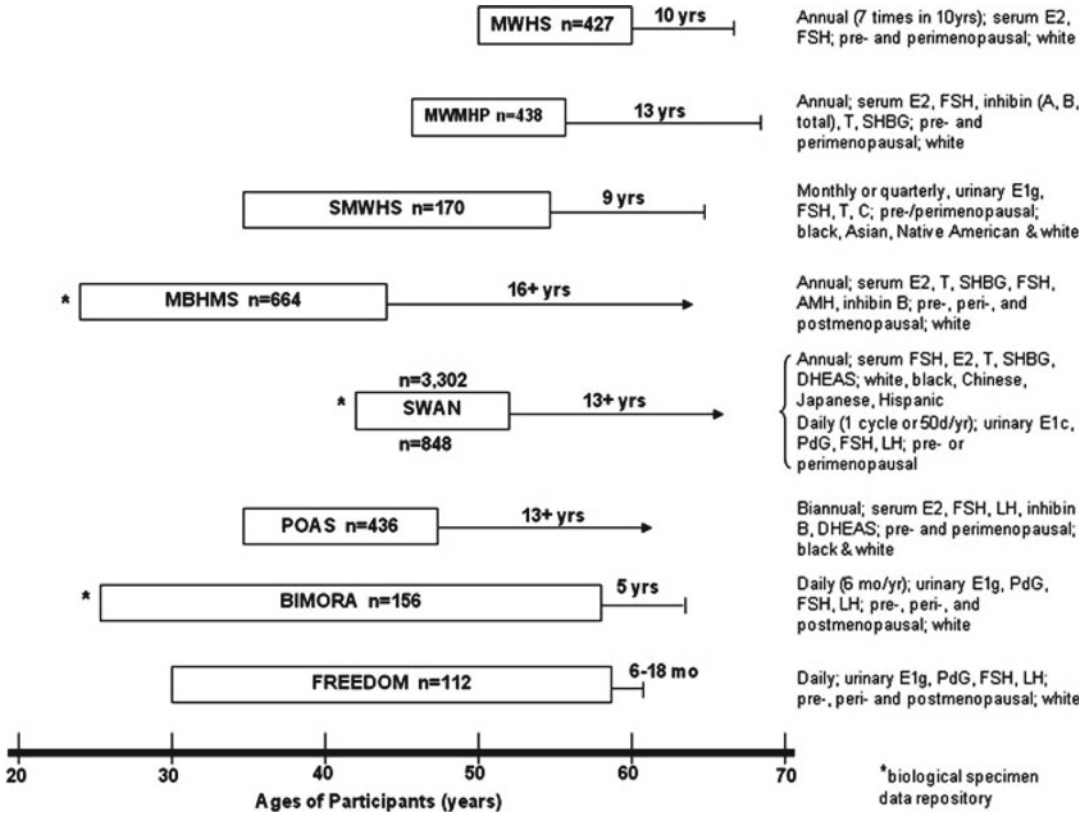

Fig. 1.4 Longitudinal, epidemiologic studies of female reproductive aging that include substantial endocrine data. Studies are in order from least to most recent start date (*top* to *bottom*). Box width depicts the baseline age range of participants for each study. Number of years listed on line to the *right* of each box is the maximum number of years during which endocrine data were/are collected; *arrow* indicates that a study is ongoing. Information to the right includes sampling strategy, hormones measured, allowable menopausal stages at baseline, and ethnicity. All annual or monthly samples were taken during the early follicular phase of the menstrual cycle. Across all studies, women were excluded if they did not have at least one ovary, were pregnant or breastfeeding, or were taking exogenous hormones or other medications known to affect reproductive hormone values. *MWHS* Massachusetts Women's Health Study, *MWMHP* Melbourne Women's Midlife Health Project, *SMWHS* Seattle Midlife Women's Health Study, *MBHMS* Michigan Bone Health and Metabolism Study, *SWAN* Study of Women's Health Across the Nation, *POAS* Penn Ovarian Aging Study, *BIMORA* Biodemographic Models of Reproductive Aging Project, *FREEDOM* Fertility Recognition Enabling Early Detection of Menopause Study. *Hormones*: *C* cortisol, *AMH* anti-Müllerian hormone, *E2* estradiol, *E1c/E1g* estrogen conjugates, *FSH* follicle-stimulating hormone, *LH* luteinizing hormone, *PdG* pregnanediol glucuronide, *T* testosterone, *SHBG* sex hormone-binding globulin, *DHEAS* dehydroepiandrosterone sulfate. Reprinted from [108] with permission from John Wiley and Sons

to produce luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH and FSH are the regulators of follicle development and hormone secretion by the follicle. In the follicular phase of the menstrual cycle, the granulosa cells of the antral follicle produce estradiol and inhibin B. Estradiol exerts feedback actions on the pituitary and the hypothalamus, whereas inhibin B mainly acts on the pituitary to reduce FSH secretion [17].

Several epidemiological studies have yielded important information on the hormonal changes throughout female reproductive life; they are summarized in Fig. 1.4. When follicles decrease in number, the number of fully functioning granulosa cells also decreases. This initially leads to differentially decreased secretion of inhibin B, as a result of which FSH secretion increases [18, 19]. As a consequence, follicle development will be initiated earlier, and the follicular phase of the still regular menstrual cycles will become shorter. In older women, at least some of their cycles are characterized by elevated follicular phase FSH levels, corresponding to STRAW stage 3.

It is yet unknown what the causes are for cycle irregularity; several mechanisms have been postulated, which are well summarized by Burger et al. [16]. It has been suggested that at the initiation of a cycle, there may be no follicles responsive to the FSH increase between cycles. As a result, the ovarian negative feedback is lacking, inhibin B and estradiol levels remain low, and FSH increases until responsive follicles appear, with the subsequent initiation of the events leading up to ovulation [16, 20]. An alternative theory is that decreasing follicle production might lead to high levels of estrogen secretion around the time of menstrual bleeding, which appear to be associated with shortened cycles. If FSH levels are sufficiently high and sustained, it is possible that other antral follicles may be stimulated to grow and develop in other parts of the cycle, with high estradiol levels, which may explain the wide range of estradiol levels seen in women in the transition [18]. Such elevations may lead to delayed menses or to breakthrough bleeding. Further follicle depletion may then result in failure to ovulate and the progressively increasing frequency of anovulatory cycles in the late menopausal transition. However, occasionally it may be possible to respond normally to gonadotrophin stimulation, with the development of a normal ovulatory cycle as a result. The changes in follicle production may lead to a diminished function of the corpus luteum. Rapid declines in estrogen levels occur during late perimenopause, the last 2 years before the FMP, so mainly in STRAW stage 1 [21, 22].

Epidemiology

The mean age at which natural menopause occurs is generally considered to be 50–51 years. Since the report of age at menopause in different European countries by Backman in 1948 [23] there has been discussion whether there is a secular trend in age at menopause, just as has been observed for age at menarche [24]. A secular trend is defined as an increasing or a decreasing age at which an event occurs.

Backman observed an increasing trend for age at menopause, using reports of menopause to begin at age 40 in ancient times, and increasing from a little bit lower than 46 in 1840 to a little bit over 48 in 1940, as displayed in Fig. 1.5. However, a later more extensive review of ancient Greek and Roman literature concludes that the most cited age at menopause is 50 years [25]. The same investigators also studied European medieval sources from the sixth to the fifteenth century, and conclude that again the most frequently cited age of menopause is 50 years, just like what is currently reported [26]. These reports cast doubt on the existence of a secular trend in age at menopause.

Treloar asked single female students attending the University of Minnesota in the fall of 1934 and the freshmen of the next 3 consecutive years to keep a menstrual diary, basically for the rest of their reproductive life. In 1970, for 324 from the 2,700 enrolled who had reached natural menopause, the mean age at menopause was estimated to be 49.5 years [27]. In 1981, this information was updated and again, the estimate for the mean age at menopause was 49.5 years.

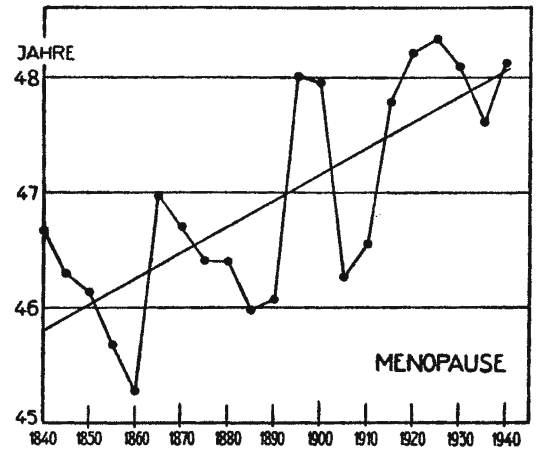

Fig. 1.5 Course of the mean age at menopause per 10 years and for every 5 years in Europe, 1840–1940. Reproduced from [23] with permission from S. Karger AG, Basel

Assessment of mean age at menopause sounds easy, but is in fact difficult. In the oldest reports, ages are often just listed as "between 45 and 50 years." In populations where not all women have become postmenopausal, means and medians are not accurate reflections of the true population means or medians, as they just take into account the menopausal ages of the still premenopausal women, and will therefore be an underestimation [28, 29]. It is well known that women tend to round off their age at menopause to the nearest 5 or 0; therefore, clusters occur at age 40, 45, 50, and 55 [30–32].

Besides these more methodological problems, there are also factors affecting age at menopause, which hamper comparison of mean ages at menopause in different time periods in different populations. Women who had surgical menopause usually have this at younger ages than natural menopause would have occurred. Also smoking advances age at menopause with a year [33]. This may lead to a lower estimated mean age at menopause in populations with a large proportion of smoking or surgically menopausal women. In addition, it has been suggested that nutritional status, geographical altitude, and genetics may affect the age at menopause [29].

In 1985, McKinlay summarized 13 studies covering a period between 1960 and 1985 that provided information on median age at menopause in a more reliable manner using appropriate statistics. A median age at menopause between 50 and 51 years was consistently reported [34]. In 1998, the results were published of a large study on the variability in reproductive factors among 18,997 women in Europe, the Americas, Asia, Australia, and Africa. The median age at natural menopause was estimated to be 50 years overall, and the median ages at menopause ranged moderately between 49 and 52 years among the centers [14]. The authors concluded that there is not much international variation in age at menopause.

Later studies from Sweden, the USA, and The Republic of Chuvasia, Russian Federation, have suggested that there is a secular trend visible in age at menopause [35–39], but also in these studies a median age of 50 was observed, with some variation around that age; and not all studies used proper methods, and sometimes no secular trend was seen after adjustment for education, smoking, and physical activity.

In conclusion, most studies observe a median age at menopause somewhere between 49 and 51, already since ancient Greek and Roman times. Because of influences of external factors on age at menopause, such as surgery, smoking, and oral contraceptive or hormone use, it is questionable whether more precise estimates can be reliably made. The fact that estimates are around the age of 50 for centuries argues against the existence of a secular trend in age at menopause.

Physiology

Vasomotor Menopausal Symptoms

Menopause is associated with many physiological changes, one of the most distinct being vasomotor menopausal symptoms (VMS), i.e., hot flushes or hot flashes and night sweats. VMS are defined as subjective sensations of heat that are associated with objective signs of cutaneous vasodilatation and a subsequent drop in core body temperature [40]. Intensity of VMS widely varies, between women, but also within individual women. Mild VMS can be experienced as a transient warming sensation. With severe VMS, women report abrupt and very intense heat that spreads over the face and the upper body, together with reddening of the face and severe perspiration. These symptoms are objectified by measurement of skin temperature and skin conductance, an electrical measure of sweating [41]. Very frequently these symptoms are followed by chills and shivering. The duration of a hot flush is in general quite short, around 5 min, but can also be up to 15 min [42].

VMS seem to result from a reduced thermoneutral zone [43]. The core body temperature is regulated between an upper threshold for sweating and a lower threshold for shivering. Between these thresholds is a neutral zone within which thermoregulatory responses such as sweating and shivering do not occur [44]. In women without VMS, the null zone is about 0.4 °C. This means that temperature fluctuations of as much as +0.4 °C do not cause sweating or shivering in women without VMS. However, in women with VMS, the thermoneutral zone disappears and temperature fluctuations quickly lead to sweating or shivering as explained in Fig. 1.6 [45].

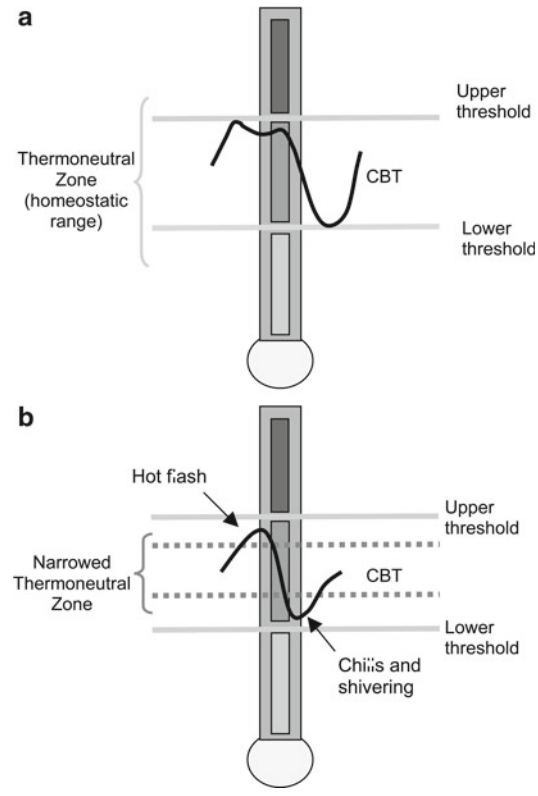

Fig. 1.6 Maintenance of core body temperature (CBT). CBT is critical to organ integrity and optimal function [48]. (**a**) Normal temperature regulation. (**b**) Dysfunctional temperature regulation. Reprinted from [48] with permission from Springer

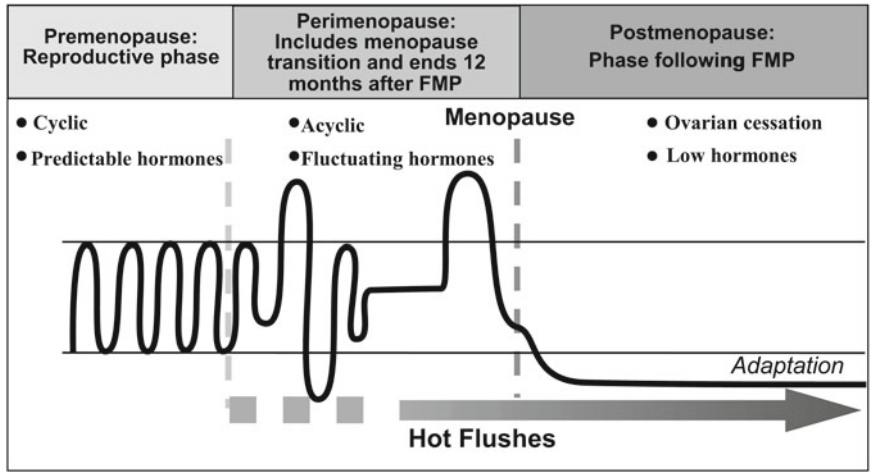

Fig. 1.7 Relationship between estrogen and a woman's reproductive phases and the occurrence of hot flushes. Reprinted from [48] with permission from Springer

Given the observation that VMS occur in most women experiencing dramatic lowering of estrogen levels due to natural or surgical menopause, it is very likely that estrogens do play a role in the initiation of VMS [41]. Strong support for this observation is the fact that estrogen administration practically eliminates VMS [46]. However, studies investigating plasma, urinary, or vaginal levels of estrogens have not been able to find an association with the presence of VMS. Furthermore, estrogen concentrations remain low throughout menopause while VMS usually subside with time after menopause. Therefore, it is not very likely that estrogen deficiency as such is a sufficient risk factor for symptoms, although estrogen deficiency seems to be necessary to explain the occurrence of VMS [41, 47]. It has been suggested that the fluctuations in estrogen levels during perimenopause play a role in the occurrence of VMS [48, 49], as outlined in Fig. 1.7.

Prevalence of VMS in women varies over the lifetime. From approximately 2 years before the FMP, prevalence starts to increase from around 10 % of women reporting VMS to a peak around the first year after the FMP with a mean of 55 % of women [50]. In some studies percentages of women experiencing VMS in the first year after the FMP of as high as 70–80 have been reported [51, 52]. Six to seven years after the FMP, the prevalence of VMS falls to approximately half of the peak prevalence, and it takes until 8 years after the FMP before VMS prevalence has returned to premenopausal levels [50]. Data from the Multiple Outcomes of Raloxifene Evaluation trial show that 10–19 years after menopause still 12 % of women report VMS that were symptoms that were bothersome "some," "most," or "all" of the time, while this was reported by 8 % of women who were 20 years or longer after menopause [53]. VMS seem to be more common in 90 % of women reporting this in the first year, and more abrupt and more severe in women who underwent surgical menopause [54].

Other Menopausal Symptoms and Complaints

Several other symptoms and complaints, i.e., urinary complaints, vaginal dryness, sleep disturbance, and mood symptoms, have been reported to be associated with menopause, although the literature is not completely consistent on whether it is the menopause per se that causes these symptoms and complaints, or whether aging also plays a major role [55]. Studies using factor analysis have shown that

menopausal status is more consistently associated with VMS than with psychological or physical symptoms [56], which argues against the existence of a universal menopausal syndrome that includes them all [55].

Urinary incontinence may occur more frequently as a result of atrophy of the bladder trigone, decreased sensitivity of alpha-adrenergic receptors of the bladder and urethral sphincter, or thinning of the urethral mucosa [57]. Urinary tract infections may be a result of increased vaginal pH and vaginal microflora changes to gram-negative organisms [57].

Vaginal atrophy is associated with menopause [58] and may lead to symptoms of dyspareunia, vaginal dryness, itching, and irritation, and the estrogen withdrawal after menopause seems to play a role in its occurrence, as systemic or vaginal estrogen therapy can be used as a relief [57].

The literature on mood changes, development of mental disorders, and depression as a result of menopause is conflicting with several studies that were unable to find such associations, where some were [55]. It has been reported that the increased rate of perimenopausal depression was primarily found in women with a history of depression, suggestive of increased vulnerability in women who are known to have affective disorders [59, 60].

Cardiovascular Disease

Cardiovascular diseases (CVD) are the major cause of disease and death in Western countries, accounting for 30 % of deaths. Morbidity and mortality graphs by sex suggest that women are relatively protected against coronary heart disease until around the age of 50, the age at which menopause occurs [61].

Protection by endogenous estrogens has long been considered a likely explanation for this risk difference. Circulating estrogen levels decline to about 20 % of premenopausal levels around menopause. Early menopause, caused by bilateral oophorectomy, increases the risk of CVD in younger women, but not when estrogen supplementation therapy is given [62–65]. Observational studies support the hypothesis that a later age at menopause decreases CVD risk [66–69]. Whether endogenous estrogens are the key driver of cardiovascular protection is unclear up to now. The Women's Ischemia Syndrome Evaluation study showed that premenopausal women with angiographic coronary artery disease suffered more often from hypoestrogenemia in combination with low FSH and LH levels, as is present in menopause [70]. The few studies that are available on postmenopausal estrogen levels and CVD risk generally do not support an association [71–73], but postmenopausal estrogen levels do not necessarily reflect premenopausal levels.

A logical consequence of increased coronary risk due to ceased estradiol production would be that this risk be reversed by increasing estradiol levels in postmenopausal women through supplementing estrogens after menopause, with the so-called postmenopausal hormone therapy (HT). Extensive data from observational studies support a beneficial effect of HT on the occurrence of CVD in postmenopausal women, amounting to a risk reduction of 35–50 % [74–76]. Moreover, observational data in women who have experienced a cardiac event or a coronary intervention agree with the data from healthy women on HT [77]. This led to the paradigm that estrogen deficit causes CHD and supplying hormone therapy is good for postmenopausal women. However, randomized trials on hormone therapy and clinically manifest CVD did not confirm the findings of the observational studies. None of the large trials observed clear coronary risk reduction in the hormone therapy arms (summarized in [78]). These findings raise serious questions on the validity of the paradigm.

The randomized trials on HT typically targeted older women 10–15 years after menopause and showed no overall benefit. Yet, women randomized to hormone therapy closer to menopause did experience CHD protection, whereas women starting further from menopause did not [79]. These findings suggest that estrogen benefits are not the same across all postmenopausal women at large.

The most critical difference between women using HT in trials and in real life is that outside trials women tend to receive HT because of a reason, e.g., for an indication. The typical indication for HT is suffering from VMS, because HT is the most effective treatment to reduce VMS, and after cessation of HT VMS often recur [80]. In the randomized trials, women with severe VMS were largely excluded as these symptoms could reduce adherence to placebo treatment or giving placebo was considered unethical. In contrast, women enrolled in the observational studies will usually have started HT because they experienced VMS [81].

We have hypothesized that women with VMS are different from women without such symptoms [82]. This difference may lie in their cardiovascular risk profile, or their response to exogenous hormone therapy. Indeed women with VMS have an adverse cardiovascular risk profile [83], which could not be explained by the absolute estradiol level [47], and have increased arterial calcification and a 1.33-fold increased risk of incident CHD [84]. The findings support the view that VMS are associated with increased cardiovascular risk. However, there is no consensus in the literature [85–87].

Whether VMS are a marker of sensitivity to beneficial effects of estrogens on CVD is also currently unclear. The two post hoc analyses of HT trials suggest that in women with baseline VMS HT *increased* the risk of CHD events. However, these findings should be interpreted cautiously. In both trials the mean age of participants was in the mid to late 60s, and the percentage of women reporting VMS was small, in particular in HERS (16 %). Therefore, these women seem to be a selected group and not a reflection of the average group of women experiencing VMS when going through the menopausal transition. Moreover, effect estimates are based on small number of cases, and in HERS the difference in HT risk between women with and without VMS was significant in the first year only, suggesting that a chance finding cannot be excluded [88]. Data from our own group in an observational setting suggest exactly the opposite; among women with intense VMS, ever HT use significantly decreased CHD risk compared with never HT use (HR 0.39 [95 % CI 0.18–0.87]). On the other hand, among women without intense VMS, ever HT use was associated with a borderline significantly increased CHD risk (HR 1.29 [95 % CI 0.97–1.72]) ($P = 0.03$ for interaction) [89].

Osteoporosis

Early menopause is consistently associated with lower bone mineral density (BMD); whereas the premenopausal loss in BMD is small, after menopause studies have reported 3–5 % annual decreases [90–92], which is a factor 5–10 higher than the premenopausal loss in BMD. Oophorectomy leads to rapid bone loss from the trabecular and cortical compartments of the skeleton; although longitudinal studies are scarce, the average loss of trabecular bone from the spine has been estimated to be between 12 and 19 % in the first year after bilateral oophorectomy [93, 94]. Evidence for a role of menopause in osteoporosis is strengthened by many observational studies reporting that early menopause increases the risk of fractures, which are nicely summarized by Gallagher in 2007 [95].

There is compelling evidence that in the case of osteoporosis, the effect of early menopause can be attributed to the decrease in estrogen levels. Several observational studies pointed to a 50 % reduction in fracture risk in women using estrogen therapy versus women who do not [96–98], whereas meta-analyses clearly pointed in the same direction [99–101]. A systematic review and meta-analysis including data from the Women's Health Initiative study, the largest randomized trial on postmenopausal hormone therapy, estimated that estrogen therapy for 6.2 years is associated with 52 % reduction in incident fractures [78]. Discontinuation of estrogen therapy leads to rapid bone loss in the first year of 3–6 %, and a loss of fracture protection [102].

Breast Cancer

There is wide consensus that a late menopause increases the risk of breast cancer. Every 1-year increment in age at menopause confers an increase of breast cancer by approximately 3 % [103, 104]. Noteworthy is the marked protective effect from a premature oophorectomy performed before age 40, the risk of breast cancer being reduced by about 50 %. This effect is ascribed to the longer exposure to endogenous estrogens if menopause occurs later. In fact, for breast cancer all available evidence, be it on reproductive factors, endogenous estrogen levels, or exogenous estrogen supplementation, points to an important harmful role of estrogen exposure [105].

Conclusion

Menopause is defined as the permanent cessation of menstruation, and defined present 1 year after the last menstrual cycle. Menopause is due to depletion of the follicle pool. The menstrual cycle and changes in the cyclic pattern until a complete stop are orchestrated by gonadotrophins, steroids, and inhibins.

The median age at natural menopause is around 50–51, for centuries and across populations.

Onset of menopause is associated with VMS, the so-called hot flushes and night sweats, the prevalence of which around the FMP is as high as 80 %. Of other symptoms, such as incontinence, depressed feelings, and vaginal dryness, it is not clear whether it is the menopause per se that causes these symptoms and complaints, or whether aging also plays a major role.

Early menopause is associated with increased risk of CVD and osteoporosis and a decreased risk of breast cancer. These effects are generally ascribed to estrogens, but for osteoporosis and breast cancer this is much more clear than for CVD.

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