Antonio Cano
Editor

Menopause

A Comprehensive Approach

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Preface

The increase in life expectancy is a global phenomenon. Women live longer than men, and the gained number of years keeps expanding the postmenopausal period, because menopausal age has not moved substantially. Menopause, therefore, has evolved from an event that only a century ago was identified with the end of life to an endocrinological episode that affects women at midlife.

Much has changed in the view of menopause in the latter 4–5 decades. The confirmation of the fall in the production of estrogens as the main feature of menopause, and the corresponding impact on symptoms and susceptibility to disease, was the basis for the development of hormone therapy. For years, hormones were the solution for controlling symptoms, of course, but also and more importantly for many women and doctors, for risk reduction against important threats linked with aging, like osteoporosis, cardiovascular disease, cognitive decline, or mood deterioration. Hormones were a sort of panacea to preserve health and quality of life, and their use became a recommendation to almost every postmenopausal woman, even in the absence of symptoms.

The Women's Health Initiative study defined a turning point that, in a sort of pendular reaction, drastically reduced the use of hormones to the control of symptoms, only if they altered the quality of life and for the shortest possible duration. The subliminal message was that this option involved concern and risk.

The latter years have provided data suggesting that the messages prior to the WHI study were not totally erroneous. The concept of the window of opportunity to accomplish cardiovascular benefits is a good example.

So, menopause is seen nowadays as a crucial event in the series of changes that women experience at their maturity. It is the loss of fertility, which severely threatens the reproductive options of many women who need to postpone them because of the demands of their jobs, but it is also an excellent moment to implement strategies to prevent many of the non-communicable chronic diseases that increase their prevalence because of the growing longevity. Also, it is a demanding moment when menopause presents with symptoms, which may severely affect quality of life and interfere with the daily activities of women with growing professional responsibilities.

This new view coexists with more prepared and more informed women, who want to actively participate in the decisions related to their care. Also, the strategies for management emerge in a more evidence-based and sophisticated medicine.

Finally, this all should add to the emergence of the new technologies, which dramatically expand and spread up-to-date information worldwide.

This is the frame in which this book has been conceived. I cannot but thank my excellent group of coauthors, who have written admirable chapters presenting updated knowledge and the advances in diagnosis and management. Also my thanks to Springer, which has enthusiastically supported this initiative.

Valencia, Spain Antonio Cano

Contents

Part I

Biological Background

Menopause, A Stage in the Life of Women

1

Gita D. Mishra

Natural menopause is defined as the permanent cessation of menstruation due to the natural loss of ovarian follicular function [1]. It marks the end of the reproductive life span. It is accompanied by changes in the neuroendocrine and immunology systems [2, 3]. Natural menopause is distinct from cessation of the menstruation due to medical treatments or surgical interventions, such as radiation and bilateral oophorectomy.

Humans, gorillas, killer whales, and short-finned pilot whales are the only species known to experience menopause [4, 5]. While discussion on the reasons for the existence of menopause is still under debate, from an evolutionary perspective there are three main explanatory hypotheses. The *grandmother hypothesis*, which speculates that older (nonreproductive) mothers help their child-bearing daughters and thus increase her reproductive fitness. The *mother hypothesis* assumes that older women stop reproducing because it is too risky for them to give birth, and to increase the chance of survival of their offspring [5]. A more recent proposition, *the reproductive conflict hypothesis* (also known as *the mother-in-law conflict hypothesis*), suggests that the cost of intergenerational reproductive conflict between older females and younger females of the same social unit impacts the reproductive fitness calculations [6]. A Finnish study, using birth, death, and marriage records kept by the Lutheran church from 1702 to 1908, found that when both mothers-in-law and daughters-in-law gave birth around the same time, their offspring had a 66% lower chance of survival, with offspring of the older mothers having even lower chance of survival (50%) [7].

For most women, age at natural menopause (ANM) usually occurs between the ages of 40 and 60 years. Findings from our meta-analysis of 46 studies across 24 countries showed that the mean ANM was 48.8 years (95% confidence interval 48.3–49.2). There was substantial heterogeneity across nations: African 48.4 (48.1–48.7); Asian 48.8 (48.1–49.4); Latin American 47.2 (45.9–48.6); Middle

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Eastern 47.4 (46.9–47.8); USA 49.1 (48.8–49.4); Europe 50.5 (50.0, 51.1); and Australia 51.3 (49.8, 52.8) [8].

A woman's age at natural menopause is not only a marker of reproductive ageing, but also an indicator of underlying health and can even act as a sentinel for her future health status [9]. For instance, earlier age at menopause has been shown to be associated with increased risk of cardiovascular disease, stroke, atherosclerosis, and osteoporosis, and by contrast with a reduced risk of breast cancer and ovarian cancer [8]. This does not necessarily imply any causal relationships, but could result from common risk factors, including genetic factors and exposures in early life. For example this may be the case for cardiovascular disease, where recent findings suggest that pre-existing risk factors, such as raised total serum cholesterol and blood pressure, are associated with both earlier menopause and CVD [10]. Our meta-analysis revealed that overall, each year of delay for ANM is linked with a 2% reduction in all-cause mortality [8].

Factors across the life course have been shown to be associated with the timing of menopause, which appears to reflect a complex interplay of factors, from genetic to cumulative socioeconomic and lifestyle factors. Family and twin studies have revealed a significant genetic influence on ANM with estimates of heritability ranging from 30 to 85% [11, 12]. Supporting evidence from observational studies also demonstrates that a direct relationship between a woman's ANM and her mother's reported ANM [11, 13–18].

Epidemiological evidence indicates an important role for factors in early life, including postnatal nutrition. For instance, women in the Medical Research Council 1946 British birth cohort who had been breastfed experienced later ANM than those who had not [18, 19], and women who had a low weight at age 2 years had earlier ANM [19]. Similarly Dutch women who experienced severe caloric restriction as a result of the famine of 1944–45, especially those who were aged 2–6 years at that time, had earlier ANM than those who were not exposed [20]. Lower family socioeconomic position (SEP) in childhood has also been associated with earlier ANM. More specifically, emotional stress at a young age may impact reproductive aging, with evidence that women who experienced parental divorce early in life tended to have earlier ANM [19, 21].

The timing of menarche is another key reproductive marker that has been shown to be associated with ANM. The International collaboration for a Life course Approach to reproductive health and Chronic disease Events (InterLACE) is a large-scale multinational study that provides pooled data, including for over 50,000 women from nine observational studies in the UK, Scandinavia, Australia, and Japan. From this InterLACE data, we showed that almost one in ten women had premature menopause (ANM <40 years) or early menopause (ANM <45 years). Having early menarche (11 years or younger) increased the risk of premature and early menopause by 80%, while the risk doubled for nulliparous women. Furthermore, the combination of early menarche and nulliparity resulted in a fivefold increased risk of premature menopause and twice the risk of early menopause compared with women having later menarche and two or more children [22]. The sparse evidence from low- and middle-income countries also

suggests that earlier age at menarche is associated with earlier age at natural menopause [23, 24].

Of the various lifestyle and environmental factors in adulthood known to affect the timing of menopause, only cigarette smoking [8, 25] and nulliparity [22, 25] are consistently related to an earlier ANM. Some studies have found that women with lower adult SEP, which may indicate greater exposure to stress, tend to experience ANM earlier than women of higher SEP even after adjustment for smoking and parity [26–29]. A recent systematic review found a modest association of moderate to high physical activity with earlier ANM in unadjusted, but not adjusted, meta-analysis, whereas for BMI it was found that being overweight had a modest association with later ANM. As with many other aspects of the menopausal transition, further research is needed on the combined effects of BMI, weight change, and physical activity.

While a significant body of research has been conducted on identifying the factors associated with the timing of menopause, limited evidence exists on the timing and duration of perimenopause. The length of perimenopause has been shown to have an adverse effect on the quality of life. Using data from the 1946 British birth cohort, it was found that women who experienced prolonged perimenopause had a higher decline in two aspects of quality of life: perceived physical health (including energy level) and psychosomatic status (such as nervous emotional state, ability to concentrate) [30]. This is consistent with an earlier study from the USA that found that longer perimenopause was associated with a higher rate of medical consultations [31].

While vasomotor symptoms are among the most frequently reported physiological symptoms during and after menopause [32, 33], their prevalence among women in high-income countries ranges widely from 30 to 75% [34, 35]. Recently, epidemiologic studies have attempted to provide a more detailed picture of the various distinct trajectories of symptoms experienced through the menopausal transition and into postmenopause. For instance, findings from two studies have both shown that groups of women whose vasomotor symptoms peaked strongly either before or after ANM tended to decline relatively quickly in postmenopause [36, 37]. Such trajectories for the severity of these symptoms were not evident when based on chronological age, but only when their timing was examined with respect to the ANM. In the future this information may help guide women in the management of their symptoms in selection of appropriate treatment options.

Overall, risk factors from prenatal stage through to adult life influence the age at menopause, with consequent implications for health risks in later life. Our understanding from epidemiological studies of the effects of menopausal transition on women and the factors that influence its duration and timing remains unclear and incomplete, especially on those from low- and middle-income countries. Expanding life course research in these countries will demonstrate whether social trends, such as growing income inequality during childhood and adulthood and upward mobility, similarly relate to women's age at menopause as is the case in rich nations. Basic questions, such as the variation in the length of perimenopause globally or the impact of the menopausal transition on weight gain, remain essentially unanswered.

One way forward lies in expanding studies such as InterLACE that combine individual-level data from numerous international studies of women's health [38, 39]. This would provide a more comprehensive and detailed picture of the menopausal transition, its timing, and long-term health implications, for women not just in high-income countries but from across regions and from diverse populations.

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Menopause: The Concepts and the Biological Background

2

Antonio Cano

2.1 Menopause and the Menopause Transition

Natural menopause is the permanent cessation of menses as a consequence of ovarian follicle depletion. This is a peculiarity of the ovary, which differs from the testicle in that it undergoes spontaneous functional demise at a relatively young age. The lack of follicle replication after the period of fetal life, approximately the 20th week of pregnancy [1], leaves a predetermined endowment with a limited duration. The specific pattern of follicular wastage, with successive waves of growing follicles at regular time intervals, progressively reduces the resident population in the ovary until its final exhaustion.

Because the number of follicles that start growing is proportional to the remaining population, the follicle cohorts in the latter years of the ovarian life span have lower numbers. Of additional interest, and due to a negative selection whose reasons are not totally clear, the latter follicular cohorts include oocytes of poorer quality. The lower number of follicles is sometimes accompanied by less efficient cycle support of the menstrual cycle, which translates into a great heterogeneity in cycle pattern. Therefore, some women maintain an acceptable regularity until the very last menstrual period (LMP), while others suffer from cycle irregularity with a changing mixture in which ovulation and anovulation are present. The high prevalence of anovulation causes cycle irregularity, with periods of amenorrhea that may last for several months. There may be bleeding disturbances too, and a list of symptoms conditioning frequent medical consultation and cost. The strong clinical implications of this changing pattern in the years prior to menopause is at the base of another important concept, the menopausal transition, also termed perimenopause.

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The World Health Organization proposed this conceptual difference in 1994. Menopause, therefore, was defined only when 1 year has elapsed since the LMP in the absence of no other obvious physiological and pathological cause [2]. It is obvious that with this definition menopause can be known only in retrospect. Perimenopause is the interval in which some women have irregular menstrual cycles before menopause. This distinction of the WHO has been incorporated by most scientific societies in the world.

The term "climacterium" has been used as a more holistic concept, which integrates the whole period of the change, and includes psychological and other domains. This very broad approach has limited clinical usefulness [3].

The Staging of Reproductive Aging Workshop (STRAW) was proposed in 2001 with the purpose of integrating the ovarian changes during the whole reproductive period of women's life [4]. Stage 0 defines the LMP, while stages −2 and −1 correspond to the early and the late menopausal transition. Perimenopause extends one more year, since it also integrates the 12-month period that is required to identify menopause after the LMP.

A refined version, the STRAW +10, was published in 2012 to incorporate data from some longitudinal studies to improve comparability and clinical decision making (Fig. 2.1). As main features, the new proposal simplified the bleeding patterns in

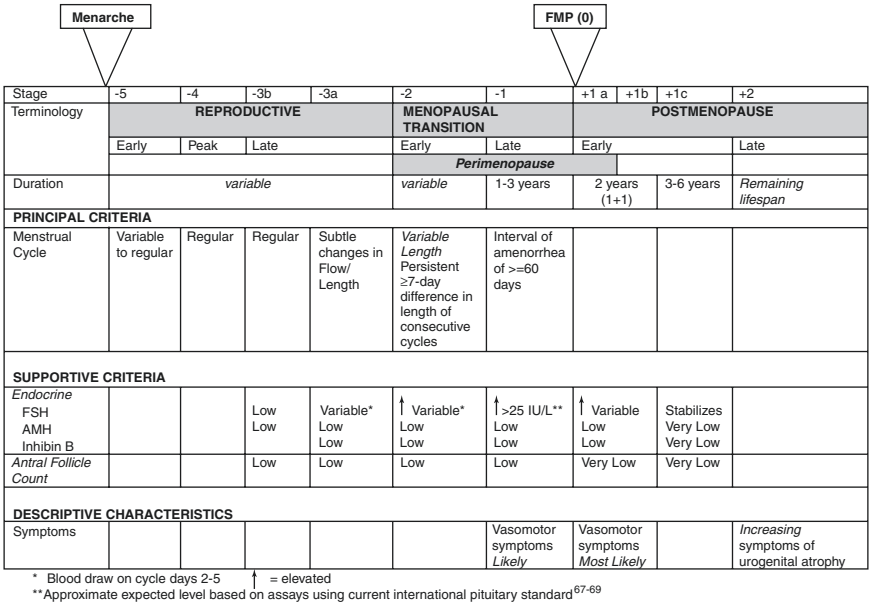

Fig. 2.1 The Stages of Reproductive Aging Workshop (STRAW) outline the seven principal stations of the reproductive life of women, including the perimenopause and the postmenopausal phases. Each stage is typified by the pattern of the menstrual cycle, principal accompanying symptoms, and supportive information in the form of biochemical or imaging features. With permission of the American Society for Reproductive Medicine from Harlow et al. Fertil Steril. 2012;97:843–851. Permission conveyed through Copyright Clearance Center, Inc

early and late menopausal transition and recommended application regardless of women's age, body size, or lifestyle [5].

For obvious reasons, both the WHO definition and the STRAW classification apply with difficulty to women who undergo natural menopause but are hysterectomized, or are subjected to hormonal treatments, either the pill or the progestogen-wearing intrauterine devices.

2.2 Epidemiological Data

The age at menopause seems relatively stable across the history and between the world regions. More or less, the age of 50 years has been considered as a good approximation. However, there are some differences whose mechanisms are still unclear. The interest is not only anecdotic, since some studies have suggested that age at menopause may be a marker of general health. Later menopause seems to predispose to cancer of reproductive tissues (endometrium, ovary) and breast, but confers an advantage against osteoporosis and cardiovascular disease. The balance appears positive and later menopause associates with longer survival [6] while just the opposite occurs in women with premature menopause or early-onset menopause [7].

A systematic review [8] has found that, generally speaking, natural menopause presents slightly later in developed countries. The highest mean age is found in Australia (51.3 years) and Europe (50.5 years), followed by the United States (49.1 years). Age at menopause is lower in Asia (48.8 years) and Africa (48.4 years), followed by the Middle East (47.4 years) and Latin America (47.2 years). The possibility that the difference might be influenced by an increase of the age at menopause in developed countries is a possibility proposed by some studies [9]. This information suggests that environmental factors, nutrition or others, might have an effect. Some biological influence, genetic and/or other, is possibly at work too, as indicated by the considerable variation from woman to woman, which may oscillate between 45 and 55 years. Most of the population, however, accumulates around the mean age, with 95% confidence intervals that do not exceed 3 years in any of the studies.

The duration of the perimenopause is also subjected to some variation, as indicated by the variable duration of the early phase of the menopausal transition (Fig. 2.1). Data from the Massachusetts Women's Health Study (MWHS) showed that the median age at inception of perimenopause was 47.5 years and that the length was almost 4 years in that population [10]. Moreover, longer perimenopause is associated with more symptom reporting and with more medical consultations.

2.3 The Menstrual Cycle During Perimenopause

The advent of irregular menstrual cycles identifies the initiation of the menopausal transition. More precisely, the −2 STRAW stage defines menstrual cycles of variable length persistent ≥7-day difference in length of consecutive cycles, while the −1 stage already requires amenorrhea intervals ≥60 days.

Much of what is known about menstrual patterns during the menopause transition still derives from the huge prospectively collected database initiated in the 1930s by Alan Treloar [11]. Variability in cycle length, including short and long cycles, was already reported by 10–15% of women at 6 years before menopause. An additional 30% of women reported variability between 3 and 2 years prior to menopause. Interestingly, a residual 4.5% of women will still have one more menstruation after 1 year of amenorrhea at age 52. This observation should be accounted for when assessing the population of postmenopausal bleeders, who should be investigated to discard malignancy but that, fortunately, will only translate the activity of remaining follicles in a considerable number of cases.

The cycle irregularity of women undergoing the menopausal transition may be accompanied by heavy bleeding episodes. There is already a progressive increase in the volume of blood loss with age in regular cycles, which was described quite long ago [12]. Irregular cycles during the menopausal transition define an additional increase in the bleeding volume, often in the context of cycle irregularity. A changing pattern of anovulatory and ovulatory cycles underlies that irregularity, in which anovulation creates a status of persistent estrogen stimulation. Breakthrough or withdrawal heavy bleeding is the consequence.

The incidence of endometrial proliferative or hyperplastic changes often accompanies the anovulatory substrate. The possibility of a pathological background in the form of benign (leiomyoma, adenomyosis, etc.) or malignant conditions should prompt adequate evaluation of these women.

2.4 Variables Affecting Menopause Age

Menopause occurs when the residual follicle population in the ovary is unable to produce enough estrogen to generate uterine bleeding. The prediction of menopause age is elusive at present but it is assumed that the follicle endowment of the ovary in the yeas prior to menopause is potentially a relevant variable. This is why attention has been given to a series of factors with known impact on the size of follicle population across the reproductive life span of women.

2.4.1 Genetics

The heritability of the age at menopause has been detected in twin registries and family history studies. Also community-based epidemiological studies, like the multigenerational Framingham Heart Study, confirmed the association and determined that genetic factors explain at least 50% of the interindividual variability in menopausal age [13].

Much of the genetic basis of menopause has been identified in studies on premature ovarian insufficiency, and more detailed information may be found in the corresponding chapter of this book. When considering natural menopause the task has become more difficult. A systematic review reports that bot linkage analyses and genome-wide

association studies (GWAS) have found regions containing promising candidate genes. The association studies, nonetheless, have given poor results. A GWAS analysis on nearly 70,000 women identified 44 common susceptibility loci for age at natural menopause [14], but they only accounted for 2.5–4.1% of the observed variation [15].

The identified genes suggest a common genetic background for aging of the organism and menopause, something that again underlines the concept that reproductive performance may be taken as a marker of a woman's general health [15].

2.4.2 Lifestyle

Environmental and socioeconomic factors seem to have an effect on menopausal timing, as suggested by the later age at menopause in wealthy countries. Lifestyle translates, at least in part, some of those factors.

Current smoking is one persistently detected variable [16–18]. Tobacco consumption seems to be toxic on the follicle pool, possibly via the polycyclic aromatic hydrocarbons in cigarette smoke [19]. According to a systematic review, smoking accounts for a 1-year reduction of age at natural menopause [8] and for about 5% of the risk of early menopause [20]. Perimenopause seems to be shortened by smoking too [21]. The sparse data on ex-smokers do not seem to detect an association with age at menopause [8] or, when an association is detected, it is weaker [22].

The notion that diet affects the age at menopause derives from both indirect and direct evidences. Increased weight and significant weight oscillations have shown some impact on delaying the age at menopause in old [22] and more recent [8, 23] studies. The suggestion that this finding may be translating the influence of diet has been reinforced by data showing that food deprivation conditions earlier menopause, even when at infancy [24].

Physical activity has been linked with anovulation and amenorrhea when attaining intensive level, but whether it is associated with changes in age at menopause is unclear. The Study of Women Across the Nation (SWAN) found that less physical activity is related with later age at menopause [25].

Little is known about the effects of other environmental or occupational factors, but being employed also is related with later age at natural menopause in the SWAN [25]. This factor may translate the effect of the stress associated with unemployment or lower socioeconomic condition, since exposure to stress, even at early life, has been associated with earlier menopause [26].

2.4.3 Other Factors

The availability of data from different cohorts has shown that both early menarche ($\leq$11 years) and nulliparity (vs. women with two or more children) increase the risk for premature (LMP <40 years) and early menopause (LMP 40–44 years). Indeed, women with early menarche and nulliparity were at over fivefold increased risk of premature menopause and twofold increase of early menopause [27].

Attempts have been made to predict the age at menopause based on other factors, like mother's age at menopause. However, individual prediction at the clinical setting is still elusive [28].

2.5 The Biological Basis of Menopause

As repeatedly described above, menopause occurs when the follicular population is unable to produce significant amounts of estrogens. Endometrium, therefore, will not proliferate enough to allow for a subsequent sloughing and concomitant bleeding.

This ovarian depletion ensues because follicles are not replaced, at least in clearly detectable form [29], after fetal life. The loss is exponential since that intrauterine phase, with dramatic changes in the follicle population that change from a peak of 6–7 million to only 300,000 at puberty. Despite the considerable fall, the follicle population continues declining at a good pace and only some 450 oocytes will be taken to ovulation.

2.5.1 Subclinical Phase

The clock marking the endocrinological life span of the ovary is governed by the mechanisms determining the initiation of folliculogenesis. Each follicle wave further decreases the finite endowment of the ovary despite the absolute normality of the menstrual cycle. A complex set of local factors act on the population of primordial follicles, the basic follicular structure, to determine which of them will start growing or, instead, will remain quiescent [30]. Anti-mullerian hormone (AMH) acts to limit the size of the follicular cohort and contributes to maintaining an adequate ovarian reserve. This key function of AMH was demonstrated in classical experiments with rodents in which the silencing of the AMH gene was followed by early follicle exhaustion in the ovary [31].

Once initiated, the growth of the follicular cohort is mainly governed by the gonadotropins, follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which are produced in the pituitary gonadotropes. Gonadotropins regulate the granulosa and the theca cells, which extend along the follicle wall and around the oocyte, to stimulate ovarian steroidogenesis. The hormonal output includes estrogens, but also androgens and progesterone. An updated review of these concepts may be found elsewhere [32].

The landmark contributions of Gougeon clearly showed that, against previous conceptions limiting folliculogenesis to the 2 weeks prior to ovulation in each menstrual cycle, follicle cohorts start growing around 3 months prior to ovulation [33]. A high number of follicles integrate the initial cohort, but they will progressively become apoptotic and only one will get the ovulation stage.

Folliculogenesis includes two phases of growth, tonic and exponential, the latter including approximately the 3 weeks prior to ovulation and being characterized by a high sensitivity to gonadotropins [33]. This does not mean, however, that the tonic phase is insensitive to gonadotropins, since receptors for FSH are already detected at the granulosa cells of the secondary follicles, at the beginning of the tonic phase of growth. The precise contribution of FSH in those early phases of folliculogenesis is still unclear.

Together with AMH, inhibins A and B are dimeric proteins also secreted by the granulosa cells in the ovary (Fig. 2.2). Both inhibin isoforms are composed of two subunits, alpha and beta, the difference residing in the beta-isoform, which may be A and B for inhibins A and B, respectively. Isoforms of inhibin differ in their expression during the menstrual cycle [34]. Interestingly, the output of inhibin B decreases several years prior to menopause [35] (Fig. 2.3). This has been attributed the main

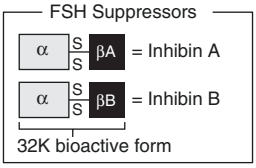

Fig. 2.2 Molecular structures of inhibin A and inhibin B. Both isoforms are heterodimers deriving from precursors, peptides of bigger size that generate the corresponding subunits after proteolytic cleavage. The specificity of each isoform is dependent on the β-subunit, since the α-subunit is common. With permission of Elsevier from Soules et al. Maturitas. 1998;30:193–204. Permission obtained through Copyright Clearance Center, Inc

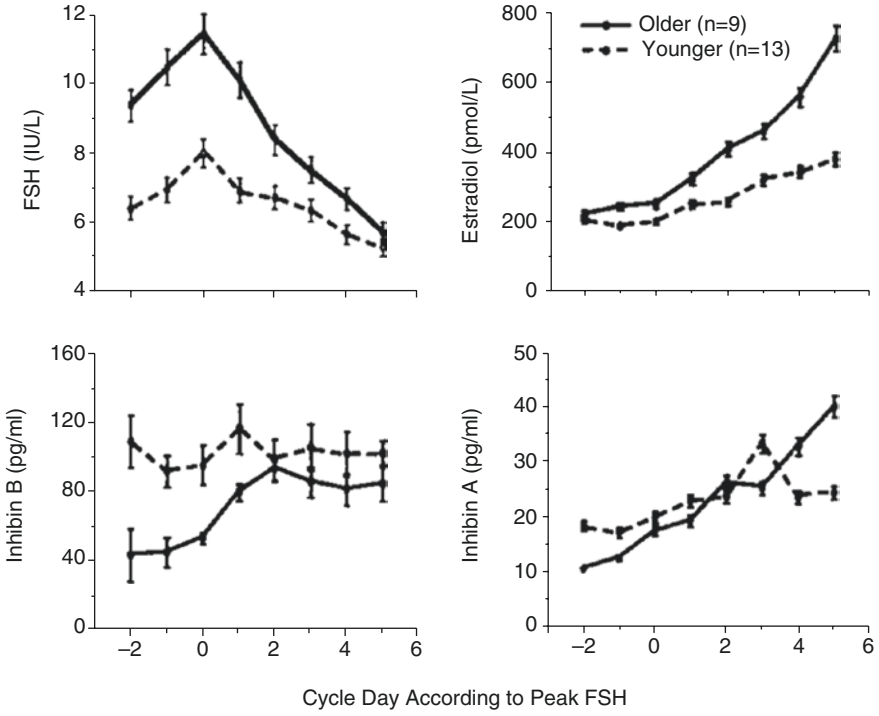

Fig. 2.3 The panel shows the pattern of FSH, inhibin B, estradiol, and inhibin A as obtained from two groups of ovulatory women, who were divided into older (age 40–45) and younger (age 20–25). The "monotropic" increase of FSH in older women is a reflection of the corresponding decrease in inhibin B. The production of estradiol is higher in older women during the follicular phase of the cycle. With permission of Oxford Academic from Klein NA et al. J Clin Endocrinol Metab. 1996;81:2742. Permission obtained through Copyright Clearance Center, Inc

responsibility for the monotropic increase of FSH, i.e., a selective increase in circulating FSH that is not accompanied by LH, which is detected some years prior to perimenopause [36] (Fig. 2.4). The FSH increment has been ascribed the responsibility in the trend to shorter, although still regular, cycles that women experience in the years prior to perimenopause. The higher levels of FSH would accelerate the growth of the latter surviving follicles, just before the process of selection and dominance of the ovulatory follicle.

One key feature of the aging ovary is the asynchrony between the fertility potential and the hormonal output. While fertility is dramatically decreased after the age of 40 years, the steroidal production of the remaining follicles is preserved. Oocytes seem more sensitive to age than the steroidogenesis machinery of the theca-granulosa complex. This explains that in some women follicles at the later stages of the exponential growth phase respond to the overstimulation of the increased FSH with higher estrogen production, an apparently paradoxical feature of the final reproductive stages of women [37]. In consistence with that observation, the expression of P450aro (aromatase) is increased in granulosa cells aspired from the follicles of older women [38].

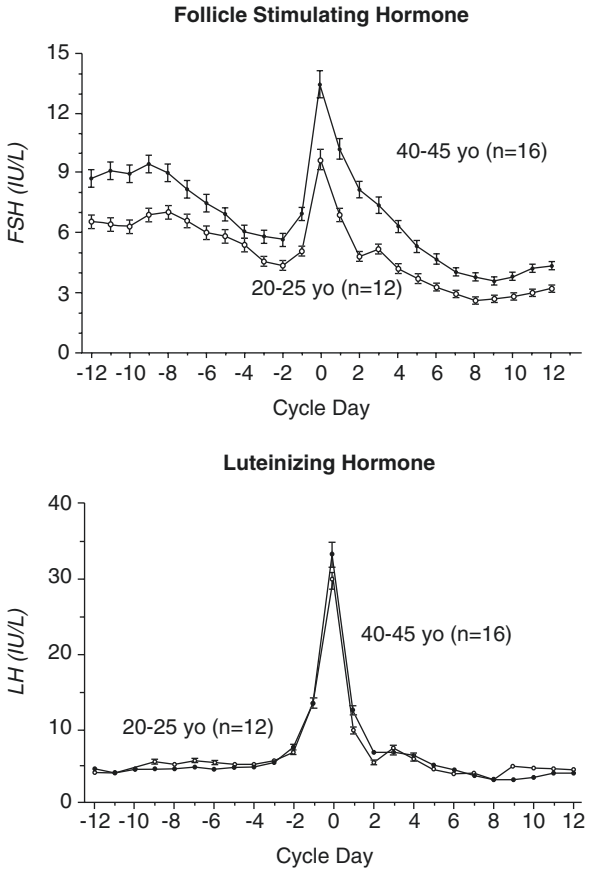

Fig. 2.4 FSH is increased in older ovulatory women (age 40–45) as compared with younger women (age 20–25). LH, however, maintains at similar levels and only increases late, very close to menopause (not shown in the figure). Day 0 corresponds to the day of the LH surge. With permission of Elsevier, Soules MR et al. Maturitas. 1998;30:193. Permission conveyed through Copyright Clearance Center, Inc

2.5.2 Cycle Irregularity

The initiation of irregular cycles during the perimenopause is accompanied by altered patterns of gonadotropin levels. This translates the changes in the secretion of estradiol, which is already reduced and irregular. Consequently, FSH keeps increasing, and concomitant increments of LH also occur, although usually at later stages, already close to menopause. It is important to stress, however, that cycles do not follow an established pattern and often change between and within individuals.

This drastic change in gonadotropin secretion translates the increase in GnRH, which changes both the pulsatile pattern and the mass of released peptide as a result of the diminished estradiol feedback. Local changes in brain peptides, kisspeptin and others, mediate the change [32].

There has been some debate on whether there is also a contribution of a concomitant aging process of the central nervous system. Experiences in rodents have clearly shown that the positive feedback to estradiol by the hypothalamic-pituitary block deteriorates at middle age [39]. A reduced availability in hypothalamic neuropeptides and a loss of their required coordination to produce adequate GnRH bursts are at the base of the dysfunction [39]. Similar dysfunctions are known since years in women suffering from perimenopausal anovulatory cycles with severe bleeding disturbances [40].

In contrast, negative feedback keeps unaltered for longer, as shown by the reduction in the circulating gonadotropin levels when estrogens or a combination of estrogen and progesterone is administered [41].

2.5.3 Postmenopause

The postmenopausal state is divided into two periods in the STRAW + 10, the early and the late postmenopause. Although unable to provide the hormonal changes capable of endometrial proliferation to a stage that will end in a bleeding episode, there is still a residual follicular population with a certain hormonal activity. Nonetheless, this keeps being progressively reduced, because the continuous follicle wastage persists. The declining estradiol levels stabilize around a couple of years after menopause [42]. Gonadotropins remain stable, but also decrease by approximately 30% at age 75. This change results from a 22% reduction in the GnRH pulse frequency and a 30% reduction in the pituitary sensitivity to GnRH in older women [31].

The postmenopausal ovary maintains some steroidogenic activity from spindle cells in the ovarian stroma. These cell populations meet conditions for keeping hormonally active, as there is a preserved vascular structure and a good population of LH receptors. Indeed, studies in blood from the ovarian vein of postmenopausal women have shown that the postmenopausal ovary significantly contributes to the circulating pool of testosterone, and that the contribution may persist up to 10 years past menopause [43].

This androgen production may have an impact on some psychological states or the libido, and has been the basis of some clinical effects observed with testosterone replacement in surgical and natural menopausal women [44, 45].

The output of testosterone from the ovary may act as a substrate for aromatase, the enzyme converting androgens into estrogens. Aromatase is expressed in multiple tissues, including fat and brain, which may act as alternative sources of estrogens. Thanks to the aromatase expression, the local estrogen production has provided the biological basis for the new concept of *intracrinology* [46, 47]. This sort of self-sufficiency is achieved without affecting other tissues and taking as substrate steroids from the ovary or the adrenal. For example, circulating dehydroepiandrosterone (DHEA) may feed steroid-forming enzymes to meet the physiological needs of different target tissues. A good example of a tissue with high local estrogen level is the breast, which may amplify this function in the case of malignant transformation [48], and the bone, which may provide local estrogens for reducing bone remodelling.

Conclusion

The ovary is a gland with two main hormone-producing compartments, the follicular apparatus and the stroma. Follicles enclose the oocytes surrounded by different layers of theca and granulosa cells, which are responsible for most of the steroidal hormone output. Three steroid hormone species, estrogens, progesterone, and androgens, are produced. The stromal compartment produces androgens, and survives the follicular decline for an undetermined number of years. The decline in the follicle endowment conditions different endocrinological patterns, which are the basis of the clinical forms of the menopausal transition. These include varying patterns, including irregular bleeding and a mixture of symptoms translating hormonal deprivation, like hot flashes or mood changes, or hormonal excess, like breast tenderness. The reduction of the resident follicular population below a certain threshold involves the end of the withdrawal bleeding, which is consensually considered definitive after 1-year amenorrhea. Of course, subsequent bleeding episodes may occur and, although their investigation is advised to discard malignancies, most of them will still result from estrogen bursts deriving from sporadic follicular growth.

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Primary Ovarian Insufficiency

3

Agnieszka Podfigurna, Adam Czyzyk, Monika Grymowicz, Roman Smolarczyk, and Blazej Meczekalski

3.1 Introduction

Premature ovarian insufficiency (POI) can be defined as a cessation of ovarian function in women younger than 40 years old and is linked to the development of hypergonadotropic hypogonadism. The hypogonadism clinically presents as amenorrhea, which sometimes is preceded by oligomenorrhea and decreased circulating estradiol levels. Different clinical definitions of POI have been proposed (see below).

Many other terms have been proposed for POI. In the professional literature, aside from being termed POI, it is most frequently called premature ovarian failure (POF) and premature menopause [1]. Our current understanding of this condition makes it impossible to consider it as an "early menopause." There are several important differences between POI and normal menopause. First, normal menopause is a physiological process, whereas POI is a pathology. In menopause, the cessation of gonadal function is complete, while some POI patients sporadically produce estrogen and ovulate. For the same reason, professional societies recommend to omit the "premature ovarian failure" term, which also suggests the permanent lack of gonadal function [2]. The last, but very significant, difference between menopause and POI is long-term consequences. The POI is related to a number of specific issues related to physical health, reproductive function, and psychological problems, which are not present in women undergoing menopause (see Sect. 3.5). Some authors suggest the term early menopause for describing menopause occurring between the 40th and 44th years of life.

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3.2 Pathogenesis of POI

The pathogenesis of POI is very complex and still not fully understood. Genetic causes are regarded as the leading pathomechanism of POI. Other causes are referred to autoimmune, metabolic, and infectious backgrounds. Due to oncological treatment of adolescents and young women, iatrogenic actions constitute an essential part of the causes of POI. Idiopathic causes of POI still require elucidation.

3.2.1 Genetic Causes

It is reported that up to 40% of POI can be attributed to genetic causes. The POI genetic background is referred to a polygenic nature. Chromosomal abnormality accounts for approximately 10–12% of POI patients. The majority of these are referred to as X chromosome abnormality [3]. Therefore, the karyotype examination should be performed in all POI patients without an iatrogenic background.

The classification of the POI genetic background can be arranged in different ways. Here we present a classification based on non-syndromic and syndromic POI causes [4].

The genetic background of POI still requires further elucidation. New technologies in molecular biology such as the genome-wide association study (GWAS) and next-generation sequencing (NGS) are regarded as promising tools for the POI genetic research.

Classification of POI genetic background

1. Non-syndromic POI
   - Ligands of TGF-beta family
   - BMP-15
   - GDF-9
   - INHA
   - FMR1
   - G-protein-coupled receptors
     Gonadotropin receptors
     GPR3
   - NR5A1 (SF-1)
   - Other transcription factors
     FOXO3a
     NOBOX
     FIGLA
2. Syndromic POI
   - Turner syndrome
   - CDGs syndrome and galactosemia
   - Pseudo-hypoparathyroidism type 1a (PHP1A)
   - Autoimmune polyglandular syndrome type 1
   - Progressive external ophthalmoplegia

- Ovarioleukodystrophy
- Ataxia telangiectasia
- Demirhan syndrome
- Blepharophimosis, ptosis, epicanthus inversus syndrome (BPES)

3.2.1.1 Non-Syndromic POI

Ligands of the TGF-Beta Family

BMP-15

BMP-15 encodes for an oocyte-specific member of the TGF-β superfamily factor of growth factors [5]. This protein plays an essential role in the stimulation of follicle development and follicle maturation. For the first time, in 2004, Di Pasquale et al. reported the heterozygous missense mutation p.Tyr235Cys, which results in the functionally compromised mutant BMP15 protein and POI [6]. The possible mechanism of this is referred to the impairment of the signaling of granulosa cells and the augmentation of follicle atresia.

GDF-9

GDF-9 is a member of the transforming growth factor beta (TGF-β) superfamily and, like other TGF-β proteins, it is translated as a preproprotein [7]. GDF-9 protein is responsible for the proper functioning of steroidogenesis and granulosa cells.

Numerous studies have confirmed the role of GDF-9 variants in POI pathogenesis [8]. However Takebayashi et al. [9] did not find any GDF-9 mutations in women with polycystic ovary syndrome and POI.

Inhibin A (INHA)

The inhibin a-subunit (INHA) is responsible for regulating the pituitary secretion of FSH, acting in the negative feedback control of FSH. It is essential in the recruitment and development of follicles during folliculogenesis. A decrease in serum INHA concentration occurs when the ovarian follicular pool begins to reduce [10].

Mutations in the INHα gene, which may cause a decrease in the amount of bioactive inhibin, result in an increased FSH concentration, leading to a premature depletion of follicles, a typical feature of POI ovaries [11, 12]. It is possible that some GDF-9 variants may occur in POI women of some ethnicities more than in others [13].

FMR1

The FMR1 gene is located in Xq27.3 outside the Xq POI critical region [14].This gene codes for a protein called the fragile X mental retardation protein, or FMRP. The FMR1 gene is expressed in oocytes and encodes an RNA-binding protein involved in translation [15]. The accumulation of FMRP may impair the expression of genes required for oocyte development.

FMR1-related POI, defined as the cessation of menses before age 40 years, has been observed in carriers of premutation alleles. POI occurs in approximately 20%

of females who have an FMR1 premutation. Premutation carriers have been identified in 0.8–7.5% of women with sporadic forms of primary insufficiency [16]. According to the ESHRE Statement, fragile X permutation testing is indicated in POI women [2].

G-Protein-Coupled Receptors

G-protein-coupled receptor 3 is a protein encoded by the GPR3 gene in humans and is involved in signal transduction [17]. GPR3 plays an important role as a link between oocytes and the surrounding somatic tissue and is expressed in mammalian oocytes, where it maintains meiotic arrest [18]. The results of two studies suggested that mutations in GPR3 are not a common cause of POI in Chinese women [19, 20].

SF-1 (NR5A1)

Steroidogenic factor 1 (SF-1) also known as NR5A1 is described as a nuclear receptor and regulator of multiple genes involved in adrenal and gonadal development, steroidogenesis, and reproductive axis [21]. Several variants of the SF-1 gene have been identified and are characterized as associated with POI pathogenesis [22].

Other Transcription Factors

FOXO3a

The FOXO3a gene belongs to the forehead gene family [23]. Watkins et al. [24] found that potentially causal mutations in FOXO3A (2/90; 2.2%) and FOXO1A (1/90; 1.1%) were identified in POI patients. Functional studies should be used to clarify the role of different FOXO3a variants in POI pathogenesis.

NOBOX

NOBOX is an oocyte-specific homeobox gene that plays a critical role in early folliculogenesis. Studies performed by Qin revealed the role of NOBOX mutations in POI pathogenesis [25, 26]. Bouilly et al. [27] found that NOBOX mutations can be responsible for 5–6% of POI in the Caucasian and African population.

FIGLA

The FIGLA gene is localized on chromosome 2 (2p12) [8]. FIGLA is expressed in the human fetal ovary and plays an essential role in primordial follicle formation [28].

Different variants (p.140 delN); p.Arg83Cys) of FIG alpha were found, respectively, in the Chinese and Indian populations with POI [29, 30].

3.2.1.2 Syndromic POI

Turner Syndrome

Turner syndrome is characterized as a chromosomal abnormality associated with a complete or partial absence of one X chromosome in a phenotypic female [31]. Germ cell atresia and extent of ovarian failure vary based on the mosaicism level. The prevalence of Turner syndrome is approximately 1:2500 live female births.

Congenital Disorder of Glycosylation [Carbohydrate-Deficient Glycoprotein Syndrome (CDGs) Syndrome] and Galactosemia

Congenital disorder of glycosylation is one of several rare inborn errors of metabolism in which the *N*-glycosylation of a variety of tissue proteins is deficient or defective [32]. POI occurs in approximately 60–70% of women with diagnosed galactosemia [33]. The pathomechanism is related to the negative influence of galactose and its metabolites on follicle development and the FSH receptor function [34].

Pseudohypoparathyroidism Type 1a (PHP1A)

Pseudohypoparathyroidism type 1a (PHP1a), also known as Albright's hereditary osteodystrophy (AHO), was first described by Albright in 1942 [35]. It is a genetic disorder caused by maternally inherited mutations of the GNAS (guanine nucleotide-binding protein, alpha stimulating) gene. The preferential expression of a mutant maternal allele in the gonads, as in other target tissues of peptide hormones acting through the same GPCR-Gsα-cAMP pathway, explained the coexistence of gonadotropin resistance and POI in patients with PHP1A [36].

Autoimmune Polyglandular Syndrome Type 1

Autoimmune polyglandular syndrome type 1 (APS 1), also known as autoimmune-polyendocrinopathy-candidiasis-ectodermaldystrophy (APECED) or as Whitaker syndrome, was first described in 1946 [37]. This syndrome includes chronic mucocutaneous candidiasis, hypoparathyroidism, and autoimmune adrenal insufficiency. APS 1 is a disorder with sporadic autosomal recessive inheritance [38]. Less common clinical manifestations of APS 1 could be hypergonadotropic hypogonadism, diabetes mellitus type 1, autoimmune thyroid disease (not including Graves' disease), chronic active hepatitis, pernicious anemia, or asplenia and others [38].

Progressive External Ophthalmoplegia

Progressive external ophthalmoplegia (PEO) is a disorder of the ocular muscles. It is characterized by a symmetrical inability to move the eye and is the most common manifestation of mitochondrial myopathy [39]. PEO can occur also as a part of a syndrome involving more than one part of the body, such as Kearns-Sayre syndrome. Pagnamenta et al. [40] studied POLG and showed that mutations can segregate with POI and parkinsonism. The researchers demonstrated that the Y955C mutation can lead to mtDNA depletion.

Ovarioleukodystrophy

The "ovarioleukodystrophies" comprise a group of rare leukodystrophies associated with POI [41]. Generally the age of onset of the neurological degeneration correlates positively with the severity of the ovarian dysfunction [42].

Ataxia Telangiectasia

A-T is caused by mutations in the ATM gene located on chromosome 11q22–23 [43]. The main characteristic features include early onset of progressive cerebral

ataxia, ocular apraxia, telangiectasias, immunodeficiency, chromosomal instability, hypersensitivity to ionizing radiation, increased incidence of malignancies, and ovarian dysgenesis [44]. Mutation in the ATM gene causes a complete absence of mature gametes in adult gonads [45].

Demirhan Syndrome
Demirhan syndrome is an acromesomelic chondrodysplasia, which is a rare group of hereditary skeletal disorders. It is caused by homozygous mutations in growth differentiation factor 5 (GDF5), being an autosomal recessive inheritance pattern [46]. Demirhan et al. [47] presented a 16-year-old girl with homozygous mutation in BMPR1B acromesomelic manifesting chondrodysplasia, genital anomalies, amenorrhea, and hypergonadotropic hypogonadism.

Blepharophimosis, Ptosis, Epicanthus Inversus Syndrome (BPES)
BPES is an autosomal dominant eyelid malformation characterized by BPES and telecanthus associated (type I) or not (type II) to POI [48]. At present, mutations in FOXL2 are the only identified cause of BPES type I and type II. It is estimated that 2–3% of isolated POI cases have a *FOXL2* mutation [49].

3.2.2 Autoimmune Causes of POI

According to contemporary data, autoimmune disorders occur more frequently in POI patients than in the general population. On the other hand, POI is more frequently presented in patients with specific autoimmune diseases. Relation of POI to other autoimmune diseases is described below (Sect. 3.4.6.2.3).

3.2.3 Metabolic Disorders

Galactosemia can be referred to as a rare metabolic genetic disorder in which galactose is not metabolized properly. POI is a long-term consequence of this disorder. Patients with hypergonadotropic hypogonadism present primary or secondary amenorrhea. The incidence of POI in women with profound GALT deficiency is around 80% [50]. The mechanisms by which the ovarian function is destroyed are not clear. The most possible mechanisms are referred to the accumulation of galactose and its toxic products of metabolism (galactose-I-phosphate and galactitol), which after birth can lead to direct ovarian impairment [51].

3.2.4 Infectious Causes

Different viral diseases such as HIV, cytomegalovirus, varicella, herpes zoster, or malaria have also been considered as a cause of POI. Among these viral infections, however, only mumps oophoritis has been confirmed as a definite cause of POI [52].

According to ESHRE, POI consensus infection screening in POI women is not recommended [2].

3.2.5 Iatrogenic Causes

Iatrogenic causes are regarded as a common and increasing cause of POI.

They are related to oncological treatment and include the gonadotoxic effect of chemotherapy, radiotherapy, and also surgery.

The incidence of cancer in adolescents and young women is increasing [53]. It should be stressed that the above-mentioned oncological treatment can cause a whole spectrum of POI with the leading consequence being infertility.

Chemotherapy causes a gonadotoxic effect on the ovary, which is represented in such a histological picture as the apoptosis of ovarian follicles, cortical fibrosis, and vascular damage. Chemotherapy-induced POI is related to the type of agent, the dose of the agent, and of course the age of the patient. The age of the patient is important because with increasing age physiological follicular depletion is observed. Alkylating agents (cyclophosphamide is an example) present a strong gonadotoxic effect, and in approximately 40% of cases can cause POI. Other chemotherapeutic agents such as anthracycline antibiotics, antimetabolites, or vinca alkaloids are classified as less gonadotoxic [54].

Acute POI can occur after the irradiation of such regions as the hypothalamus, pituitary gland, and pelvis. The dose of the radiation is critical in the sense of the ovary function. It has been proved that the application of a dose of 14.3 Gray to an ovary of women younger than 30 years old can lead to irreversible POI [55]. When the dose is lower, such as 6 Gray, the ovarian dysfunction can be reversible. Similarly to chemotherapy, the effect of irradiation depends on the age of the patients. Younger patients pose a higher number of follicles in the early stage of development.

The type and extent of surgery can implicate the POI risk. Coccia et al. [56] revealed that bilateral surgery for bilateral endometrioma can cause POI.

Oncological therapy should be discussed with the patient in the perspective of its risk for POI and POI-related infertility.

3.3 Epidemiology

Generally, the incidence of POI is estimated as affecting 1% of women [57]. Specifically, it can be stated that it occurs in 1% of women younger than 40 years old and in 0.4% of women aged less than 35 years old [58]. The detailed epidemiological data regarding POI, however, is very limited. In one large longitudinal study, ethnic differences have been reported for the prevalence of POI. In comparison to the Caucasian population (1.0%), some ethnicities were affected more often (African-American—1.4%, Hispanic—1.4%), whereas others more seldom (Chinese—0.5%, Japanese—0.1%) [59]. These results, nevertheless, must be interpreted cautiously, since these are self-reported, and other authors have found conflicting results [60].

The data regarding lifestyle and environmental risk factors for POI is also scant. Among the proposed risk-factors for developing POI, the following have been reported: smoking, a small waist-to-hip ratio, and lack of alcohol consumption [57, 61].

3.4 Definition and Clinical Presentation

3.4.1 Definition

Premature ovarian insufficiency (POI) is the triad of amenorrhea, elevated gonadotropins, and estrogen deficiency occurring in women before the age of 40 years [62–65]. The term POI encompasses both the spontaneous loss of ovarian activity and ovarian function decline as a result of iatrogenic interventions.

The definition in common use, applied by most authors when establishing a diagnosis of POI, is at least 4 months of amenorrhea in association with a menopausal level of serum follicle-stimulating hormone (FSH) concentrations on two occasions (4 weeks apart) [66]. However, a duration of amenorrhea ranging from 3 to 6 months and various levels of FSH ranging from 10 to 40 IU/L have been used by different authors in the diagnosis of POI (reviewed in [67]).

The European Menopause and Andropause Society (EMAS) since 2010 uses the former term, premature ovarian failure (POF), and defines the condition as menopause before the age of 40, confirmed with an elevated FSH >40 IU/L and an estradiol level below 50 pmol/L (Table 3.1) [68].

The European Society of Human Reproduction and Embryology (ESHRE) proposed in 2016 guidelines on the management of women with POI (Table 3.1) [2]. The guideline development group agreed that the term "premature ovarian insufficiency" should be used to describe this condition in research and clinical practice. The authors define POI as a clinical syndrome with a loss of ovarian activity before the age of 40 years, which is characterized by menstrual disturbance (amenorrhea or oligomenorrhea) with raised gonadotropins and low estradiol. The following diagnostic criteria were proposed: (1) oligo/amenorrhea for at least 4 months, and (2) an elevated FSH level >25 IU/L on two occasions >4 weeks apart. Due to the

Table 3.1 Diagnostic criteria of premature ovarian failure/insufficiency

	EMAS	ESHRE
Nomenclature	Premature ovarian failure (POF)	Premature ovarian insufficiency (POI)
Definition	Menopause before the age of 40	Loss of ovarian activity before the age of 40 years, characterized by menstrual disturbance (amenorrhea or oligomenorrhea) with raised gonadotrophins and low estradiol
Diagnosis	Elevated FSH >40 IU/L and an estradiol level below 50 pmol/L	Oligo/amenorrhea for at least 4 months and elevated FSH >25 UI/L on two occasions >4 weeks apart

EMAS European Menopause and Andropause Society; *ESHRE* European Society of Human Reproduction and Embryology [2, 68]

unpredictable and intermittent ovarian function in POI patients, the diagnosis should be made on the basis of 4 months of disordered menses (oligomenorrhea or amenorrhea) in association with high FSH levels. This approach will allow to include a larger population of patients in the group of women experiencing POI and help to avoid delayed diagnosis. This may be of paramount importance as POI is potentially associated with reduced life expectancy and accelerated health risks such as cardiovascular and neurodegenerative disorders and osteoporosis [69].

Adding to the complexity of the picture, there are conditions that represent milder forms of premature ovarian senescence, termed as premature ovarian ageing (POA), also called occult primary ovarian insufficiency (OPOI), or early menopause, covering a group of women, who before 45 years prematurely enter menopause [70]. It is estimated that 88% of women experience menopause over 45 years of age, and 9.7% before 45 years [62].

Moreover, advanced infertility treatments identified subgroups of patients with a diminished ovarian reserve (DOR) or patients with poor ovarian response (POR). There is considerable heterogeneity in the definition of DOR, including patients under the age of 40 years with regular menses and different levels of mildly elevated FSH levels (7–15 IU/L) and diminished antimüllerian hormone (AMH) levels (<0.5–1.1 mg/mL) [66]. In women before 40 years with regular cycles but with FSH concentrations greater than 12–15 IU/L, the ovaries are unlikely to respond to the stimulating agents [4]. To define poor ovarian response, at least two of the following three features must be present: (1) advanced maternal age (≥40 years) or any other risk factor for POR (i.e., Turner syndrome, *FMRI* premutations, pelvic infection with chlamydia, chemotherapy, or endometriosis); (2) a previous POR (≤3 oocytes with a conventional stimulation protocol); and (3) an abnormal ovarian reserve test (i.e., AFC <5–7 follicles or AMH <0.5–1.1 ng/mL) [71]. The definition of POR covers not only those women older than 40 years that presented a poor response during ovarian stimulation undergoing infertility treatment, but also the POI patients with an expected poor ovarian response.

3.4.2 Clinical Presentation

In patients with spontaneous POI, amenorrhea or oligomenorrhea may be accompanied by vasomotor symptoms (hot flushes and night sweats), dyspareunia related to vaginal dryness, lack of libido, sleep disturbance, and arthralgia. Symptoms of estrogen deficiency develop in many, but not all, patients. In women experiencing menopause induced by surgery or cancer treatment, the symptoms of estrogen deficiency are often more severe and longer lasting [72].

Postpubertal patients usually have established regular menstrual cycles prior to the onset of POI. Therefore, most frequently, they present with secondary amenorrhea. However, about 24–50% of women with POI have intermittent and unpredictable menses, rather than complete amenorrhea [62, 73].

Ferrarini et al. [62] studied a cohort of 50 POI patients without detectable iatrogenic causes of their condition. The mean age of the onset of POI in this group was 29 years. The majority of them presented normal puberty and secondary

amenorrhea (94%), and only 6% normal pubertal development with primary amenorrhea. Among the studied patients 15% had a family history of POI. Bidet et al. [73] described 358 patients with non-iatrogenic POI. The mean age at diagnosis was 26.6 years. Most of the patients (78.5%) presented secondary amenorrhea and only 21.5% primary amenorrhea.

Premature ovarian insufficiency before the age of 20 years is extremely rare. Among these young women, Turner syndrome and gonadal dysgenesis are the best known causes of early POI.

Cameron et al. [74] reviewed a cohort of adolescent patients with non-chromosomal, non-iatrogenic POI that most commonly presented primary amenorrhea (58.8%), less frequently secondary amenorrhea (23.5%), and oligomenorrhea (17.6%). Some of the patients (13.3%) were investigated due to delayed puberty.

Massin et al. [75] analyzed 63 patients with a normal karyotype and early (before the age of 20 years) onset of POI. Only 16% of the patients presented a familial history of POI. Among the studied patients 23 were presented due to lack of pubertal development, 18 with primary amenorrhea with interrupted puberty, and 22 with secondary amenorrhea with normal puberty [75].

3.4.3 Personal and Family History

Patient's detailed personal and family history can reveal some risk factors for POI. Surgery and chemo/radiotherapy are becoming increasingly common as causes of iatrogenic POI. There is strong evidence that alkylating agents and radiotherapy to which the ovaries were potentially exposed increase the risk for developing POI. There are anecdotal reports of infections such as tuberculosis, mumps, malaria, varicella, or shigella followed by POI [67]. Chronic medical illnesses such as diabetes mellitus or celiac disease are also associated with POI. Patients should be queried about autoimmune disorders such as hypothyroidism, adrenal insufficiency, and hypoparathyroidism that may relate to an autoimmune polyglandular syndrome. The incidence of cases of POI, early menopause, mental retardation, and autoimmune dysfunction in the family history is important, as the heritability of the age of menopause has been estimated at 30–85%, and about 15–30% of cases of POI are considered to be familial [62, 72].

3.4.4 Physical Examination

Clinical features of absent, interrupted, or normal pubertal development should be observed. The signs of androgen excess or the presence of galactorrhea suggest other potential causes of secondary amenorrhea. Physical examination may reveal evidence of associated disorders such as hyperpigmentation, vitiligo, or thyroid enlargement, suggesting autoimmunological involvement. Moreover, stigmata such as short stature, webbed neck, cubitus valgus, low posterior hair line, or high-arched

Table 3.2 Clinical features of Turner syndrome

Turner syndrome
Short stature
Peripheral lymphedema
Nail dysplasia
Webbed neck
Low posterior hairline
Low-set posteriorly rotated ears
Bushy eyebrows
Shield chest
Widely spaced nipples
Cardiovascular defects
Renal anomalies
Primary ovarian failure
Delayed puberty
Infertility
Strabismus, ptosis
Recurrent otitis media
Multiple nevi
Hypothyroidism
Skeletal abnormalities
Metacarpal shortening
Madelung deformity (wrist)
Knee abnormalities
Skoliosis
Micrognathia
Cubitus valgus
High-arched palate

palate may suggest Turner syndrome (Table 3.2). The height of the patients should be measured and their body mass index calculated as a part of their general examination.

3.4.5 Initial Laboratory Assessment

The initial laboratory assessment should confirm the POI diagnosis and exclude other common causes of oligo/amenorrhea such as pregnancy, hypothyroidism, hyperprolactinemia, polycystic ovary syndrome, and lifestyle habits (excessive exercise, poor caloric intake, emotional stress). Therefore, appropriate tests should include follicle-stimulating hormone, luteinizing hormone, estradiol, pregnancy test, thyroid hormones, prolactin, androgen, and cortisol levels (Table 3.3). In cases of hypothalamic amenorrhea (due to eating disorders, excessive stress or exercise) the serum FSH and LH levels are in the low range. If the serum levels of FSH are in the menopausal range, the test should be repeated in 1 month's time.

The progesterone challenge may be misleading as half of the women will respond, despite the presence of menopausal level gonadotropins, and this may lead to a delay in diagnosis [67]. Therefore, a progestin-withdrawal test is not recommended in the diagnosis of POI.

Table 3.3 Investigations recommended in POI patients

	EMAS	ESHRE
Initial investigation	Endocrine screen to diagnose other causes of oligo/amenorrhea: FSH, LH, PRL, estradiol, progesterone, testosterone, thyroid function tests	
Genetic testing	Chromosome abnormalities, especially in women younger than 30 years	Chromosomal analysis in all women with non-iatrogenic POI
		Gonadectomy recommended for all women with detectable Y chromosomal material
		Fragile-X premutation testing is indicated in POI women (the implications should be discussed before the test)
		Autosomal genetic testing is not at present indicated unless there is evidence suggesting a specific mutation
Further assessment	Coexisting diseases must be detected: hypothyroidism, diabetes mellitus, autoimmune screen for polyendocrinopathy, BMD by DXA (optional), ACTH stimulation test if Addison's disease is suspected (optional)	Screening for 21 OH-Ab/ ACA (if positive refer to endocrinologist)
		Screening for thyroid (TPO-Ab) antibodies (if positive measure TSH every year)
		Insufficient evidence to recommend routine screening of POI women for diabetes
		There is no indication for infection screening
		Measurement of BMD at initial diagnosis of POI should be considered
Ovarian biopsy	The diagnostic usefulness of ovarian biopsy outside the context of a research setting is unproven	

EMAS European Menopause and Andropause Society, *ESHRE* European Society of Human Reproduction and Embryology, *FSH* follicle-stimulating hormone, *LH* luteinizing hormone, *PRL* prolactin, *BMD* bone mineral density, *DXA* dual-energy X-ray absorptiometry, *ACTH* adrenocorticotropic hormone, *21-OH-Ab* 21-hydroxylase autoantibodies, *ACA* adrenal cortex antibodies, *TPO-Ab* antiperoxidase antibodies, *TSH* thyroid-stimulating hormone [2, 68]

3.4.6 Further Investigation

The etiology of POI is highly heterogeneous. It may be the consequence of iatrogenic factors such as surgery, chemotherapy, or radiotherapy. Other causes include genetic and autoimmune components. In 90% of the cases of non-iatrogenic primary ovarian insufficiency, the cause remains unknown [62].

3.4.6.1 Genetic

The association between the menopausal age between sisters or mothers and daughters suggests that genetic factors play a role in the reproductive ageing process. Almost half of the cases of primary amenorrhea may be associated with genetic causes, whereas in women with secondary amenorrhea as a sign of POI about 13% of patients will have some genetic defects [76]. The genetic background of POI is described above.

3.4.6.2 Autoimmune

Autoimmune mechanisms are involved in the pathogenesis of 4–30% of POI cases. There is a lack of specific and sensitive tests to detect autoimmune pathogenesis of POI.

Anti-ovarian Antibodies

Several autoantibodies such as antibodies to steroid-producing cells (StCA), antibodies to gonadotropins and their receptors, granulosa cells, zona pellucida, oocyte, and corpus luteum as well as anticardiolipin and antinuclear antibodies have been proposed as the markers of ovarian autoimmunity [77]. The prevalence of anti-ovarian antibodies in POI women varies greatly, ranging from 3 to 66.6% [77]. Moreover, these antibodies are frequently found in significant amounts in control groups. Therefore, the clinical diagnosis of autoimmune POI should not be based on the presence of anti-ovarian antibodies.

Lymphocytic Oophoritis

Although the diagnostic usefulness of ovarian biopsy is unproven and therefore is not routinely performed, there is some insight into histological evidences of autoimmune ovarian involvement gathered by clinical research. In the cases of coexisting POI and adrenal autoimmunity, histological examination almost always shows characteristic signs of an autoimmune oophoritis: infiltration of follicles by T-lymphocytes, macrophages, and natural killer cells [78]. In the whole population of nongenetic, non-iatrogenic POI patients, only 9.1–11% of the ovarian tissue samples show the histopathological evidence of autoimmune ovarian involvement [77].

Association with Other Autoimmune Disorders

The strongest evidence of autoimmune mechanisms involvement in the pathology of POI comes from the high incidence of the coexistence of POI with other autoimmune disorders. It is estimated that around 10–55% of patients with POI have associated autoimmune diseases. Hypothyroidism is the most common autoimmune disorder associated with POI (25–60%) [77]. The coincidence with diabetes mellitus is 2.5% [77]. The most dangerous autoimmune condition that might occur in women with POI more frequently than in controls is Addison's disease (2–10%). ESHRE guidelines include screening for antiperoxidase antibodies (TPO-Ab) and for 21-hydroxylase autoantibodies (or alternatively adrenocortical antibodies) in women with POI of unknown cause or if an immune disorder is suspected. If the tests are positive for adrenal antibodies, the patient should be referred to an

endocrinologist for testing of adrenal function to rule out Addison's disease. In patients with a positive TPO-Ab test, the thyroid-stimulating hormone (TSH) should be measured every year [2].

Autoimmune disorders often gather into constellations grouped and named as autoimmune polyglandular syndromes. Autoimmune polyglandular syndromes (APS) comprise APS-1 (primary adrenal insufficiency, mucocutaneous candidiasis, and hypoparathyroidism) and APS-2 (primary adrenal insufficiency with autoimmune thyroid disease and/or diabetes mellitus type 1). Autoimmune polyglandular syndrome type 3 (APS-3) is defined as the coexistence of autoimmune thyroiditis with other autoimmune diseases without primary adrenal insufficiency. The fourth type of APS (APS-4) includes autoimmune adrenal insufficiency with other autoimmune disorders but does not fulfill the criteria of APS-1 and APS-2.

Reato et al. [79] found that the prevalence of POI in patients with different types of APS varied: the highest prevalence was in patients with APS-1 (>40%), lower in patients with APS-4 (30%), and the lowest in APS-2 (16%). POI in APS-1 and APS-4 usually developed after Addison's disease was diagnosed, whereas POI preceded Addison's disease in patients with APS-2. Moreover, the results indicated a strong relationship between POI and autoantibodies to steroid-producing cells (StCA) [79].

Around one-third of patients with APS-3 develop POI [62, 80]. Autoimmune thyroiditis, is the most frequent presentation of autoimmunity in this group [62]. Premature ovarian insufficiency may also be associated with dry-eye syndrome, myasthenia gravis, rheumatoid arthritis, and systemic lupus erythematosus [62].

In young patients with POI, the incidence of autoimmune comorbidities might be lower. Massin et al. [75] assessed a group of POI patients diagnosed before 20 years of age. Less than 10% of patients were found positive for antithyroid antibodies. Neither ovarian nor adrenal antibodies were found.

Concluding, for many women with POI, autoimmunity may be the pathogenic mechanism of ovarian function decline. Moreover, POI patients are at high risk of other coexisting autoimmune diseases, of which hypothyroidism is the most frequent, and adrenal insufficiency the most dangerous. Therefore, women with POI should be screened for autoimmune polyendocrinopathy. At least antithyroid and antiadrenal antibodies should be tested. Apart from research settings, there are no recommendations for the assessment of ovarian antibodies nor ovarian biopsy.

3.4.7 Risk Assessment for Premature Ovarian Senescence

Premature ovarian senescence frequently progresses undiagnosed until becoming clinically symptomatic in outright premature ovarian failure. Risk factors for POI are generally known (Table 3.4). However, the statistical weight of individual predictive risk factors remains to be determined.

The risk of POI among young cancer survivors is increased and reaches approximately 8% by 40 years [81]. Compelling evidence suggests that treatment with

Table 3.4 Risk factors for premature ovarian insufficiency (POI)

Risk factors for POI	
Genetic	Turner syndrome
	FMR1 mutations and premutations
	AIRE gene
	Other genetic causes
Iatrogenic	Ovarian surgery
	Chemotherapy
	Radiotherapy
Autoimmunity	Thyroid autoimmunity
	Adrenal autoimmunity
	Autoimmune polyglandular syndromes
	Other autoimmunity
Familial	POI or early menopause in mother or sibling
Other	Endometriosis

alkylating agents and/or radiotherapy to which the ovaries are potentially exposed increases the risk of POI development. Other factors such as the age of the patient at treatment, the cumulative chemotherapy and radiotherapy dose, combinations of these modalities, and genetic variation may play a role in individual susceptibility to ovarian failure. Laboratory evaluation with FSH and estradiol has been recommended on the basis of the clinical indication or when the patient desires assessment of potential future fertility [81].

3.4.7.1 Pelvic Ultrasonography and Ovarian Biopsy

Metha et al. [81] detected that the ovary could be identified unilaterally or bilaterally in 84% of POI patients, and follicles were observed in 41% of patients. Knauff et al. [82] in a nationwide prospective cohort study in the Netherlands conducted pelvic ultrasonography on 68 patients with normal menses and elevated FSH (incipient ovarian failure—IOF), in 79 with cycle disturbances and elevated FSH (transitional ovarian failure—TOF), and in 112 patients with amenorrhea for 4 months and FSH exceeding 40 IU/l (POI). The ovaries were not visible on ultrasound in 19% of patients with IOF, in 29% of patients with TOF, and in 33% of patients with POI. The antral follicle count (AFC) was defined as the total number of visible follicles with a diameter between 2 and 10 mm. An AFC lower than five follicles was found in 92% of patients with IOF, in 79% women with TOF, and in 81% of POI patients, compared with 29% in controls [83]. The ability to distinguish between various AFC subgroups decreased significantly with increasing age. No follicles were observed in 10% of IOF, in 26.6% of TOF, and in 33% of POI patients.

Massin et al. [83] performed pelvic ultrasonography on 61 patients with nongenetic POI. They calculated the surface area of the ovaries and the presence of follicles of ≥2 mm. Only 22 patients (36%) had a normal surface area (≥2 cm^2), and follicles were observed in 32 patients. The parameters observed on ultrasonography did not correlate with the presence of follicles observed in the histology [83].

Ovarian biopsy has been used to differentiate the POI patients with some follicles within the ovary from those depleted of ovaries [83, 84]. Abe et al. [84] conducted minilaparoscopy and ovarian biopsy on 47 POI patients in which transvaginal

ultrasonography failed to identify the ovary. They found follicles in the histology in 21% of the studied patients.

However, the usefulness of ovarian biopsy has been questioned due to its invasive nature and the concern of postoperative adhesion, impairing the already reduced fertility in POI patients. There is a risk that the sparse follicles may be further reduced as a result of the ovarian biopsy. Moreover, there is concern over whether the minute biopsy tissue is adequate to evaluate the presence or absence of follicles in the whole ovary (reviewed in [85]). Therefore, EMAS states that the diagnostic usefulness of ovarian biopsy outside the context of a research setting is unproven [68].

3.4.7.2 AMH and Inhibin B

There are two glycoproteins of the superfamily of transforming growth factors β (TGF- β), inhibin B and antimüllerian hormone (AMH), reflecting the ovarian reserve. In normal ovulatory cycles, the serum concentration of inhibin B is inversely correlated with FSH levels, reaching maximum levels in the middle of the follicular phase of the cycle. The use of the inhibin B as a marker of ovarian reserve has been demonstrated to correlate with the antral follicular count (AFC), normal response to the test of stimulation with clomiphene citrate, and a number of oocytes obtained in in vitro fertilization programs (reviewed in [86]). However, some authors consider inhibin B more as a marker of ovarian activity rather than the ovarian reserve [82]. Inhibin B has a direct relationship with the number of granulosa cells in growing small antral follicles. Compared to inhibin B, AMH is relatively stable throughout the menstrual cycle. AMH represents the follicular number and ovarian age. The total ovarian reserve is made up of still unrecruited primordial follicles and a smaller number of small growing follicles. AMH represents this latter pool of small growing follicles. In the perimenopausal age, AMH levels decline earlier than the FHS. Gleicher et al. [87] proposed a screening paradigm for patients with POI risk factors and subsequent sequential AMH levels deviating from ageing curves. Identification of high-risk females at very young ages would give the opportunity to change their pregnancy timing or pursue fertility preservation. The sensitivity of AMH in the diagnosis of POI is more than that of FSH, but both tests have almost equal specificity [88].

Knauff et al. [82] described the direct ovarian reserve markers AMH, inhibin B, and AFC in young women presenting various degrees of hypergonadotropic ovarian failure. They found that AMH in POI patients is consequently below the menopausal threshold and in the vast majority of cases even undetectable, despite fluctuations in FSH levels and incidental vaginal bleedings. Moreover, their data also suggest that AMH is more consistent than inhibin B or AFC as a measure to assess the extent of the follicle pool in young hypergonadotropic patients.

Inhibin B along with FSH and estradiol at the time of POI diagnosis appeared to be predictive of a resumption of ovarian activity [73]. However, AMH levels are not predictive of a resumption of ovarian activity in POI patients, neither for the arrest following the resumption of the ovarian function [73, 89]. Therefore, Bidet et al. [73] concluded that AMH appears to be an excellent quantitative, but not good

qualitative marker of ovarian reserve, and seems to be more a marker than a predictor of ovarian function. Similarly, AMH and Inhibin B are not good predictors of graft function or the probability of achieving pregnancy after the retransplantation of cryopreserved ovarian tissue.

There are several studies determining AMH levels in the specific subgroups of patients. Saglam et al. [90] showed that women with autoimmune thyroiditis have lower AMH levels compared with age-matched controls, and concluded that data from the study added support to the hypothesis that women with autoimmune thyroiditis have prematurely ageing ovaries.

The prognostic and predictive value of AFC and AMH for the diagnosis after childhood cancer has not been established. However, AMH may be of additive value in conjunction with FSH and estradiol for the identification of POI in at-risk survivors aged >25 years [82].

3.5 Long-Term Consequences and Follow-Up

3.5.1 Bone Health

The effect of POI-associated estrogen deficiency on bone is the most clearly established adverse consequence of the POI condition, even though hypoestrogenism can be asymptomatic in the aspect of bones for many years in most women, until fracture occurs. Low bone mineral density (BMD), usually assessed by dual-energy X-ray absorptiometry (DEXA), is a risk factor for fracture and widely used as a surrogate in assessing fracture risk and treatment effects. However, fracture itself is often the primary outcome of interventional trials.

DEXA can identify osteoporosis, defined as bone mineral density more than 2.5 standard deviations below peak BMD for the appropriate reference group (i.e., young women from the same population) and with the *T*-score used to show the difference in number of standard deviations. Osteoporosis is therefore a *T*-score of ≤ -2.5, with osteopenia defined by a *T*-score ≤ -1 and > -2.5. *Z*-scores are also frequently reported and express the number of standard deviations a patient's BMD differs from the average BMD of an age- and sex-matched control group [91].

The prevalence of osteoporosis in POI appears to be in the range of 8–14% [92].

Women with POI have a reduced BMD, and this has been associated with the presence, degree, and duration of estrogen deficiency. Reduced BMD in POI has been established in many studies investigating women with POI of different etiologies, compared to reference populations.

The beneficial effects of estrogen on bone have been recognized, and likewise the adverse effect of natural menopause on bone loss, mineral density, and fracture risk [93]. Estrogen deficiency results in increased bone remodelling. Increased osteoclast activity results in increased bone resorption, and that in turn induces an increase in osteoblast activity and bone formation, but with resorption exceeding formation. The rapid remodelling of estrogen deficiency means the loss of BMD,

amounting to 2–3% per year early on after menopause. Additionally, the slow mineralization of new bone (over at least 6 months) causes new bone to be less mineralized than older bone. The effects on bone resorption are mediated by increased activity of the nuclear factor kappa-B ligand (RANKL) on RANK receptors on osteoclasts and their precursors. Bone resorption is also mediated by an increase in pro-inflammatory cytokines such as interleukin 1 beta and tumor necrosis factor, also leading to an increased bone resorption. The increased bone remodelling is reversible in the short term, but with time, the high osteoclast activity results in the perforation of the cancellous bone plates so that there is a loss of the bone's microarchitecture. This form of bone loss is irreversible, and primarily affects trabecular rather than cortical bone. However, the rate of bone loss after the menopause slows after approximately 10 years [94].

The postmenopausal period, characterized by estrogen deficiency and its impact on bones, has been clearly established (North American Menopause Society).

The consequence of a too early emerging shortage of estrogen is mainly the reduction of bone mineral density (osteopenia, osteoporosis).

Even in young women with POI osteoporosis may occur, hence the need for prescribing densitometry in such patients. Women with POI have a higher risk of bone fracture than women with osteoporosis also due to other causes (hyperthyroidism, steroids, hyperparathyroidism).

Albright publications are the first to demonstrate the relationship between estrogen deficiency, menopause, and an increased incidence of fractures in women [95].

Women with POI are characterized by decreased bone density in comparison to women who regularly menstruate. Compared to Caucasians, women from minorities with estrogen deficiency are more likely to have a BMD below the expected range for their age. Racial variance seems to be associated with a combined effect of several variable risk factors. Any delay in making a POI diagnosis also contributes to reduced bone density by delaying proper therapy.

There is also the relation between the follicle-stimulating hormone (FSH) and estradiol levels with bone mineral density. It is said that serum FSH concentrations, but not estradiol, are positively associated with bone mass loss in skeletal regions (both in the lumbar spinal column and femoral neck) in patients with spontaneous POI [96]. The lumbar part of the spine was the most affected by the BMD decrease. Hormone replacement therapy should be substituted early and consistently among POI women [97].

Long-term physiological transdermal estradiol replacement therapy with oral medroxyprogesterone acetate restores the mean BMD in the femoral neck in women with POI. However, the addition of physiological transdermal testosterone replacement therapy did not provide additional benefits [98].

Age, reproductive age, and BMI are factors associated with the BMD of the lumbar spine. Women with the diagnosis of POI need early investigation and treatment to prevent bone loss and to minimize fracture risk in the future [99].

The fracture risk in women with POI has also been discussed. Premature menopause is associated with a higher risk of fractures during a patient's lifetime. Women with premature menopause have relatively higher risks for fracture, especially

vertebral fracture, of approximately 1.5. POI is thought to be an important predictor of fractures [100].

3.5.2 Cardiovascular Disease

The main reason for shortened life expectancy in POI patients is cardiovascular disease; therefore some studies have addressed the issue of cardiovascular risk in this group of women. To date it has been shown that POI women present several risk factors for the development of cardiovascular disease: endothelial dysfunction, autonomic dysfunction, metabolic disturbances, and increased inflammatory factors.

Endothelial function measured as the flow-mediated dilation of the brachial artery has been shown to be significantly reduced in POI women. Similarly the number of circulating endothelial progenitor cells is decreased and correlated with a decreased serum estradiol concentration [101, 102]. The POI women show an increased carotid intima media thickness and left ventricular diastolic function [102]. Interestingly hormonal therapy of 6 months' duration is able to improve the flow-mediated dilation by 2.4-fold, to the same levels as in healthy controls [102]. Goldemeier et al. [103] also showed normal endothelial dependent vasodilation in POI women under hormonal therapy. Despite this, in the same study the authors also showed an impaired baroreflex sensitivity and reduced heart rate variability of POI women ($N = 17$) in comparison to healthy controls [104].

POI patients present metabolic abnormalities, including an increased incidence of dyslipidemia, insulin resistance, and elevated amounts of abdominal fat [105]. Regarding the lipid profile, the results are conflicting regarding particular lipoproteins. As Knauff et al. [104] reported, POI women show significantly higher TG levels and lower HDL cholesterol levels in comparison to controls after correction for age, body mass index, and smoking. This difference has not been confirmed in a smaller study by Gulhan et al. [106]. This group revealed significantly higher TC and LDL levels in POI patients and a significant negative correlation between E2 and TC levels. Recently Ates et al. [107] reported increased TC and HDL cholesterol in POI women. The analyzed population presented similar levels of glucose, insulin, HOMA-IR, low-density lipoprotein cholesterol (LDL-C), and triglyceride as the controls, but the incidence of metabolic syndrome was significantly increased. On the contrary, other authors detected increased serum glucose, insulin, and homeostasis model of assessment-insulin resistance (HOMA-IR) in POI women [108]. Other reported risk factors found in POI women were increased C-reactive protein, hypertension, and impaired kidney function [105].

Even though there are conflicting data regarding the lipid profile and insulin resistance indices, the overall cardiovascular risk in POI women seems to be significantly increased [109]. In recently published meta-analyses, the risk of ischemic heart disease was reported to be increased by 1.5 times in POI women in comparison to women who had undergone menopause after 40 years of age [110]. On the other hand, in comparison to other classical risk factors for cardiovascular disease, POI can be considered as a modest risk factor for ischemic disease [111].

3.5.3 Psychological Aspects

The psychosocial aspects of POI are most often ignored in the context of the diagnosis.

POI is not a homogenous and fixed state. Distinct aspects of POI such as the absence or presence of vasomotor symptoms, as well as current treatment (e.g., fertility treatment), may have an impact upon a different quality-of-life domains in distinctive ways. These effects may be mitigated by a number of variables, such as the absence or presence of a stable and satisfying relationship and/or children, and pre-POI mental health. Importantly, social and economic status is associated with the access to social privileges and can powerfully influence the quality-of-life domains, so that the confounding effects of education, occupation, and income may need to be controlled for.

The decrease in mood of women who suffer from/have POI can be caused not only by concerns about their own health, but also by reproductive problems that occur in younger women who want to have children. Being diagnosed with POI can be an unexpected and upsetting diagnosis. Women with POI experience significant psychological disturbances, such as high levels of depression and low levels of self-esteem, with negative effects on sexuality [112]. The diagnosis of POI can be an extremely devastating life experience and patients often express anger, depression, anxiety, loss, and sadness. Women after being informed of a POI diagnosis can be shocked and confused. These words describe their emotional trauma. Some women with POI feel various emotions and caregivers should propose support regarding unstable patient's self-image, neurocognitive decline, or sexual dysfunction.

Long-term medical conditions like POI are associated with a higher prevalence of psychological and mental health difficulties. Also, poorer psychosocial adjustment is seen in POI patients [113]. Poorer mental health is known to detrimentally affect the capacity to self-manage health maintenance regimes and lifestyle changes leading to worsened health outcome and higher usage of healthcare services.

In women with POI there is a higher prevalence of psychological distress. POI is said to be associated with an increased lifetime risk for major depression [114].

High levels of depression and perceived stress and lower levels of self-esteem and life satisfaction are observed in women with the diagnosis of POI [115]. Moreover, the onset of depression frequently occurs after signs of altered ovarian function but before the diagnosis of POI. More attention should be paid to the presence of depression in POI.

3.5.4 Mortality

Overall mortality is increased in women with POI. According to data from a cohort of 19,731 women from Norway menopause before 40 years old was linked to a significantly increased mortality rate of 1.06 in comparison to women who had menopause at age 50–52 [116]. Also early menopause has been shown to reduce overall life expectancy. Data from a prospective cohort study of 68,154 US adult

women showed that all-cause mortality rates were higher among women who reported that their menopause had occurred at age 40–44 years compared with women who reported that their menopause had occurred at age 50–54 years (rate ratio (RR) = 1.04, 95% confidence interval (CI): 1.00, 1.08) [117].

The increased risk of all-cause mortality is mainly dependent on higher mortality rates from coronary heart disease, respiratory disease, genitourinary disease, and external causes [105, 109].

3.6 Management

Premature ovarian insufficiency results in lifelong steroid deficiency. It is also potentially associated with accelerated health risks such as cardiovascular problems, cognitive disorders, and osteoporosis. Moreover, the patients experience high psychological distress. Therefore, in dealing with the physical and emotional needs of POI patients, a multidisciplinary approach including an endocrinologist, fertility specialist, oncologist, osteoporosis specialist, cardiologist, psychologist, dietician, and patient support groups is crucial. General lifestyle modifications and dietary measures are recommended to reduce the cardiovascular and osteoporosis risk. Adequate dietary intake of calcium and vitamin D, as well as the avoidance of smoking, and maintenance of normal body weight involving weight-bearing exercises are recommended [2].

3.6.1 Hormonal Therapy

3.6.1.1 Hormonal Supplementation in Postpubertal POI Patients

Early initiated estrogen replacement is recommended in POI women to treat menopausal symptoms, maintain bone health, and prevent osteoporosis and control the future risk of cardiovascular disease [2]. The treatment should be continued at least until the average age of the natural menopause.

There is no agreed consensus on the optimum estrogen and progesterone replacement regimens in women with POI. Currently, combined hormone replacement therapy (HRT) is commonly prescribed. According to ESHRE recommendations, 17-β estradiol is preferred to ethinylestradiol or conjugated equine estrogens for estrogen replacement [2]. Transdermal application of estrogen has the theoretical advantage of delivering bioidentical estradiol directly into the systemic circulation, lowering risk of thromboembolism, and preserving sexual function by minimizing an impact on SHBG [67, 72]. There is no consensus on optimal estrogen doses in women with POI. It has been suggested that a transdermal administration of around 100 μg of estradiol results in serum levels equivalent to premenopausal mid-follicular concentrations [62]. Cyclical progestogen should be administered in combination with estrogen therapy to protect the endometrium and to induce the monthly withdrawal bleed. Many young women prefer a cyclical regimen of hormonal treatment with regular monthly bleeding restoring a semblance of normality; however, a

no-bleed regimen can also be adopted in some patients. There might be some metabolic and endometrial advantages associated with vaginal micronized progesterone [62, 118]. However, the strongest evidence of endometrial protection is for the oral cyclical combined treatment [2].

POI is associated with a decrease in bone mineral density, although the increased risk of fracture has not been clearly demonstrated [2]. The beneficial effects of estrogen on bone metabolism result from a reduction of osteoclastic and an enhancement of osteoblastic activity as well as an increase in calcium intestinal absorption and calcium renal reabsorption [119]. A randomized controlled trial demonstrated that transdermal estradiol at the dose of 100 μg in a regimen with oral medroxyprogesterone acetate restored bone density in 145 women with POI to that of healthy controls over 3 years [98].

Women with POI are at an increased risk of cardiovascular diseases [2, 69]. Although there is lack of longitudinal outcome data in POI patients, the potential beneficial effects of estrogen treatment on the cardiovascular system might result from vasodilatation through endothelium and endothelium-independent mechanisms, favorable lipid and lipoprotein profile changes, as well as an advantageous impact on glucose metabolism and fibrinolysis mechanisms (reviewed in [119]).

The oral contraceptive pill (OCP) is an option for patients who do not desire pregnancy. Combined menopausal or bioidentical hormonal therapy is considered to be more physiological as it contains natural estrogen, whereas OCPs contain ethinylestradiol, carrying a higher risk of thromboembolism, and higher doses of progestogen. However, many young women dislike the idea of treatment with specimens dedicated to menopausal women. Cartwright et al. [120] assessed the effects of oral HRT, the OCP, and no treatment on bone density and turnover over 2 years in women with spontaneous POI. The HRT group had a significantly increased bone density at the lumbar spine compared with the OCP group. In the no-treatment group there was a decrease in bone density at all sites compared to the HRT and OCP groups. Crofton et al. [121] performed a similar study in POI patients comparing the impact on the skeletal health of transdermal natural estradiol and vaginal micronized progesterone treatment with the oral contraceptive pill over 12 months. The study demonstrated that physiological sex steroid replacement therapy might be more efficient in improving bone health, particularly in the aspect of the lumbar spine's BMD, than OCP. Therefore, women choosing OCP as a form of hormone therapy due to POI should be informed that the effect on bone mineral density might be less favorable.

POI patients complain of worse sexual performance, with more pain and poorer lubrication [122]. Systemic hormonal therapy reestablishes the epithelium cells, vaginal pH, and vaginal microflora; however, it might not be effective enough in decreasing the incidence of dyspareunia [123]. Local estrogen may be required to normalize sexual functioning. Knowledge of the long-term efficacy and safety of testosterone supplementation in improving sexual function is incomplete [2].

There is a strong contrast in the hormonal state of patients experiencing spontaneous POI and women in whom the abrupt absence of ovarian function results from

surgical treatment or chemo/radiotherapy [124]. The menopausal symptoms may be more severe in the latter group. Moreover, in spontaneous POI, the number of follicles is reduced, with a slow fluctuating decrease in estradiol production; but the ovarian stroma still produces some androgens, whereas in iatrogenic POI ovarian steroid production drops sharply. Therefore, patients with iatrogenic POI may require higher doses of hormone replacement therapy [69]. Androgen treatment is only supported by limited data and is not routinely advocated [2].

There is no evidence that estrogen replacement in spontaneous POI increases the risk of breast cancer in comparison with normally menstruating women [125]. Therefore, hormone therapy is recommended until the average age of the natural menopause and there is no need to start mammographic screening early [68].

3.6.1.2 Puberty Induction

Young patients with primary amenorrhea due to ovarian dysgenesis or very strong POI fail to initiate their ovarian function and do not manifest normal puberty. The initiation of hormonal therapy solely with estrogen is usually adopted to achieve pubertal maturation. The treatment prescribed by pediatric endocrinologists and adolescent gynecologists aims to achieve complete secondary sexual characteristics, sufficient uterine development, and adequate bone density, without an adverse effect on adequate growth,

In prepubertal girls with POI, the dose and combination of hormone replacement therapy are adjusted according to the patient's height and the Tanner's stage of development to mimic puberty. The ESHRE recommends puberty induction with 17-β estradiol at the age of 12 years, with a gradual increase over 2–3 years [2]. Cyclical progestogen should be added after at least 2 years of treatment or when breakthrough bleeding occurs [2]. According to these guidelines, oral contraceptive pills are contraindicated for the induction of puberty.

The uterine volume in women with POI might be reduced to 40% of the normal adult range, with poor blood flow and a thin endometrium (reviewed in [126]). Women with primary amenorrhea are at the highest risk of a decreased uterine volume. However, even girls with 5 years of menstrual cycles might not achieve a uterine development comparable with healthy peers [127]. Moreover, the patients exposed to radiation may have a reduced uterine volume, and decreased elasticity. The optimal hormonal treatment regimen to maximize the reproductive potential for young women with POI remains unclear. Most studies that have attempted to evaluate the effect of hormonal treatment on uterine cavity development were carried out in women with Turner syndrome. Better results were achieved in women with the mosaic karyotype, with the earlier age of hormonal treatment commencement, and with natural estrogen regimens (reviewed in [128]). Some studies suggested better results with the transdermal application route of natural estradiol.

Long-lasting estrogen deprivation might have particularly deleterious effect on the skeletal and cardiovascular systems in adolescents experiencing POI. The impact of estrogen deficiency on bone health is clearly related to the onset of ovarian impairment [127]. Papagianni et al. [119] investigated the impact of hormone treatment on several endocrinological, metabolic, and bone parameters in young

women with POI. The study group consisted of 40 women aged 14–20 years, including 12 subjects with Turner syndrome, 19 with Swyer syndrome, and nine with very premature spontaneous ovarian insufficiency. The patients were treated for 2 years with conjugated estrogens on an oral daily dose of 0.625 mg and a daily oral dose of 5 mg medroxyprogesterone on days 17–28 of an artificial cycle. Hormonal treatment resulted in adequate and stable serum estrogen levels in all patients. A significant favorable effect on HDL was noted from the first year of treatment and onwards in patients with Turner syndrome and with Swyer syndrome, but not in patients with nongenetic POI. The impact on bone density was beneficial. All patients with osteopenia recovered their *z*-scores after 1 year of treatment, and a significant gradual increase in bone density was noted during the second year of treatment.

3.6.1.3 Nonhormonal Therapies

The mainstay of POI therapy consists of different forms of HRT. Women who decline hormonal therapy or in whom it is contraindicated might benefit from nonhormonal treatment with selective serotonin reuptake inhibitors and norepinephrine reuptake inhibitors, or gabapentin, to control vasomotor symptoms [2]. Such treatment, however, will have no benefit on the future risk of osteoporosis and cardiovascular diseases.

There is no evidence for the use of complementary or herbal preparations in POI patients.

Estrogen replacement is recommended to maintain bone health. If it is contraindicated or insufficient, other therapies may be considered. Bisphosphonates are not recommended in women who wish to achieve pregnancy [2].

3.6.2 The Management of Patients with Turner Syndrome

Turner syndrome affects approximately 1 in 2000–2500 newborn females. The syndrome is caused by X chromosome absence, structural abnormalities, or mosaicism, and is characterized by an increased risk of primary or secondary POI due to the accelerated loss of germ cells before or after puberty. The specific karyotype can to some degree predict the potential ovarian function in Turner syndrome patients. Monosomic patients (45,X) usually are born with streak gonads, whereas those with 45,X/46,XX mosaicism have the best chance of spontaneous puberty and fertility [129]. Lunding et al. [129] showed that AMH is a predictor for spontaneous puberty in prepubertal Turner syndrome girls, and imminent POI in adolescents and adult Turner syndrome patients.

The patients with Turner syndrome need multidisciplinary team care because of their short stature, typical renal anomalies, heart defects, hearing problems, hypothyroidism, delayed puberty, and menstruation. Among the cardiovascular defects in Turner syndrome, the left-sided anomalies are the most common (coarctation of the aorta, bicuspid aortic vessel, and aortic atresia).

The ESHRE gives specific recommendations for the management of women with Turner syndrome [2]:

1. A diagnostic workup for POI which includes karyotyping for the diagnosis of Turner syndrome.
2. If the test from peripheral blood lymphocytes is negative, a second analysis of the karyotype in epithelial cells is recommended in case of high clinical suspicion.
3. Women with Turner syndrome should be assessed by a cardiologist with expertise in congenital heart disease.
4. Cardiovascular risk factors such as blood pressure, smoking, weight, lipid profile, fasting plasma glucose, and HbA1c should be monitored annually.
5. Girls and women with POI due to Turner syndrome should be offered HRT throughout the normal reproductive life span.
6. Pregnancies in women with Turner syndrome are at very high risk of obstetric and non-obstetric complications and should be managed in an appropriate obstetric unit with a cardiologist's involvement.

3.6.3 Surveillance of Cancer Survivors

Recommendations for POI surveillance for female survivors of childhood, adolescent, and young adult cancer published in 2016 by the International Late Effect of Childhood Cancer Guideline Harmonization Group in Collaboration with the PanCareSurFup Consortium revised the already existing national guidelines and literature evidence, and identified gaps in the knowledge of and future directions for research [80]. Harmonized recommendations in cancer survivors advice counseling regarding the risk of POI and its implications for future fertility in the patients treated with alkylating agents and radiotherapy. After the treatment, annual monitoring of growth and pubertal development and progression (Tanner's stage) is recommended for prepubertal survivors. For postpubertal survivors a detailed history and physical examination with specific attention to POI symptoms, e.g., amenorrhea or irregular cycles, are recommended. FSH and estradiol are recommended for the evaluation of patients who fail to initiate or progress through puberty, in women with menstrual cycle dysfunction, or who desire assessment about potential future fertility. AMH is not recommended as the primary surveillance modality. However, it may be reasonable to assess AMH in conjunction with FSH and estradiol in patients over 25 years.

Hormonal therapy with estrogen and progestogen is regarded as contraindicated in breast cancer survivors [130]. Adolescent patients experiencing acute ovarian failure after cancer treatment will not go through puberty without estrogen treatment [131]. However, the subsets of childhood cancer survivors, such as those surviving Hodgkin's disease, those with the greater risk of breast cancer, heart disease, and stroke, should receive individualized hormonal therapy implementation [132].

3.6.4 Supportive Management

The physical consequences of diminished ovarian function in women with POI have been studied extensively. However, much less is known about the repercussions of the loss of gonadal function on psychological and social factors in these women. Patients with spontaneous POI experience high level of distress at diagnosis. Nearly all the women described the diagnosis as traumatic, even when reported as having been sensitively handled [133]. Clinicians have to communicate information about a sudden, unexpected diagnosis that is life altering but not life threatening. The way it is delivered has a profound effect on patients' satisfaction, compliance with treatment, quality of life, and other health outcomes [134]. In the research performed in the USA by Groff et al. assessing women's emotional responses to learning the diagnosis of POI, more than 70% were unsatisfied with the manner in which they were informed by their clinician. This is not surprising, considering that only 53% of women were informed in an office setting, and a substantial proportion (43%) was informed by a telephone call, in many cases while at work. Moreover, 75% of the interviewed women reported that the clinician spent 15 min or less speaking about their diagnosis, with over one-third of women recalling spending 5 min or less. The majority of women got the impression that the physician had limited or very limited knowledge of POI [134]. There are several steps that are important when communicating "bad news" to patient. Giving the indication that things are serious before giving the details may be helpful. After getting the physical context right, establishing how much the patient knows and how much she wants to know, as well as responding to the patient's feelings, is helpful in decreasing the patient's distress [135]. The diagnosis and plan for management should take place during an office visit, when sufficient time can be given to discuss the implications of POI [134].

Young women with POI have to deal with psychological distress, the feelings of loss, anger, sadness, anxiety, fear of growing old, and low self-esteem [136]. For many women, the inability to reproduce is a profound loss. These women feel less feminine, sexually unattractive, and unproductive, exacerbating the effect of their loss of fertility [133, 136]. Although no statistical differences were found in the perception of quality of life between the women with POI and those with normal ovarian function, poorer scores were identified in the physical health and psychological domains. Women with POI felt "less healthy" in general. POI patients report the presence of negative feelings (blue moods, despair, anxiety, depression, a feeling that their life is meaningless) with scores three times higher than control groups [136]. Almost half of them requested psychological support.

Women with idiopathic POI tend to report less support and satisfaction in their relationships compared to women with infertility resulting from known causes [136]. Most patients perceive a need for clinicians to spend more time with them and provide more information about POI. Unfortunately, the study assessing POI patients' experience of health services in the UK disclosed that the main source of the information was the Internet. More than two-thirds of women affected by POI commented that insufficient information had been provided by their health

professionals. The results of the study showed that the patients would expect information, understanding, and support at the time of the diagnosis, and regular follow-ups and psychological support later [133]. Women value continuity of care, and seeing the same professional on a regular basis. In these circumstances they are more likely to feel sufficiently comfortable to ask about intimate issues as they arise such as vaginal dryness, lowered libido, or impaired sexual well-being.

Informational and practical support can be provided sufficiently by specialist health professionals, the Internet, family, and friends. Emotional needs, however, are more demanding to address. For many patients, fertility concerns are associated with stigma and silence. Disclosure of the problem tends to be generally restricted to a small number of close friends or the immediate family. Actual fear of rejection by a partner adds to feelings of isolation and distress. Women with POI should be offered individual and group support when dealing with their emotional needs. In the study carried out by Groff et al. only one-third of women reported seeking out professional help in dealing with the emotional and mental health aspects of POI, yet of those who did most (76%) found this to be helpful. Only 20% of women had been involved in a support group, and most who had been found this to be helpful (85%) [134].

The emotional aspects are even more complicated in cancer survivors experiencing POI. Although most cancer patients receive the necessary information from health providers on treatment options and procedures at diagnosis, they often fail to receive support and guidance after acute treatment has been completed [137]. The cancer diagnosis is a shocking experience for many patients; however, the cancer survivors have to face serious psychosocial problems after the treatment too. Compared with postmenopausal women, premenopausal women with cancer may need to consider additional potential side effects of therapy. Receiving information on fertility and reproductive issues is important for younger women diagnosed with cancer. It helps to engage them in decision making concerning treatment options. It should not be assumed that having children should not be a cancer patient's first priority. Moreover, the discussion about the treatment consequences in the future strongly indicates a hope for survival and recovery. The cancer patients that have had extensive reproductive health counseling, including information on the risks to fertility from cancer therapy, fertility preservation, and menopause, have a reduced distress and anxiety through cancer treatment. In general, patients who are better informed experience greater emotional well-being, and report greater compliance with treatment and satisfaction with care [138].

3.6.5 Reproductive Issues

3.6.5.1 Resumption of Ovarian Function and Spontaneous Pregnancy Rate

Bidet et al. [73] assessed the incidence of the resumption of ovarian function and spontaneous pregnancies in a group of 358 patients with non-iatrogenic POI. The authors observed intermittent ovarian function in 24% of patients, mostly within

1 year of diagnosis. Twenty-one spontaneous pregnancies (16 births, 5 miscarriages) occurred in 15 (4.4%) patients. Moreover, the authors reported on predictive factors for the resumption of ovarian function in POI women. Among clinical features, age and secondary amenorrhea appeared to be critical factors for the resumption of ovarian function in POI patients. Only two patients with primary amenorrhea showed a resumption of ovarian activity. A familial history of POI was a good predictive factor for the resumption of ovarian activity. FSH, estradiol, and inhibin B at the POI diagnosis appeared to be predictive of the ovarian capacity to maintain partial activity. An FSH level between 30 and 50 IU/L at diagnosis suggested a better prognosis than higher levels. Surprisingly, AMH levels were not predictive of the resumption of ovarian activity in the presented study. The authors designed a follow-up study of POI women after their first evaluation in a larger cohort of 507 patients [139]. Among the patients with episodes of a resumption of ovarian function (23%), the mean age of POI onset was 31.1 years, and almost all patients (98.2%) were initially presented with secondary amenorrhea. During the follow-up period, 47% experienced an arrest of ovarian function. Higher FSH and DHEA levels were risk factors for arrest following the resumption of ovarian function. The AMH level was not a predictive factor for the arrest of the resumption of ovarian function.

3.6.5.2 Fertility, Pregnancy, Pregnancy Outcome

Premature ovarian insufficiency in half of the affected women has an intermittent and unpredictable course, and there is still 3–10% chance of spontaneous conception [139].

Little progress has been made to improve reproduction with patients' own gametes. Several different interventions have been proposed to induce ovulation and achieve pregnancy in POI patients that were denied oocyte donation. The principles of proposed strategies include the improvement of the ovarian responsiveness by the suppression of circulating gonadotropins, or immunomodulating treatment when an autoimmune origin was suspected. There are several studies evaluating the effectiveness of estrogen, standard hormonal replacement therapy, GnRH analogues, corticoids, or danazol pretreatment continued with ovarian stimulation with gonadotropins [140]. Generally, the ovulation and pregnancy rates for most of the strategies, assessed in a systematic review performed by Robles et al. [140], were similar to the spontaneous pregnancy rates for these patients. However, some trials have reported improvements in ovulation rates when pharmacological doses of estrogen were used before gonadotropin therapy [141]. The authors suggested that a threshold of FSH $\leq$15 mIU/mL after estrogen pretreatment should be achieved for the successful induction of ovulation. The studies using immune-modulating agents would require a larger number of participating patients to have the adequate power to prove an influence on ovulation and pregnancy rates.

3.6.5.3 Obstetric Risks Associated with POI

According to ESHRE guidelines, women should be reassured that spontaneous pregnancies after idiopathic POI or most forms of chemotherapy do not show any higher obstetric or neonatal risk than in the general population [2].

Oocyte donation is the only proven and recommended treatment for women with POI. The cumulative pregnancy rates of oocyte donation treatment are very high and after four cycles reach 70–80% [140]. However, such treatment is not available in some countries and not all patients would accept oocyte donation. Oocyte donation pregnancies are characterized by high rates of primiparity, advanced maternal age, and multiple gestations, and are associated with increased rates of gestational complications such as gestational diabetes, hypertensive disorders, placental abnormalities, preterm delivery, and a high rate of caesarean section [142]. There is strong evidence also that oocyte donation is a significant and independent risk factor for preeclampsia and gestational hypertension compared with pregnancies after other assisted reproductive technology methods or natural conceptions. The risk is independent of the maternal age and multiple gestations [143].

Some other obstetric problems could be anticipated in women with POI. Primary ovarian insufficiency manifested by primary amenorrhea and lack of normal puberty may result in inadequate development of the uterus despite estrogen replacement administration. Similarly, women who have received radiation to the uterus are at a high risk of obstetric complications, such as early pregnancy loss, premature labor, or low birth weight.

A cardiologist should be involved in the care of pregnant women with Turner syndrome, and those who have received anthracyclines or cardiac irradiation before gestation [2].

Turner Syndrome and Pregnancy

Turner syndrome is caused by partial or complete loss of one of the X chromosomes. It is characterized by ovarian dysgenesis and a varying number of extragonadal abnormalities. In most of Turner syndrome patients accelerated follicular atresia leads to primary amenorrhea, absence of pubertal development, primary amenorrhea, and infertility. In some cases of mosaicism (45,X/46,XX) puberty and menstrual cycles occur. However, ultimately the patients develop POI and have a limited time period during which they can become pregnant. The development of assisted reproduction technologies allowed women with Turner syndrome to achieve pregnancy through oocyte donation. Hormonal therapy in adolescents with Turner syndrome is implemented in order to achieve proper development of the uterine cavity. Pregnancy rates in women with Turner syndrome after in vitro fertilization with donor oocytes are comparable to the rates achieved in women without this condition undergoing similar treatment [144]. However, these pregnancies carry a higher obstetric and non-obstetric risk. Therefore women with Turner syndrome should be counseled and closely monitored. There are two large studies reviewing the outcomes of almost 200 pregnancies in women with Turner syndrome after oocyte donation [145, 146]. The fetal and maternal risks in Turner syndrome patients, based mainly on the aforementioned two large studies, are summarized in an excellent review performed by Bouet et al. [144]. There is a higher risk of miscarriage (29%), perinatal fetal death (2%), being small for gestational age (18–28%), and prematurity (12%) and a possible increased risk of fetal chromosomal abnormalities in pregnancies with autologous oocytes [144–146]. The maternal risks

include thyroid dysfunction (22%), gestational diabetes (4–9%), gestational hypertension (15–17%), preeclampsia (21%), and caesarean section (82%) [39–41]. However, the most dangerous for the mother are cardiovascular complications: worsening of congenital heart disease (1%), heart failure (1%), aortic dissection (1–2%), and a resulting maternal mortality of 2% [39–41]. Therefore, in 2010 the national guidelines were published in France for the management of women with Turner syndrome [147]. According to the recommendations, tests assessing thyroid, liver, and kidney function should be performed as well as blood pressure and gynecological assessment of uterine morphology should be done. Detailed recommendations concerning checkup before pregnancy include cardiovascular examination with ultrasound examination and mandatory magnetic resonance angiography of the heart and aorta. According to these guidelines, pregnancy should be contraindicated in patients with a history of aortic surgery or dissection, when the diameter of the ascending aorta indexed for the body surface area exceeds 2.5 cm/m^2 and in cases of a coarctation of the aorta or resistant hypertension.

The American Society for Reproductive Medicine underlines that women with Turner syndrome at the greatest risk of aortic dissection and rupture include those exhibiting baseline or progressive aortic root dilatation, a bicuspid aortic valve, coarctation of the aorta with or without prior surgical repair, and hypertension [148]. Women with Turner syndrome interested in oocyte donation should be carefully evaluated. Because of their small stature and body surface area, the aortic diameter may not be an appropriate predictor of the aortic dissection risk and should be adjusted by calculating the aortic size index (ASI). An ASI >2.0 cm/m^2 identifies those patients who are at a particularly increased risk for dissection, and represents an absolute contraindication for attempting pregnancy in a woman with Turner syndrome. Women with Turner syndrome having a normal cardiac magnetic resonance and evaluation are at a still much higher risk for associated morbidity and mortality and require careful observation throughout pregnancy and postpartum.

Apart from pregnancy resulting from oocyte donation, other techniques have been proposed to Turner syndrome patients in experimental settings. A spontaneous beginning of puberty occurs in 15–30% of girls with Turner syndrome, but only 2–5% reach menarche with the possibility of achieving pregnancy [149]. Apparently the dynamics of the disappearance are very individual. Borgström et al. [149] performed laparoscopy in 57 adolescent Turner patients. They obtained ovarian tissue in 47 of the patients. In 15 (26%) patients the existing follicles were identified histologically. In six out of seven (86%) girls with mosaicism, follicles were found. Among the 22 girls with structural abnormalities of their X chromosome, only six (27%) had follicles. Girls with the 45X karyotype (10.7%) had the least chance of follicle incidence within the ovary. Within the group of Turner girls with spontaneous onset of puberty, 58% had follicles in their tissue. In 13 girls that reached spontaneous menarche, 68% had follicles, while the girls with no signs of spontaneous puberty had only a 10% chance to have follicles identified during histological assessment. In general, five factors determined the chances of finding remaining follicles in girls with Turner syndrome: karyotype, low FSH, high AMH, spontaneous onset of puberty, and spontaneous menarche. The authors of the study admitted

that it was more unexpected that still some follicles were found in three girls without spontaneous puberty and in four girls with high serum concentrations of LH and FSH and low AMH levels.

Moreover, the retrieval of immature oocytes from excised ovarian tissue followed by in vitro maturation and oocyte vitrification can be offered as an adjunct to ovarian tissue cryobanking [150]. One important concern relates to the chromosome status of oocytes retrieved from young women with Turner syndrome. According to Borgström et al. [149] this question cannot be neglected and possibly all women with Turner syndrome should be offered preimplantation diagnosis, chorion villous sampling, or amniocentesis if fertilization with their own oocytes is successful.

3.6.6 Oncofertility

There is an overall increase in cancer prevalence followed by an increase in long-term survival of the affected patients these days compared to the past. The 5-year survival rate for childhood, adolescent, and young adult cancer currently exceeds 80% [80]. The risk of nonsurgical POI among young cancer survivors is increased, with a cumulative incidence of 8% by the age of 40 years. Protection against iatrogenic infertility caused by chemotherapy, radiation therapy, or surgery assumes a high priority. Evaluation of the likelihood of POI after chemotherapy or radiotherapy is often highly problematic. Before cancer therapy, the issue of possible infertility should be addressed and all patients having their reproductive years ahead of them should be informed of possible fertility-preservation options. None of the suggested methods is ideal and none guarantees future fertility in survivors. Therefore, a combination of methods can be recommended for maximizing the chances of future fertility [151].

3.6.6.1 Fertility-Sparing Surgery

It is estimated that 15–25% of women diagnosed with gynecological cancers are younger than 40 years old. Fertility-sparing surgery, after adequate counseling including oncological, fertility, and obstetrical outcomes, can be undertaken in some cases. This approach should only be discussed with women who want to be pregnant and whose chances of successful treatment of cancer would not be severely compromised by fertility-sparing surgery. The most common utilization of fertility-sparing surgery in genital tract tumors is unilateral oophorectomy in borderline ovarian cancer, and radical vaginal trachelectomy in cervical cancer [152].

3.6.6.2 Shielding to Reduce Radiation, Ovarian Transposition

The damage to female reproductive organs by radiation therapy is dose dependent. Age is also an important factor. Young women with a high ovarian reserve may survive cancer treatment with a greater number of remaining primordial follicles and avoid POI and infertility problems. Apart from the irradiation of ovaries, uterine radiation exposure may impair its growth during the pregnancy and increase the risk of spontaneous abortion, premature labor, or intrauterine growth retardation. When

possible, shielding to reduce radiation in young females should be applied. When shielding of the gonadal area is not possible, ovarian transposition should be considered. This procedure has been most commonly applied in gynecological cancers and in pelvic and abdominal Hodgkin's disease or sarcomas [153]. Unfortunately, the procedure can be ineffective due to scattered radiation and damage to the blood vessels that supply the ovaries.

3.6.6.3 Decreasing the Impact of Chemotherapy

The gonadotoxic effect of various chemotherapeutic agents is diverse. High-risk chemotherapeutic agents include alkylating agents such as cyclophosphamide; medium-risk agents include platinum agents and anthracycline antibiotics; whereas low-risk chemotherapeutic agents include vinca plant alkaloids and antimetabolites. The high-risk chemotherapeutic agent cyclophosphamide is also used to improve survival and reduce organ damage in severe connective tissue diseases and vasculitic syndromes (systemic lupus erythematosus, systemic sclerosis, Wegener's granulomatosis) with a high incidence of POI, ranging from 30 to 60% [151].

The degree of depletion of the ovarian follicles depends also on the woman's age, chemotherapeutic regimen, and initial ovarian reserve. The reported POI rate after Hodgkin's lymphoma or breast cancer chemotherapy increases 2–3 times in women over 30 years old, comparing to younger patients [151]. The administration of GnRH analogues before and during chemotherapy treatment has been proposed to decrease the POI incidence by simulating a prepubertal hormonal state. Numerous randomized trials assessing the impact of GnRH analogue (GnRHa) treatment during chemotherapy on POI incidence and fertility preservation have presented conflicting results. Therefore, the American Society of Clinical Oncology in 2013 stated that there is insufficient evidence regarding the effectiveness of ovarian suppression with GnRH analogs as a fertility-preservation method, and these agents should not be relied on to preserve fertility [154]. Two of the most recent meta-analyses, evaluating the efficacy of GnRHa given before and during chemotherapy in randomized controlled trials, concluded that GnRHa significantly reduces the risk of POI in young cancer patients, but does not exhibit its protective effects in fertility [155, 156].

3.6.6.4 Oocyte and Embryo Cryopreservation

Several other methods have been proposed to preserve fertility. Cryopreservation of embryos and mature oocytes is a clinically established method [154, 157]. These options require controlled ovarian stimulation that will postpone cancer treatment for at least 2 weeks. There are some concerns about the possible impact of exposure to high estradiol levels during ovarian stimulation in breast cancer patients. Therefore, several safer protocols can be offered, including natural cycle IVF or ovarian stimulation with letrozole or tamoxifen alone or in combination with gonadotropins [158]. After oocyte retrieval, in vitro fertilization and embryo cryopreservation are offered to a woman having a partner. For women without a partner, and not accepting in vitro fertilization with donor sperm, cryopreservation of oocytes should be offered. The results of freezing mature oocytes have been improved with

the implementation of the vitrification method, and the pregnancy rates and live births after thawing and fertilizing oocytes are currently reaching those obtained after embryo cryopreservation (around 25%) [153, 157]. A study published in 2014 reported the birth of more than a 1000 babies resulting from vitrified-warmed oocytes, with no apparent increase in birth anomalies [159].

In 2011, a study by Kim et al. [160] reported the birth of the first baby after oocyte vitrification in a patient with chronic myeloid leukemia. Following the report of Kim et al., several successful live births have been reported after oocyte vitrification in patients diagnosed with cancer. Still, it is difficult to predict the possibility of having a live birth according to the number of cryopreserved oocytes in cancer patients. More reports with regard to the efficacy of the cryopreserved oocytes followed by IVF are expected in the near future.

Remaining options such as retrieving immature oocytes aiming at maturing them later in vitro, and freezing of gonadal tissue, are still considered experimental [154]. However, ovarian tissue cryopreservation is increasingly being adapted into practice in many countries and the results demonstrate that it might be a highly effective technique for fertility preservation, providing a realistic chance for future pregnancy [161].

3.6.6.5 Ovarian Tissue Cryopreservation

Cryopreservation of ovarian tissue is an option for prepubertal girls and women who cannot delay the start of chemotherapy. Ovarian tissue is retrieved by laparoscopy. Then cortex tissue of the ovary is sliced and undergoes slow freezing or the vitrification procedure. Once the cancer treatment is completed and the patient is disease free, the thawed ovarian tissue is reimplanted into the pelvic cavity (orthotopic site) or a heterotopic site like the forearm or abdominal wall. It takes 3.5–6.5 months after the reimplantation before a rise in serum estradiol and a decrease in FSH are observed. AMH and inhibin B are not good predictors of graft function or the probability of achieving pregnancy [162]. Therefore, repeated measurements of FSH and estradiol levels inform about the resumption of ovarian function after transplantation.

Donnez et al. [163] reviewed the results of three centers (Belgium, Denmark, Spain) evaluating 60 orthotopic ovarian transplantations in women after cancer treatment (80%) and because of benign pathology (Turner syndrome, family history of POI, endometriosis, etc.). A restoration of ovarian activity was observed in a vast majority of patients (93%). Moreover, the authors showed the data of the worldwide series of 24 live births obtained by the year 2013. More than 50% of pregnancies were obtained naturally. Mean birth weight in singleton pregnancies was 3300 g and the mean gestational age at the time of delivery was 38–39 weeks [164].

Dittrich et al. [165] reported the results of 20 orthotropic retransplantations of cryopreserved ovarian tissue after cancer treatment. In 19 cases (95%) hormone activity in the ovary was observed at least in the form of an increase in serum estradiol levels. Initial signs of an increase in the estradiol level or follicle growth were documented on average at 3–6 months after transplantation. Seven women became pregnant. Six of these pregnancies were spontaneous and one followed IVF.

Meirow et al. [161] described the results of ovarian tissue cryopreservation and reimplantation in 20 patients by a single team. Among the patients without any ovarian activity before the transplantation, almost all (93.7%) regained their menses and half of the patients had FSH levels below 16 IU/L. A total of 14 patients underwent ovarian stimulation and IVF cycles with the following pregnancy rates: 18% per cycle and 26% per transfer. The live birth rate was 10.7% per cycle and 16% per transfer. The live birth rate per cycle was 8.8% in cases of preharvesting chemotherapy versus 13.6% in cases of no chemotherapy. In four patients, an additional six pregnancies occurred spontaneously. Out of ten live births, one newborn had a major malformation (arthrogryposis). None of the patients have experienced cancer recurrence, including the two women who had leukemia (mean time of follow-up after transplantation 3.18 years).

More than 60 live births worldwide have been reported so far after the transplantation of frozen-thawed ovarian tissue, with an approximate pregnancy rate of 27% [57, 58]. However, significant heterogeneity exists among different groups regarding selection criteria for ovarian tissue cryopreservation as well as different techniques used for tissue preparation, freezing, and transplantation [161]. The procedure of ovarian tissue for freezing is invasive and may be even more dangerous in some patients with cancer who might be immunocompromised. Moreover, some hematological cancer can involve the ovary. These uncertainties dictate that this technique should only be offered to girls and young women who are at high risk of POI. Specific selection criteria should be established in order to help the clinicians and their patients to make decisions [166].

3.6.6.6 Cryopreservation of Immature Oocytes

An important concern that still remains is the safety of ovarian tissue transplantation. There is the potential risk that malignant cells present in the frozen tissue may lead to the recurrence of the primary disease after transplantation [165]. Retrieval of immature oocytes is performed in the natural cycle and therefore can be offered to women who do not want any delay in cancer treatment or whenever a hormonal stimulation treatment is contraindicated. Immature oocytes can also be obtained from the ovarian tissue being prepared for cryopreservation, giving the additional strategy of fertility preservation. In vitro maturation of oocytes is still considered experimental and is not offered by many centers. However, it is quite conceivable that the technique may be successful in humans within the next few years [165].

3.6.6.7 National Oncofertility Networks

Fertility-preservation techniques for medical reasons are increasingly offered by national networks: FertilPROTEKT, spanning Germany, Austria, and Switzerland; the Task Force of the ESHRE; the Fertility Consortium in the USA; and the International Society of Fertility Preservation. Recent report published by FertilPROTEKT revealed that 41% of the total number of counseled patients in 2013 had breast cancer, 28% lymphoma, 23% other malignancies, and 7% benign diseases (systemic lupus erythematosus, vasculitis, mosaic Turner syndrome) [167]. In 2013 the distribution of implemented treatment options was as follows: 41%

GnRHa treatment, 38% tissue freezing, and 21% oocyte or zygote cryopreservation. National registers and collaborative research will help to fill key gaps in knowledge concerning the thresholds of both alkylating agents and radiotherapy and other factors determining the degree of ovarian injury, which should finally be integrated into a risk model predicting POI.

3.6.6.8 Timing of the Conception After Therapy

It is not clear how much time should elapse between the end of chemotherapy and conception. Immediate pregnancy after completion of treatment is contraindicated due to the DNA toxicity of chemotherapy. If chemotherapy is administered in the first trimester of pregnancy, there is a 16% incidence of fetal malformations [158]. Although "the gold standard time" has not been defined, preventing conception is recommended in the first 1–2 years after chemotherapeutic insult. Other reasons for abstaining from pregnancy are the high rate of recurrence and frequent need for tomography and other diagnostic tools during the first 2 years after treatment. Nevertheless, the risk of congenital anomalies in children born to mothers soon after the completion of chemotherapy is similar to that found in the general population [158, 168]. However, data from the Swedish Medical Birth Registry concerning the course of pregnancy in breast cancer survivors revealed an increase in preterm births, low birth weights, and delivery complications including higher rates of instrumental and cesarean section deliveries [168]. Therefore, these pregnancies should be regarded as higher risk pregnancies and carefully monitored. Historically, pregnancy after breast cancer was not recommended due to the potential negative impact of increased estrogen and progesterone levels on the patient's prognosis. Recent studies do not confirm the hypothesis and even show that pregnant women maintain a trend toward better survival [169]. Pregnancy after breast cancer may be considered safe in terms of the patient's prognosis [170].

3.6.7 Future Perspectives

3.6.7.1 In Vitro Activation (IVA)

New infertility treatment, named in vitro activation (IVA) of dormant follicles, has been proposed in patients with POI [171]. Women with POI still have varying amounts of residual dormant follicles in their ovaries. However, these follicles are difficult to grow spontaneously, and thus the patients are unlikely to conceive with their own oocytes. A number of intraovarian factors have been shown to be important for primordial follicle activation. IVA implements ovarian fragmentation, disrupting the Hippo signaling pathway, and providing treatment with phosphatidylinositol-3-kinase (PI3K) stimulator to activate dormant primordial and restrained secondary and preantral follicles in POI patients. The full cycle of IVA includes laparoscopic surgery to remove the ovary, which is subsequently cut into cortical strips and vitrified. After thawing of cryopreserved ovarian tissues, the ovarian strips are further fragmented and incubated for 2 days with PI3K stimulators. After this, the ovarian strips are autografted under laparoscopic surgery. Then the patient undergoes the

full protocol of the ovarian stimulation and IVF procedure. Currently, two healthy babies have been delivered, together with two additional pregnancies. The inventors of the method admit that to improve the efficiency of IVA, it is important to develop a noninvasive method to predict the presence of residual follicles before the first laparoscopy [171]. Controlled studies would be required before IVA can be advocated for more widespread clinical use.

3.6.7.2 Stem Cells

Recent studies have focused on stem cell therapy for POI. Current dogma still holds that females are born with a finite pool of follicles which continue to decline until menopause. However, it has been postulated and next to proved that the mammalian ovary contains some ovarian stem cells that can give rise to fertilizable oocytes [172]. Stimpfel et al. successfully characterized and differentiated in vitro stem cells from the adult human ovarian cortex [173].

Moreover, bone marrow mesenchymal stem cells, skin-derived mesenchymal stem cells, as well as umbilical cord blood stem cells and amniotic fluid stem cells have been used in animal models and showed some ability to prevent follicular atresia and to rescue ovarian function [172].

The future application of these cells may open a new chapter in the treatment of POI.

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Part II

Impact of Estrogen Depletion on Symptoms and Quality of Life

Clinical Symptoms and Quality of Life: Hot Flashes and Mood

4

Plácido Llaneza

4.1 Introduction

Health-related quality of life (HRQoL) is a subjective parameter which refers to the effects of an individual's physical state on all aspects of psychosocial functioning. It is defined as the value assigned to duration of life as modified by impairments, functional states, perceptions, and social opportunities that are influenced by disease, injury, treatment, or policy [1]. The specific domains of HRQoL include resilience or the capacity to respond to stress, health perceptions, physical functioning, and symptoms. Menopausal changes could affect HRQoL. Some domains of HRQoL may improve after menopause, but several transversal and longitudinal studies have reported negative effects of menopausal symptoms in HRQoL and the severity of menopausal symptoms is what reflects best the profile of quality-of-life dimensions [2–4].

Hot flushes (HF) and night sweats (NS) are the predominant symptoms of menopause and they are usually referred as vasomotor symptoms (VMS) because of the vascular reactivity with initial prominent vasodilatation and subsequent vasoconstriction associated to estrogen withdrawal [5]. Although women describe episodes similar to menopausal VMS at various stages of their reproductive life cycle, it is estimated that at some point during the menopausal transition, up to 80% of women will experience HF [6].

The prevalence of VMS varies widely and may be influenced by a range of factors, including climate, diet, lifestyle, women's roles, and attitudes regarding the end of reproductive life and aging [7–9]. A lower prevalence in Japanese and South-East Asian women was found, being reported only by 5–18% of postmenopausal

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women [10]. However, enormous differences in the experience of VMS have also been identified among women within the same culture [11].

HF may occur at any time of day or night and be spontaneous or triggered by a variety of common situations such as embarrassment, sudden ambient temperature change, stress, alcohol, caffeine, or any warm drink. The subjective features are individual and variable, but usually start with a sudden sensation of heat or warmth, often accompanied by sweating, some reddening of the skin, and sometimes palpitations. Most often this will start in the upper body and spread upwards or downwards, and infrequently all over the body. The perceived duration of HF ranges from 30 s to 60 min, with a mean between 3 and 4 min [12].

4.2 Pathogenesis

Pathogenesis of VMS still remains unknown. The mechanisms of increases in skin blood flow during HF may include the withdrawal of sympathetic vasoconstrictor activity, increases in sympathetic cholinergic vasodilator activity, or a combination of both neural mechanisms and nonneural factors [13, 14]. Peripheral estrogen levels do not differ between symptomatic and asymptomatic women, but symptomatic women have higher levels of central noradrenergic activation than asymptomatic women and elevated central noradrenergic activation narrows the thermoneutral zone [15], so the heat dissipation responses are triggered if the core body temperature crosses the upper threshold of the thermoneutral zone [5, 16] (Fig. 4.1).

There is evidence concerning the implication of central neuropeptides. In the hypothalamus of postmenopausal women, there are dramatic changes in morphology and neuropeptide gene expression in the infundibular (arcuate) nucleus. Autopsy

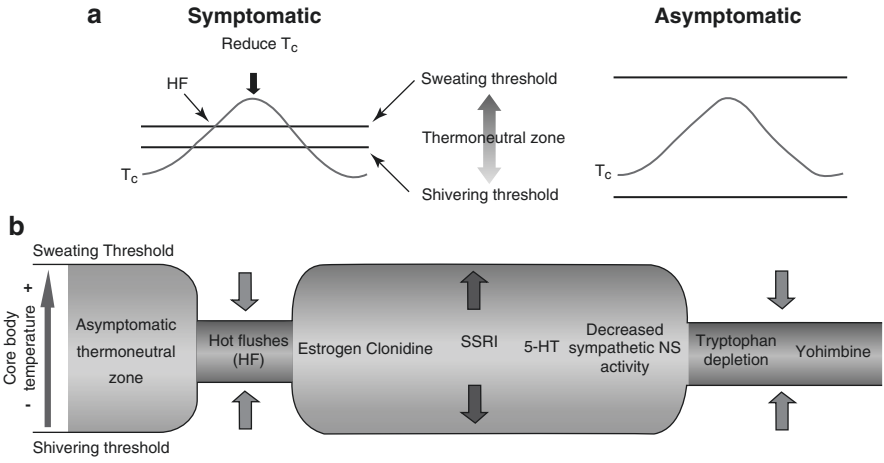

Fig. 4.1 Mechanism of HF production, according to Freedman et al. [70] and Archer et al. [5]. (**a**) Small core body temperature (T_c) elevations acting within a reduced thermoneutral zone trigger hot flushes (HF) in symptomatic postmenopausal women; (**b**) the factors that influence the thermoneutral zone. *SSRI* selective serotonin reuptake inhibitor, *5-HT* serotonin, *NS* night sweat

studies showed that these neurons increase in size (hypertrophy) accompanied by increased neurokinin B (NKB) and kisspeptin gene expression [17]. The hypertrophied neurons express estrogen receptor alpha [18], and are called KNDy neurons based on the coexpression of kisspeptin, NKB, and dynorphin [19–21]. Nearly identical changes occur in young monkeys in response to ovariectomy and the changes are reversed by estrogen replacement [20, 22]. These data provide compelling evidence that hypertrophy and increased NKB and kisspeptin gene expression in postmenopausal women are due to estrogen withdrawal.

Men and women with mutations in kisspeptin, NKB, or their receptors exhibit hypogonadotropic hypogonadism [23–25]. They do not go through puberty, are infertile, and secrete insufficient LH resulting low levels of sex steroids. Thus, KNDy neurons express two peptides that are essential for human reproduction. Basic research in multiple species (including human) has established a role for KNDy neurons in regulating pulses of GnRH into the portal capillary system [26–29]. The close timing of LH pulses with hot flushes provides a clue that estrogen-responsive KNDy neurons could play a role in the generation of flushes [30].

To determine if KNDy neurons could play a role in thermoregulation, a series of studies were performed using a rat model (for a review, see [31]). Anatomical studies showed projections of KNDy neurons to the median preoptic nucleus (MnPO), an important component of the CNS pathway that regulates heat dissipation effectors [32, 33]. Moreover, MnPO neurons express the neurokinin 3 receptor (NK_3R), the primary receptor for NKB [34]. These data provide an anatomic framework to understand how estrogen-responsive KNDy neurons could specifically interface with hypothalamic brain areas that regulate heat dissipation effectors. Further studies using a rat model showed that KNDy neurons influence cutaneous vasodilation (flushing) via projections to NK_3R-expressing neurons in the MnPO [34–36].

Clinical studies have provided strong support for the hypothesis that KNDy neurons participate in the generation of hot flushes via NK_3R signaling. For example, infusion of NKB into the peripheral circulation induces hot flushes in women [37]. Moreover, genetic variation in the gene encoding the NK_3R receptor is associated with hot flushes in women [38]. More recently, two clinical trials have shown that treatment with an NK_3R antagonist successfully reduces the number and severity of hot flushes [39, 40]. These studies open up a new avenue for treatment of hot flushes with targeted therapies that do not require estrogen replacement.

4.3 Duration of HF

It is accepted that HF persisted for about 6 months to 2 years for most women, but recent studies of the duration of HF indicate that women can expect HF to continue, on average, for nearly 5 years after the final menstrual period, while more than one-third of women who experience moderate/severe hot flushes will continue to have them for more than 10 years after the menopause [41]. The expected duration of menopausal VMS is important to women making decisions about possible treatments. In the Study of Women's Health Across the Nation (SWAN) carried out in a sample of 3302 US women enrolled during menopausal transition, the median total VMS

duration was 7.4 years with some factors related to longer duration as race/ethnicity, younger age, lower educational level, greater perceived stress and symptom sensitivity, and higher depressive symptoms and anxiety at first report of VMS [6]. Duffy et al. reported that women resilient to HF were those who had previously not been bothered by their menstrual periods; were not experiencing somatic symptoms or night sweats; and perceived their symptoms as having low consequences on their lives and women resilient to NS were nonsmokers, were not experiencing sleep difficulties, were not using psychological symptom management strategies, and perceived their menopausal symptoms as having low life consequences [42]. Moreover, Perez-Lopez et al. [43] in other study aimed to assess resilience, depressed mood, and menopausal symptoms in a sample of Spanish postmenopausal women have also reported that depressed mood and participation in regular exercise correlate with lower and higher resilience to menopausal symptoms, and depressed mood was associated with the severity of menopausal symptoms (somatic and psychological).

4.4 Hot Flushes, Depressed Mood, and Quality of Life

The impact of VMS on quality of life may be considerable and is often underestimated. VMS may interfere with work and daily activities as well as with sleep, causing subsequent fatigue, loss of concentration, and mood changes, all of which can interfere with family life, sexual function, and partner relationships affecting HRQoL [5, 44]. The impact of untreated HF on quality of life was studied in a sample of 252,000 working women with untreated HF compared to asymptomatic age-matched women. During a 12-month period, the women with hot flashes showed increased work loss, 1.1 million extra medical visits, and a health insurance bill almost $400,000,000 more compared to the asymptomatic women [45].

HF are linked to vascular changes, cardiovascular risk, and changes in the brain, with increased white matter hyperintensities suggesting that the relationship between hot flashes and cardiovascular risk observed in the periphery may extend to the brain [46, 47]. In this sense, episodes of HF are often accompanied by a feeling of irritation, anxiety, or panic that may significantly compromise overall health and decrease cognitive function [3, 48]. In a systematic review of the literature a bidirectional association between VMS and depressive symptoms has been reported in women presenting to menopause clinics [49]. Moreover, according to a recent meta-analysis, perimenopause is a phase particularly vulnerable for developing depressive symptoms and there are indications that VMS are positively related to depressive symptoms during menopausal transition [50].

Burleson et al. [51] in a study using multilevel structural equation modeling for testing whether changes in daily VMS occurrence predicted changes in occurrence of same-day sleep problems and changes in next-day positive and negative mood ratings and whether sleep problems mediated any predictive effect of symptoms on next-day mood found, after controlling for initial depression, that daily VMS predicted same same-day sleep problems and next-day positive mood, although significant direct relationships between VMS and mood were found primarily only in women with initial depression scores in the low to moderate range. The authors

suggested that any effect of VMS on mood may occur largely through a mechanism other than sleep disruption. However, Pinkerton et al. [52] in another placebo-controlled phase 3 trial using the Menopause-Specific Quality of Life (MSQoL) questionnaire found that frequency and severity of HF showed approximately linear relationships with MSQOL and sleep parameters. Lastly, Katon et al. [4] in a large sample of veteran and non-veteran US postmenopausal women found that any VMS was associated with decreased HRQoL and baseline depression and obesity amplified the negative association between VMS and HRQoL (Fig. 4.2).

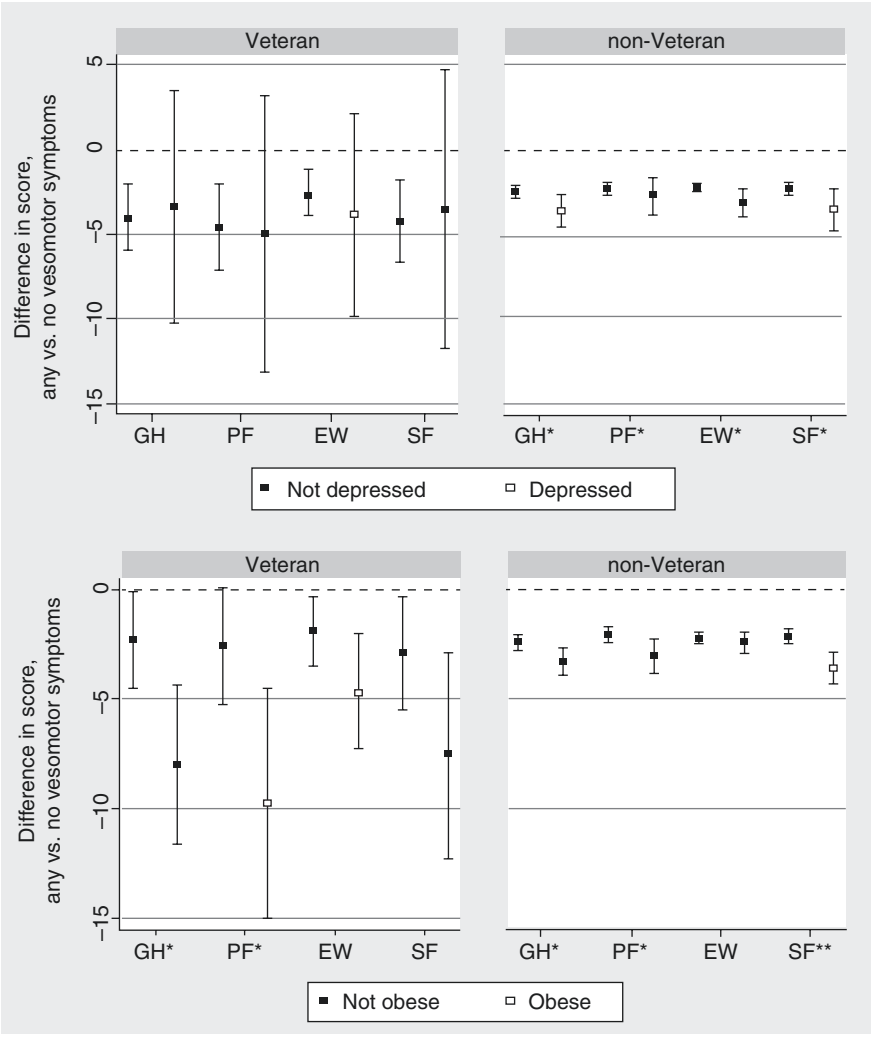

Fig. 4.2 Mean differences in health-related quality of life (HRQoL) subscales at year three follow-up associated with any vasomotor symptoms (VMS) at baseline among veteran and non-veteran women, by depression status and obesity. *GH* general health, *PF* physical health, *EW* emotional well-being, *SF* social functioning [4]

Depressed mood symptoms and other depressive disorders are common among middle-aged women. Women are more vulnerable than men to depressive disorders [53] and endocrine influences have been postulated [54–56] but the effect of hormonal changes on depression and depressed mood remains unclear due to differences in coping style and response to stress or gender differences in socialization may also lead to higher rates of depression in women [55, 57]. Risk factors for the development of depressive symptoms and depression in the menopausal transition include the presence of VMS, as well as a personal history of depression (particularly depression that is related to pregnancy or hormonal changes through the menstrual cycle), surgical menopause, adverse life events, and negative attitudes to menopause and ageing [58]. Some studies have found that women with climacteric symptoms (VMS, vaginal dryness, and dyspareunia) are more likely to report negative affect, anxiety, and/or depressive symptoms [59, 60] and the risk for new-onset depression is heightened by more severe VMS [61]. In a small Swedish study anxiety and depression were significantly greater in women with surgical premature ovarian insufficiency [62] and Kronenberg et al. [63] reported that depressed feelings during HF were more common in women after surgical menopause than with natural menopause and that suicidal thoughts during HF occurred almost twice as often (10%) in these women. However, not all studies report psychological disorders related to menopause [64] and other factors as biopsychosocial and partner factors could also have a significant influence on middle-aged women's sexuality and depressive disorders. Stress, educational level, ethnicity, socioeconomic factors, and partner status may also influence the prevalence and clinical course of both menopause symptoms and depressive disorders [55].

4.5 Hot Flushes Management with Antidepressant Drugs

Hormonal therapy (HT) reduces the frequency and severity of HF, with health benefits when started near menopause, particularly for women with early menopause. It carries small absolute risks, and has potential health benefits on reduction of heart disease and all-cause mortality for women younger than 60 years and within 10 years of menopause [65]. However, long-term health risks in some women receiving hormone therapy for VMS were reported by the Women's Health Initiative and Million Women Study [66, 67]. Although data strongly support using HT in symptomatic women started near menopause, societal factors overwhelm the findings and the use of HT has declined in a sustained fashion and some menopausal symptomatic women are treated with nonhormonal therapy.

Several nonhormonal therapies were found effective for HF over placebo include some antidepressant drugs as serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SSNIs), and gabapentin. Fluoxetine, paroxetine, citalopram, escitalopram, venlafaxine, desvenlafaxine, gabapentin, and pregabalin, as well as low-dose paroxetine salt, have shown significant reductions in HFs over placebo [68, 69]. However, doses and the incidence of side effect as nauseas,

dizziness, or even suicidal ideation when are used in higher doses as an antidepressant must be considered.

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Clinical Symptoms and Quality of Life: Insomnia and Muscle/Joint Aches

5

Juan Enrique Blümel and Eugenio Arteaga

5.1 Introduction

Health-related quality of life (HRQL) has been defined as the subjective assessment of a patient oriented to the exterior of himself and focused on the impact of the health status on the ability to lead a fulfilling life [1]. The multiplicity of symptoms associated to the climacteric and the subjective evaluation of the impact of this symptomatology in the welfare of a woman make it difficult for the clinician to evaluate the potential impact of estrogen withdrawal on the woman's health.

The evaluation of the climacteric consequences on the woman's health and her HRQL has been traditionally done through clinical scores, whose main purpose is to provide a quantitative measurement of the efficacy of different medical interventions. A significant advance has been the development of the Menopause Rate Scale (MRS) [2]. This instrument is a validated questionnaire that assesses both the presence and severity of 11 symptoms divided into three subscales: (1) somatic-vegetative including VMS, cardiac disturbances, sleep difficulties, muscular and articular discomfort, or pain (items 1–3 and 11); (2) psychological: depressive mood, irritability, anxiety, and physical and mental exhaustion (items 4–7); and (3) urogenital: sexual difficulties, bladder problems, and vaginal dryness (items 8–10). Each item is rated as 0 (absent), 1 (mild), 2 (moderate), 3 (severe), and 4 (very severe). Mean and standard deviations for each item may be obtained in defined populations. The sum of means of defined items per subscale is the final value for the subscale and the sum of the three subscales corresponds to the total MRS score. The higher the score the worse detriment in quality of life. According to this

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Table 5.1 Scores and prevalence of climacteric symptoms (MRS) in midlife women

Domains	Score MRS (means ± SD)	% Prevalence symptoms (CI 95%)	
		Any	Severe
Somatic domain			
1. Hot flashes, sweating	1.02 ± 1.14	54.5 (53.5–55.6)	9.6 (9.0–10.3)
2. Heart discomfort	0.73 ± 0.97	43.8 (42.8–44.9)	5.0 (4.6–5.5)
3. Sleep problems	1.13 ± 1.18	59.0 (57.9–60.1)	13.2 (12.5–14.0)
4. Joint/muscular discomfort	1.25 ± 1.23	63.0 (61.9–64.0)	15.6 (14.8–16.4)
All symptoms	*4.12 ± 3.36*	*84.2 (83.4–84.9)*	*10.8 (10.1–11.4)*
Psychological domain			
5. Depressive mood	1.17 ± 1.19	60.5 (59.4–61.5)	13.7 (13.0–14.4)
6. Irritability	1.20 ± 1.13	64.6 (63.6–65.6)	12.3 (11.7–13.1)
7. Anxiety	0.99 ± 1.13	53.9 (52.8–55.0)	10.7 (10.1–11.4)
8. Physical mental exhaustion	1.24 ± 1.18	64.8 (63.7–65.8)	13.8 (13.0–14.5)
All symptoms	*4.60 ± 3.83*	*84.4 (83.6–85.2)*	*28.7 (27.7–29.7)*
Urogenital domains			
9. Sexual problems	0.90 ± 1.16	46.6 (45.6–47.7)	10.8 (10.2–11.5)
10. Bladder problems	0.76 ± 1.07	42.1 (41.0–43.1)	8.2 (7.6–8.8)
11. Dryness of vagina	0.89 ± 1.15	45.9 (44.9–47.0)	11.2 (10.5–11.9)
All symptoms	2.54 ± 2.72	*66.4 (65.4–67.4)*	*31.3 (30.3–32.3)*
Total	*11.27 ± 8.54*	*90.9 (90.2–91.5)*	*24.9 (24.0–25.8)*

instrument, a severe impact on QOL is expected if the somatic-vegetative score is >8, the psychological is >6, the urogenital is >3, and the total MRS score is >16 [3].

Table 5.1 shows the score and the prevalence of climacteric symptoms evaluated with the Menopause Rating Scale in 8373 otherwise healthy women aged 40–59 years from 12 Latin American countries [4]. If we analyze separately each menopausal symptom, the most prevalent discomfort was joint/muscular discomfort, affecting 63% of women and reaching a severe intensity in 15.6% of them. Another prevalent symptom was physical mental exhaustion, with severe intensity in 13.8%. Other complaints of the psychological area are irritability, depressive mood, and anxiety, which globally provide 40.8% of the MRS total score, which constitutes it as the MRS domain with the greatest clinical deterioration in this report. Sleep problems affect 59.0% of women, with intense severity in 13.2% of them. The classical vasomotor symptoms, however, rank ninth among the 11 symptoms evaluated by the MRS scale; in Europe, instead, it is the most prevalent symptom of postmenopausal women, affecting 74% of them [5]. Finally, urogenital symptoms, although ranking in the last position, reach a high intensity in 31.3% of the women. Globally, 24.9% of this population reached a total MRS score >16, which means that these symptoms severely affect QOL [3]. Let us follow analyzing insomnia and musculoskeletal pain.

5.2 Insomnia

Sleep disorders are highly prevalent in the general population mainly in females and particularly in persons with impaired physical or mental health [6, 7]. Therefore, it is not surprising that the deterioration of the QOL associated with climacteric is

associated with a high risk of sleep disorders. The Study of Women's Health Across the Nation (SWAN), a multiethnic sample of 12,603 women, demonstrated that 38% of women aged 40–55 years presented with sleep disturbances and that menopause was significantly associated with sleep disorders [8]. This high percentage of insomnia in middle-aged women contrasts with prevalence of only 18% found in the general population [9].

Insomnia strongly affects the QOL. A German study, using the Short Form 36 Health Survey (SF-36), reported that only 3% of the interviewed who did not complain of insomnia had a bad QOL, but this percentage increased to 22% in those reporting insomnia [10]. Another study including three matched groups of severe insomniacs, mild insomniacs, and good sleepers recruited from the general French population, after eliminating those with DSM-IV criteria for anxiety or depression, showed that severe insomniacs had lower quality-of-life scores in eight dimensions of the SF-36 in comparison to mild insomniacs and good sleepers [11].

Considering that the SWAN study showed a significant variation in the prevalence of sleep disorders among different ethnics, from 28% in Japanese women to 40% in Caucasian women [8], we intended to study the sleep disorder prevalence in Latin America [12]. In Table 5.2 it is shown that almost half of these women presented insomnia and/or bad sleep quality.

However, it is difficult to compare these results with other studies, since the methodologies used are different. One of the most cited references is the Kravitz' study [8] which shows that 38% of women in the United States suffer from "sleep difficulty," but this classification was based on a single question: "Over the past 2 weeks, have you experienced difficulty sleeping?" Another study [13], conducted in Latin America using the ISI test (Insomnia Severity Index), revealed that 41.5% of women aged 40–55 years had insomnia, almost identical to the 43.6% prevalence found when we applied the Athena's scale to women of the same age. In a Japanese

Table 5.2 Impact of age and climacteric status on insomnia and sleep quality

	Women 6079	Insomnia[a] % (IC 95%)	Poor sleep quality[b] % (IC 95%)
Age (years)			
40–44	1175	39.7 (36.9–42.5)	40.3 (37.4–43.1)
45–49	1692	43.1 (40.7–45.5)	45.3 (42.9–47.7)
50–54	1761	45.4 (43.0–47.7)	48.5 (46.1–50.9)
55–59	1451	45.2 (42.6–47.8)	49.3 (46.7–51.9)
p<		0.009[c]	0.0001[c]
Stage of menopause			
Premenopause 40–44 years	711	39.5 (35.9–43.2)	38.8 (35.2–42.5)
Premenopause ≥45 years	949	36.5 (33.4–39.6)	41.0 (37.9–44.2)
Perimenopause	916	41.7 (38.5–45.0)	43.7 (40.4–47.0)
Early postmenopause	1758	47.4 (45.0–49.7)	48.5 (46.1–50.8)
Late postmenopause	1745	46.3 (43.9–48.7)	51.1 (48.7–53.5)
p<		0.0001[c]	0.0001[c]

[a]Athens Insomnia Scale: score ≥6
[b]Pittsburgh Sleep Quality Index: score ≥5
[c]Square chi

study the sleep quality was self-rated by the participants in terms of sleep duration, sleep onset, sleep satisfaction, and number of awakenings per night, concluding that 50.8% of peri- and postmenopausal women presented insomnia [14]. Another study in Turkey, using the Women's Health Initiative Insomnia Rating Scale, showed that the prevalence of sleep disturbance in women from 45 to 59 was 54% [15]. Summarizing, our results are in accordance with other studies conducted in different places in the world, in spite of the usage of different methodologies showing that almost half of middle-aged women present sleep disorders.

Many women and their clinicians think that sleep worsens around the menopause. However, there is some controversy. A well-regarded epidemiological study found that menopause does not worsen sleep quality [16]. Kalleinen, using objective methods to evaluate sleep quality as polysomnography, and specific questionnaires, found that postmenopausal women had worse sleep quality than younger women (20–26 years old), but he believes that these changes may be more because of the physiology of ageing than the rapid changes across the menopause, since similar sleep characteristics were already present in the premenopausal women [17]. We found that menopause slightly increased the risk of insomnia and it also increased somewhat more the poor quality of sleep (Table 5.2). Analyzing the different items of the Athens scale the factor which has a greater impact in the total score was awakening during the night and the item which shows the greatest increment in late postmenopause is difficulty with sleep induction. A Korean study agrees with our study showing that the most common symptom of insomnia was difficulty maintaining sleep (9.7%), followed by difficulty initiating sleep (7.9%), and early morning awakening (7.5%) [18]. This last study, as well as ours, has shown that the diurnal impact of the sleep disturbances is rather low in postmenopausal women. We may conclude stating that the menopause slightly deteriorates the sleep quality, mainly awakening during the night and sleep induction, disorders that have low impact on diurnal activities.

Although it seems that the menopause does not severely affect the prevalence of sleep disorders, our results show that the most characteristic symptom of menopause, hot flushes, is significantly associated with a higher prevalence of insomnia (Table 5.3). Furthermore, the prevalence of sleep disorders shows a parallel increase with vasomotor symptom intensity, which may increase the risk of presenting insomnia in those women with severe vasomotor symptoms.

Table 5.3 Relationship between intensity of VMS and sleep disturbances

Intensity of VMS score (MRS)	No women	Athens insomnia scale		
		Score mean ± SD	Insomnia % (CI 95%)	OR (CI 95%)
0	2708	4.42 ± 4.63	32.2 (30.4–34.0)	10.00
1	2097	5.81 ± 4.49	48.1 (46.0–50.3)	1.96 (1.73–2.21)
2	934	7.13 ± 5.07	57.6 (54.4–60.8)	2.87 (2.45–3.35)
3	266	8.31 ± 4.90	67.7 (61.7–73.3)	4.41 (3.33–5.85)
4	74	9.34 ± 5.78	70.2 (58.4–80.2)	4.99 (2.92–8.57)
p<		0.0001[2]	0.0001[3]	0.0001[3]

VMS vasomotor symptoms, *MRS* Menopause Rating Scale; *p*: 1: ANOVA; 2: Mann–Whitney; 3: Square chi tendency. Score SVM: 0: none, 1: mild, 2: moderate, 3: severe, 4: very severe

This association has been described by several authors [8, 13, 19] as well as the direct relationship between hot flush severity and a higher prevalence of insomnia [20]. The discrepancy between studies showing no or minimal impact of the menopause on insomnia, and the belief of physicians or patients concerning this topic, could be due to the fact that physicians see symptomatic patients with intense hot flushes, who are those who present more insomnia. On the contrary, in the epidemiological studies there are some women without hot flushes, which generally have lower prevalence of sleep disorders. In the same sense, insomnia was reported by 37.2% in France and Italy, 27.1% in the United States, and 6.6% in Japan [21], considering that Japanese women present with a lower prevalence of vasomotor symptoms than occidental ones [22].

Furthermore, we have observed that insomnia not only is associated to a higher risk of vasomotor symptoms, but also to other climacteric related symptoms (Table 5.4). As hot flushes do, the risk of insomnia increases with the severity of psychological symptoms, and the risk of insomnia also correlates with the severity of insomnia. Anxiety has been associated to a fourfold increment in the risk of insomnia in the general population [23]. Depression occurs more commonly during the menopausal transition in women with vasomotor symptoms (VMS) than in those without [24], but most women with VMS do not develop depression. It has been hypothesized that VMS are associated with depression because VMS lead to repeated awakenings, which impair daytime well-being; nevertheless, sleep disturbances seen in depressed participants were not consistent with the etiology of depression secondary to VMS-associated awakenings [25]. In the same way, a study from Zervas et al. noted that mood symptoms seem to affect sleep, independently of vasomotor symptoms [26]. Therefore, we could speculate that psychological and vasomotor symptoms as well as sleep disorders in postmenopausal women are independent but related entities, since all of them are triggered by a common cause: estrogen decline [27]. The three disorders above mentioned have been linked with estrogen deficiency in the central nervous system. Therefore, changes in estradiol

Table 5.4 Risk factors for insomnia (Athens scale). Logistic regression analysis

Insomnia	OR	CI 95%
Troublesome drinker	5.27	1.14–24.51
Anxiety (Goldberg)	3.57	3.09–4.14
Depression (Goldberg)	2.39	2.10–2.72
VMS	2.10	1.86–2.38
Hypnotics	1.62	1.52–1.73
HT	1.41	1.18–1.68
Diabetes	1.37	1.11–1.68
Education >12 years	0.84	0.74–0.95

Logistic regression variables: depression (Goldberg), anxiety (Goldberg), smoker (>4 cigarettes/day), troublesome drinker, obesity, hypertension, diabetes, CPOD, older ≥50 years, menopause, surgical menopause, VMS, HT, use of contraceptives, use of hypnotics, stable partner, education (>12 years)

VSM vasomotor symptoms, *HT* hormone therapy, *CPOD* chronic pulmonary obstructive disease

levels induce an elevated sympathetic activation acting through central alpha(2)-adrenergic receptors contributing to the initiation of hot flashes, possibly by narrowing the thermoneutral zone in symptomatic women; hot flashes are then triggered by small elevations in core body temperature acting within this narrowed zone [28]. The increased risk of menopause-associated depression enables us to postulate that depression is caused by the effect of fluctuations in estradiol on neurotransmitter system in brain regions that regulate mood [29]. Anxiety has been linked to four neurotransmitter systems which are affected during menopause: gamma amino-butyric acid, serotonin, noradrenaline, and dopamine [30]. Regarding insomnia, dopamine and serotonin are involved in sleep regulation [31]. Estrogen-related changes in serotonergic neuronal transmission, including changes in the number of serotonin transporter (SERT) binding sites, have been cited as a possible cause for changes in sleep, mood, and memory which occur during the menopausal transition [32]. Furthermore, selective serotonin depletion in the brain, a neurotransmitter classically involved in depression, is associated to insomnia in experimental animals [33].

Among the different risk factors for insomnia, in our logistic regression model, alcoholism appears as a strong independent factor. Cohn et al., had pointed out that in 57 abstinent alcoholics, 52 had sleep disorders [34]. Another factor associated with sleep disorders in our study was the use of hypnotics; however, this observation of a poor response of a proved efficacy therapy has been already reported in the literature for MHT [24] and for hypnotics themselves [35]. The possible explanation is that users of a drug to control sleep disorders are those who present the greatest symptomatology and, although the therapy improves the symptom, the irregular use of them, or the lack adaptation of the doses to the patient needs, can cause the symptom persistence in a greater magnitude than the average. Regarding the use of hypnotics in insomniacs, a study with peri- and postmenopausal women showed that these drugs improved the sleep disturbances [36]. MHT in that study also improved insomnia, but in our study that situation did not happen; one explanation could be the fact that Latin American women have a high prevalence of hot flushes, a risk factor for insomnia, while the study previously mentioned was done in Asiatic women who are known to have less vasomotor symptoms [22] and in them MHT could have better results on sleep quality considering they are less symptomatic. The logistic regression analysis also showed the high impact of depression and anxiety on the risk of sleep disorders. Finally, our study confirmed that educational level exerts a protective role against insomnia, a finding that was also detected in a Brazilian study [37].

Classically, MHT has been considered an effective treatment for sleep disorders, but very few studies have applied specific instruments to evaluate this problem, and most of them include a rather low number of cases [38–41]. It is biologically plausible that MHT had a positive sleep effect, since estrogen contributes to sleep through metabolizing norepinephrine, serotonin, and acetylcholine, which consequently increases REM cycles. Progesterone stimulates benzodiazepine receptors, causing the release of gamma-amino butyric acid (GABA), a sedating neurotransmitter that can potentially facilitate sleep [42]. Contradicting the evidence that MHT

improves sleep, the WHI study showed the opposite, i.e., hormonal therapy had no effect on sleep disorders [43]. However, this study has a selection bias since women recruited for the study had only mild symptomatology and for that reason they should have had less sleep disorders. Even more, the WHI study showed that in the subgroup of women 50–54 years of age with vasomotor symptoms at baseline, estrogen and progestin resulted in beneficial effect on sleep disturbance.

We may conclude saying that the sleep disorders are highly prevalent in middle-age women and affect their QOL. Hypoestrogenism is one of the factors involved in sleep quality deterioration observed in menopausal women. MHT could contribute to the improvement of insomnia in symptomatic postmenopausal women.

5.3 Muscle and Joint Aches

The International Association for the Study of Pain declared the year 2010 as the "year against muscle skeletal pain," reflecting the relevance of this type of discomfort in different populations around the world. It is not surprising since these symptoms are highly prevalent in the general population, and they are a serious public health problem which strongly impaired work capacity and QOL [44] and overload health systems [45] and have a high cost for companies [46]. It involves 10% of the general population, but affects preferentially women, starting at the median age [47]. The SWAN study also showed this problem as the main menopausal symptom, affecting 54.3% of women 40–55 years old [48]. In Thailand, it is also the most prevalent symptom and affects 56.4% of postmenopausal, during the first year of amenorrhea [49]. In Latin American, we have found the same complaint in 63% of women 40–59 years old (Table 5.1) [4].

In a study whose objective was to evaluate the risk factors associated to muscle and joint aches in middle-age women, we found that the presence of vasomotor symptoms strongly increased the risk of this symptom (Table 5.5) [50]. The association between vasomotor symptoms, a condition undoubtedly related to hypoestrogenism [51], and the presence of pain could suggest that in the pathogenesis of both symptoms could underlie common metabolic disorders. Furthermore, it has been observed that severity of muscle and joint aches correlates with a higher sympathetic activity in the CNS [52]. Coincidentally, this same disorder has been considered as a central element in the pathogenesis of vasomotor symptoms [28]. An elevated sympathetic activation acting through central alpha (2)-adrenergic receptors contributes to the initiation of hot flashes, possibly by narrowing the thermoneutral zone in symptomatic women; hot flashes are then triggered by small elevations in core body temperature acting within this narrowed zone.

When a middle-aged woman complains of diffuse muscle and joint aches, pain or stiffness associated with tiredness, anxiety, and poor sleep, the diagnosis of fibromyalgia is postulated. In its pathogenesis could be involved disorders in the neurotransmission linked both to pain perception and modulation of mood, sleep, and cognition. Cumulative evidence points to alterations in neurotransmitter systems in fibromyalgia, which is interesting because the main symptoms of

Table 5.5 Risk factors related to muscle and joint aches[a]: logistic regression analysis

Risks factors	Odds ratio	95% CI
Severe VMS[b]	6.27	5.34–7.36
History of psychiatric consulting	1.95	1.62–2.34
Premature menopause	1.73	1.13–2.65
Postmenopausal	1.20	1.11–1.29
Age ≥50 years	1.41	1.20–1.66
Use of psychotropic drugs	1.39	1.11–1.74
Current smoker	1.22	1.04–1.43
Education ≤12 years	1.16	1.01–1.34
Living at high altitude (>2500 m)	0.83	0.72–0.95
Sexually active	0.81	0.69–0.92
HT use	0.76	0.63–0.92
Access to private healthcare system	0.75	0.65–0.85
Good health (self-perception)	0.49	0.40–0.58

VSM vasomotor symptoms, *HT* hormone therapy, *OR* odds ratios, *CI* confidence intervals. Nonsignificant variables: nulliparity, stable partner, surgical menopause, use of contraceptives, alternative therapies, use of IUD, attending church ceremonies, living in cities with average maximum temperatures ≥30 °C

[a]Score MRS11 = 3 or 4

[b]Score MRS1 = 3 or 4

fibromyalgia are closely linked to neurotransmitters [53]. For example, central serotonin and noradrenalin are important in endogenous pain inhibitory pathways, substance P is a neuropeptide that is important for spinal nociception, and glutamate plays an important role in nociception, as it has excitatory and sensitizing effects. Levels of serotonin, dopamine, and noradrenaline appear to be reduced, possibly contributing to dysfunctional descending pathways and resulting in attenuated descending inhibition. Tricyclic antidepressants, dual inhibitors of serotonin/noradrenalin reuptake, and pregabalin are treatments which could be effective to decrease pain and fatigue.

If we compare fibromyalgia and climacteric, we can observe that both conditions are very similar in terms of symptoms, pathogenesis, and response to treatment. Both conditions are observed in women older than 40 years, in their pathogenesis changes in neurotransmitters and autonomic system are involved, symptomatology is almost identical, and both respond to estrogens and partially to antidepressants. Therefore, it seems reasonable to believe that an important percentage of fibromyalgia patients are women with climacteric symptoms, many of them even in the premenopausal period [54].

The relationship between pain and estrogens has been suspected noting that women have 2–6 times more prevalence of pain, in comparison with men. Phylogenetically, estrogen is the first hormone that appears in the primitive living being 500 million years ago, fulfilling a role in homeostatic systems which contribute to bodily integrity, modulating intracellular signals that cause motor responses to avoid damage (nociception) [55].

Estrogen receptor alpha is observed in the dorsal horn of the spinal cord in humans, where they are also essential in nociception, reducing glutaminergic

transmission and inhibiting pain perception. Furthermore, estradiol increases the expression of opioid mRNA in the spinal cord, blocking the sense of pain. But it does not only act in the nociceptive circuit in the spinal cord, but also in the transmission paths to the cortex, inhibiting the sense of pain, and at the CNS level it acts in different pain-related areas such as thalamus, anterior cingulate cortex, and dorsal posterior insula [56].

Estrogen declination during climacteric, through their effects on the pain pathways, could be the cause of the increase in muscle and joint aches observed in middle-age women. Another fact which reinforces this relationship would be the decrease in the sense of pain associated to MHT. The most important RCT done until now, related to HMT, has been the Women's Health Initiative (WHI), a trial including 16,608 postmenopausal women, mean age 63.3 years, randomized to 0.625 mg conjugated equine estrogen plus 2.5 mg medroxyprogesterone acetate or placebo. Changes in symptoms and treatment-related effects were analyzed at year 1 in all participants. It was observed that women assigned to MHT reported relief of joint pain or stiffness, and general aches or pain [57]. Another RCT using raloxifene, a selective estrogen receptor modulator (SERM), in patients with fibromyalgia showed that this drug, which mimics estrogen action, was also associated to a greater improving in pain and fatigue, and compared to placebo produced a significant decrease of the tender point counts and sleep disturbances and gave the possibility to reinsert in their usual activities [58]. On the contrary, it has been reported that 23% of women using aromatase inhibitors, which is associated to a profound hypoestrogenism, experience musculoskeletal symptoms [59]. Finally, a last observation in agreement with the hypothesis described above is the fact that the increase in muscle and joint aches after MHT discontinuation has been reported [60].

We can conclude by saying that there is a high prevalence of muscle and joint aches in middle-age women, and that there is a strong parallelism between these symptoms and other variables associated with the climacteric status, mainly hot flushes. This relationship could suggest that hypoestrogenism could be involved in muscle and joint ache pathogenesis in postmenopausal women. The role of estrogens is related with the pain pathway modulation. MHT is associated to a lower risk to present osteomuscular pain. Clinical randomized trials are required to evaluate the eventual utility of HTM in the treatment of muscle and joint aches in middle-age women.

Conclusions

Vasomotor symptoms are not the most frequent symptom in menopause. Both insomnia and muscle and joint aches are the most prevalent symptoms and they could significantly deteriorate the QOL in middle-aged women. In its pathogenesis, different peripheral and central neural mechanisms are involved. Menopausal hormonal therapy is an alternative that may arise to treat these symptoms, particularly when menopausal symptomatology is varied and severe.

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Genitourinary Syndrome of the Menopause: Vaginal Health and Microbiota

6

Maria Jesús Cancelo-Hidalgo and Laura Barrera Coello

6.1 Introduction

Reduced circulating estrogen levels are responsible for most anatomical cytological, bacteriological, and physiological changes that occur in female genital tract in postmenopausal women. These changes can initiate in the perimenopausal period and increase gradually.

The consequent symptoms produced by vaginal and vulva atrophy can cause vulvovaginal and urinary dysfunction that can also affect sexuality and produce changes in quality of life of menopausal women [1].

Otherwise, the term vulvovaginal atrophy related to menopause changes does not represent all symptoms, that's why in 2013 the International Society for the Study of Women's Sexual health (ISSWSH) and the North American Menopause Society (NAMS) determined the need of a new term: the genitourinary syndrome of menopause (GSM) as this will be called from now on [2].

The main objective is to integrate the big variety of signs and symptoms of vulvovaginal area, with the changes that also occur in the urethra and bladder produced because of the low estrogen levels. These symptoms, opposite of vasomotor symptoms that yield over the years, will get worse permanently if it is not diagnosed and treated. Because of that adequate knowledge of its physiopathology, the clinical signs, and the available treatments for the health providers is needed.

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6.2 Vaginal Health

Vaginal health is defined as the vaginal state that maintains adequate physiological conditions as women's age passes, which does not produce local symptoms and allows satisfactory sexual life [3]. For this to happen, the integrity of the tissue is needed to be kept and the normal function of vaginal microbiota should not be disrupted; in both cases, estrogen levels play an important role. These factors influence each other, as represented in Fig. 6.1.

The vagina is an organ that has limited physiological functions, but besides this, it becomes a main factor for women on wellness perception and quality of life. If it gets affected during periods of low estrogen levels it means the starting of bothering symptoms that interrupt women's sexual life.

Vagina has a double-embryonic origin, from Müller conduct and urogenital sinus [4]. Because of that there is an established anatomical and clinical relation with urinary tract. It does have physiological regulating mechanisms on defensive processes. Estrogens have an important influence on this mechanism related to vaginal health and these change along the different age phases of women [5].

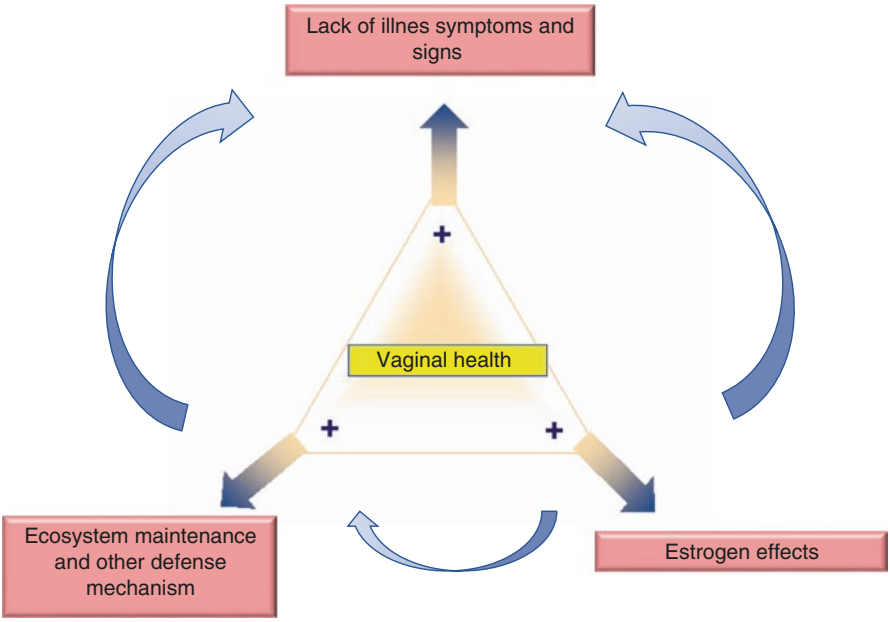


Fig. 6.1 Simple representation of factors related to vaginal health

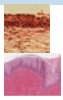
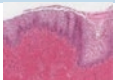
	New born	Childhood	Puberty	Fertile ages	Pregnancy	Menopause
Estrogens	++	- -	- +	++	+++	+ -
Epithelium						
Glycogen	+	- -	- +	+	++	+ -
pH	4-5	7	7 → 5	4-5	3.5-4,5	6
Microbiota	No	Low	Mixed	Lactobacilli	Lactobacilli	Mixed

Fig. 6.2 Schematic representation of the vaginal changes present in the vagina in the different vital stages of the woman

Figure 6.2 shows physiological changes that take place in the vagina along these different age phases.

6.3 Microbiota

Vaginal microbiota is the whole microorganisms (bacterium and yeast) that colonize vaginal site and create the balanced vaginal ecosystem.

First studies about human vaginal microbiology, published by Döderlein in 1892 [6], described lactobacilli as the dominating organisms in vaginal habitat.

Furthermore, these other species coexist in a delicate balance in healthy women.

Disturbing this balance, because of reduction on lactobacilli levels or because of the overgrowth of other species, will introduce the presence of symptoms and signs related to vaginitis or vaginosis and it is known as dysbiosis.

Most of its components are normal in intestinal habitat, which means that gastrointestinal tract could act as a reservoir of these agents. However, related frequency of present species in the vagina and in the bowel very different [7]. Vaginal microbiota are formed by different aerobic and anaerobic species, standing out lactobacilli, which are dominant in the vagina and are minority in the bowel, even being exclusive in vagina in some cases. Generally, the percentage of samples of vaginal exudate that presents predominance of the lactobacilli is superior to 70%. This percentage maintains when samples are processed with the use of either cultivation or genotyping [8] as if it is done by methods of genotyping [9]. On the other hand, the strict anaerobic Gram-positive or Gram-negative bacteria of the Clostridium-Eubacterium and Bacteriodes-Prevotella groups, which dominate the intestinal habitat, appear sporadically in the vagina, suggesting that in this mucus they are passersby rather than colonizers.

6.3.1 Lactobacilli: General Characteristics

Lactobacilli are considered to play a critical role in maintaining the vaginal ecosystem by preventing the overgrowth of other microorganisms such as *Gardnerella vaginalis*. They would also prevent colonization by pathogens or yeasts responsible for the production of infections.

Lactobacilli form a wide and heterogeneous group of lactic acid bacteria, characterized by being Gram positive and non-sporulated and with a strictly fermentative catabolism of sugars, which is a predominant end product in the production of this organic acid. Morphologically they vary from elongated to short forms and from straight to curved.

In general, they are aerotolerant anaerobic bacteria. They have small genomes, so they are very nutritionally demanding. Undoubtedly, their harmlessness as infectious agents is also partly due to this scarcity of genetic information; for example, genes coding for virulence factors have not been described in any of the sequenced strains.

The bacteria count in the vaginal fluid is around 100,000 per mL. With genomic sequencing techniques, about 250 species of bacteria have been identified in the vagina [10].

Table 6.1 shows a summary of the most frequent species present in the vagina of healthy women. General patterns of vaginal microbiota have been identified, which tend to differentiate between women with and without vaginosis [11].

Lactic microbiota is formed by the general lactobacillus and bifidobacterium, whose role is to acidify the medium and to compete with other microorganisms, some of which are potentially pathogenic, so that while they are present, they limit the overgrowth of these (vaginosis) [12].

Table 6.1 Most frequent species of microorganisms present in the vagina of healthy women

Present microorganisms in healthy women vagina	
Cocci and bacilli Gram + optional anaerobes	Lactobacillus
	Streptococcus
	Corynebacterium
	Gardnerella
	Staphylococcus
Bacilli Gram—optional anaerobes	Escherichia
	Klebsiella
	Proteus
Cocci and bacilli Gram + strict anaerobes	Atopobium
	Peptococcus
	Peptostreptococcus
	Clostridium
	Bifidobacterium
	Propionibacterium
	Eubacterium
Bacilli Gram—strict anaerobes	Bacteroides
	Prevotella
Mycoplasma	Mycoplasma hominis

Several species of lactobacilli have been identified. The vagina is colonized preferably by *L. acidophilus*, *L. fermentum* but *L. crispatus*, *L. gasseri* and *L. jensenii*, *L. iners*, and *L. vaginalis* [13].

6.3.2 Interaction of Lactobacilli with the Vagina

Lactobacilli species is dominant in fertile women's vagina and prevents the colonization of the mucus by undesired microorganisms, generators of urogenital pathology. However, it has been found that women colonized by alternative bacteria such as atopobium or others [14] appear to be protected as well, although lactobacilli species is still considered to be essential for the maintenance of vaginal homeostasis and it is the main candidate for use in replacement therapies during pathological conditions that affect vaginal habitat [15].

6.3.3 Mechanisms of Protection Performed by the Microbiota

Various mechanisms of action of the microbiota show a protective effect on the vagina (Table 6.2).

6.3.4 Breakage of the Balance of the Vaginal Ecosystem. Pathophysiology of Vaginitis and Vaginosis

The rupture of the balance between lactobacilli and other microorganisms is the pathophysiological mechanism of vaginitis and vaginosis. But it is not entirely clear whether the reduction or disappearance of lactobacilli is a cause or result of the proliferation of other microorganisms. Several factors were related to alterations of the microbiota (Table 6.3).

When the concentration of lactobacilli in the vagina decreases below a critical level, this circumstance is exploited by microorganisms that are usually found in the healthy vagina or by others of exogenous origin, which will proliferate until becoming dominant, thus behaving as opportunistic pathogens [17].

Table 6.2 Mechanisms of protection attributed to the microbiota

Protective mechanisms performed by the microbiota
Adhesion to the vaginal epithelium and inhibition of colonization by unwanted organisms (adhesins)
Vaginal pH modification
Formation of hydrogen peroxide
Production of bacteriocins
Formation of surfactants
Production of coaggregates
Biofilm formation

Table 6.3 Factors associated with microbiota alterations [16]

Factors associated with microbiota alterations	
Stress	
Inflammation	
Age	
Exercise	
Use of antibiotics	
Type of diet	Reduction of carbohydrates
	Restrictive hypocaloric diets (strict vegetarian)
	Low fiber content
	High in fats and sugar

Clinical symptoms that have been associated to the decrease of lactobacilli on the vaginal epithelium are:

1. Bacterial vaginosis, whose most common etiological agents are *Gardnerella vaginalis*, *Mycoplasma hominis*, Prevotella, and Peptostreptococcus
2. Candidiasis, produced by *Candida albicans* in 85% of cases, *C. glabrata*, and *C. tropicalis*
3. Trichomoniasis, a consequence of the proliferation of *Trichomonas vaginalis*
4. Lower urinary tract infections (UTI), mainly caused by enterobacteriaceae of intestinal origin such as *Escherichia coli* which is responsible for at least 80% of the cases, although sometimes Gram-positive cocci are isolated like *Enterococcus faecalis*

Although UTIs are not specifically genitals, their presence and relapse have been linked to alterations in the vaginal ecosystem. It has been determined that the urinary tract infection is practically always preceded by vaginal colonization by the urinary pathogens [18].

The frequency of UTI is inversely proportional to the presence of a normal microbiota, dominated by lactobacilli, in the vagina of healthy women. An attractive idea is to consider that the anatomical proximity and functional interrelations of the urinary, gynecological, and digestive systems for the evaluation of perineal symptoms (urinary, vaginal, and digestive) of the woman should be considered in an integral way. The microbiota is a clear example of this, being verified how modifications of the intestinal, vaginal, or urinary habitat can affect each other [19].

Table 6.4 summarizes the exogenous and endogenous factors that can modify the vaginal microbiota.

6.3.5 Estrogens and Vagina

Vaginal atrophy is caused primarily by an estrogen deficiency. It acts on the vagina, vulva, urethra, and trigone of the bladder via estrogen receptors on these structures. Estrogen helps to maintain the collagen content of epithelium and thus effects on

Table 6.4 Factors that can modify the vaginal microbiota

Exogenous factors	Endogenous factors
Sexual activity	Menstruation
Use of antibiotics	Variation of hormone levels
Use of soaps, deodorants …	Local and systemic immunity
Vaginal showers	Systemic diseases
DIU	Cofactors: tobacco
Gynecological interventions	

thickness and elasticity; it helps to maintain acid mucopolysaccharides and hyaluronic acid, which keep epithelial surfaces moist. Estrogens maintain optimal vaginal blood flow.

The vaginal epithelium becomes dry and atrophic and loses elasticity which may cause inflammation, itching, burning, dryness, bleeding, spotting, dysuria, dyspareunia, urinary incontinence, and recurrent (UTIs). The vulvar skin can become thinner; the labia flatten and shrink; and the clitoris, uterus, and ovaries decrease in size.

The bladder, urethra, pelvic floor musculature, and endopelvic fascia are affected by a hypoestrogenic state because they contain estrogen receptors [20]. Possible consequences of advanced atrophy of the urinary tract include urethral discomfort, frequency, hematuria, and dysuria. UTI is more common. The laxity from estrogen loss causes pelvic floor and organ prolapse.

Anatomic and histologic changes occur in female genital tissues, including reduction in the content of collagen and hyaluronic acid and in the levels of elastin, thinning of the epithelium, alterations in the function of smooth muscle cells, increase in the density of connective tissue, and fewer blood vessels. These changes reduce elasticity of the vagina, increase vaginal pH, lead to changes in vaginal flora, diminish lubrication, and increase vulnerability to physical irritation and trauma.

Glycogen is the substrate for Döderlein's lactobacilli, which convert glucose into lactic acid, thereby creating an acidic vaginal environment. The pH of an estrogen-primed vagina ranges from 3.5 to 5.0. This acidic range helps protect the urogenital area from vaginal and UTIs. The low glycogen content of the thinned epithelium leads to a reduction in lactic acid production by lactobacilli, resulting in an increase in vaginal pH that encourages the overgrowth of coliforms and other pathogen agents such as Candida, bacterial vaginosis, and Trichomonas. The vagina is more vulnerable to inflammation or infection and easily traumatized.

About the lower urinary tract, the urethra of the woman is covered to the full extent by a thick, nonkeratinized squamous epithelium similar to that of the vagina. Also like the vagina, the epithelium of the female urethra, although not the subepithelial layer, expresses abundant estrogen receptors, which are completely absent in the contiguous urothelium of the bladder except in the part of the trigone [21].

Lack of awareness of the association between recurrent UTIs and GSM may result in multiple unnecessary courses of antibiotic therapy, antibiotic prophylaxis, and altered patterns of antimicrobial drug resistance [22].

Hence there is the importance of the new terminology adopted to refer to the genitourinary menopause syndrome, integrating both systems into one unit.

6.4 Genitourinary Syndrome of Menopause: Justification of Terminology

The genitourinary syndrome of menopause describes various symptoms and signs associated with physical changes of the vulva, vagina, and lower urinary tract related with menopausal estrogen deficiency. It includes not only genital symptoms (dryness, burning, and irritation) and sexual symptoms (lack of lubrication, discomfort, or pain), but also urinary symptoms (urgency, dysuria, and recurrent urinary tract infections).

The terms *vulvovaginal atrophy* or *atrophic vaginitis* have been considered to be inadequate for referring to the constellation of symptoms and signs associated with estrogen deficiency because they imply a state of inflammation or infection and they do not take into account the symptoms of the lower urinary tract. For this reason, the Board of Directors of the International Society for the Study of Women's Sexual Health (ISSWSH) and the Board of the North American Menopause Society (NAMS) held a terminology consensus conference in 2013.

Because of their relationship with menopause, the genitourinary symptoms tend to affect younger women suffering induced hypoestrogenic states. Surgical menopause, use of gonadotropin-releasing hormone (GnRH) agonists, hypothalamic amenorrhea, or women under oncological treatments, like chemotherapy, pelvic radiation, or endocrine therapy, are good examples [23].

6.4.1 Prevalence

Vulvovaginal symptoms are directly related to the reduced circulating estrogen levels after menopause [24]. A 45-63% of postmenopausal women –dependending on the series- may be affected [25], the most common symptom being vaginal dryness; other symptoms include dyspareunia, vaginal irritation, itching sensation, vaginal tenderness, and vaginal bleeding or spotting during intercourse. Cultural, religious, and social influences may play a role in making women feel uncomfortable discussing concerns related to the genitourinary system. Moderate or severe symptoms can contribute to sexual dysfunction and loss of sexual intimacy and may have a negative impact on the overall quality of life [26]. Dyspareunia leads to decreased interest in coitus, and as the frequency of coitus diminishes, vaginal lubrication declines further. They make lifestyle changes such as stopping of sexual activity to avoid dyspareunia caused by vaginal dryness and pain.

In Spain data from an online survey (REVIVE) shows that the most troublesome symptom is dyspareunia (80%). Vulvovaginal atrophy symptoms significantly impact the ability to achieve sexual enjoyment (75%), relationship with partner (67%), and sexual spontaneity (66%) [27].

Estrogen deficiency after menopause causes the lower urinary tract symptoms such as dysuria, urgency, frequency, nocturia, urinary incontinence (UI), and recurrent UTI.

The incidence of UTI rises in elderly women. Studies have shown that 15–20% of women aged 65–70 years and 20–50% of women aged >80 years have bacteriuria [28]. Postmenopausal and premenopausal women may have different risk factors for UTI. Sexual intercourse is the most common cause among younger women. In older women anatomic changes such as a cystocele and diabetes are the more frequent risk factors for recurrent UTI [29].

6.4.2 Diagnosis

The diagnosis is based on history and findings at physical examination [30] (Table 6.5). Atrophic vaginal epithelium appears pale, dry, smooth and shiny, with loss of most rugation. Often, inflammation may be present with erythema, petechiae, and increased friability and bleeding. Ecchymoses and minor lacerations peri-introitally may also occur after coitus or during a speculum examination, resulting in vaginal bleeding or spotting [31]. The vagina may be shortened, narrowed, and poorly distensible. The vaginal fornices become obliterated. External genitalia show diminished elasticity, with skin that appears with less turgor, sparsity of pubic hair, dryness of labia, vulvar dermatoses, vulvar lesions, and fusion of the labia minora. The friable and poorly rugated vaginal epithelium is more prone to traumatic damage. Similar symptoms can be caused by infective processes, desquamative inflammatory vaginitis, inflammatory conditions, or allergic reactions due to environmental agents such as soaps, perfumes, deodorants, pads, spermicides, lubricants, or synthetic clothing [32]. Papanicolaou smear may confirm the presence of urogenital atrophy by showing an increased proportion of parabasal cells and a decreased percentage of superficial cells (a high maturation index value) and can be similar to those observed in women with squamous intraepithelial neoplasia. Vaginal pH of ≥5 of the vaginal vault in the absence of other causes, such as infection or semen, can be considered an indicator of vaginal atrophy due to estrogen deficiency.

Laboratory tests are unnecessary, and not diagnostic of SGUM.

A quantitative assessment of vaginal health can be performed by using the Vaginal Health Index [33] (Table 6.6). This system is used to evaluate vaginal elasticity, fluid volume, pH, epithelial integrity, and moisture on a scale of 1–5.

Table 6.5 Symptoms and signs of GSM

Symptoms	Signs
Decreased lubrication	Decreased elasticity
Genital dryness	Loss of moisture
Irritation, burning or itching	Loss of vaginal rugae
Dysuria, urinary frequency, and urgency	Labia resorption
Discomfort or dyspareunia	Tissue fragility, petechiae
	ITUs

Table 6.6 Vaginal health index score

Score	1	2	3	4	5
Elasticity	None	Poor	Fair	Good	Excellent
Fluid volume (pooling of secretion)	None	Scant amount, vault not entirely covered	Superficial amount, vault entirely covered	Moderate amount of dryness (small areas of dryness on cotton tip applicator)	Normal amount (fully saturates on cotton tip applicator)
pH	≥6.1	5.6–6.0	5.1–5.5	4.7–5.0	≤4.6
Epithelial integrity	Petechiae noted before contact	Bleeds with light contact	Bleeds with scraping	Not friable—thin epithelium	Normal
Moisture (coating)	None, surface inflamed	None, surface not inflamed	Minimal	Moderate	Normal

6.4.3 Treatment

Treatment is indicated for relief of symptoms and reverse atrophic anatomic changes.

6.4.3.1 Nonhormonal Vaginal Therapy

Nonhormonal vaginal lubricants and moisturizers as first-line therapies for women with vaginal atrophy. A combination of vaginal moisturizing agents used on a regular basis and lubricants to intercourse can alleviate symptoms of vaginal dryness. These compounds do not reverse the atrophic vaginal changes but improve coital comfort and maintain vaginal secretions. Such drugs are indicating for women with mild symptoms [34].

Mucoadhesive and controlled release formulations consisting of aqueous solutions containing 0.05–5% by weight of a natural purified polymer having xyloglucan structure and 10–70% by weight of glycerol are suitable for the application on human mucous membranes, such as vaginal mucous membranes, as moisturizing and softening agents or as pharmaceutical release system. The composition is contacted with the vaginal mucous membrane to be moisturized, and that contact is maintained for a time period sufficient to moisturize the contacted area.

Vaginal administration of hyaluronic acid, in terms of mechanisms of action details: The high-molecular-weight hyaluronic acid acts as a protective macromolecule for the vaginal mucosa and also favors the penetration of the low-molecular-weight molecule into deeper vaginal layers [35].

Through the topical remodeling of connective tissue and the production of new collagen, elastic fibers, and other components of the extracellular matrix, laser CO_2 effects appear to significantly relief related symptoms [36].

Other point is the administration of lactobacilli or probiotics as vaginal soft-gel capsule that comprises a quantity of lactobacilli in a solid form that is preserved during insertion into the vagina and released in the warm and moist vaginal

environment, considering the potential of probiotics to reinstate vaginal homeostasis following menopause. Oral and vaginal probiotics hold great promise and initial studies complement the findings of previous research efforts concerning menopause and the vaginal microbiome; however, additional trials are required to determine the efficacy of bacterial therapeutics to modulate or restore vaginal homeostasis [37].

Sexual activity plays a role in maintaining a healthy vaginal epithelium by preserving vaginal elasticity and preventing introital stenosis. Sexual activity, including masturbation, leads to fewer symptoms of atrophic vaginitis [38].

6.4.3.2 Vaginal and Systemic Hormone Therapy

Estrogen is the most effective treatment for women with moderate to severe symptoms of vaginal atrophy, given that atrophy is a direct consequence of a low estrogen level.

Estrogen therapy reverses vaginal atrophy by decreasing vaginal pH and vaginal dryness, thickens and revascularizes the vaginal epithelium, increases vaginal secretions and the number of superficial cells, produces reduction in recurrent UTI, and restores normal vaginal microbiota [39].

Estrogen or combined hormone (estrogen-progestin) therapy is highly efficacious for managing the signs and symptoms of urogenital atrophy. All routes are effective, both systemic and local estrogen replacement. Various forms of estrogen-based therapies have been shown to effectively manage menopausal signs and symptoms, including those associated with vaginal atrophy. The dose and duration of the treatment should be individualized to the woman's specific needs and her degree of vaginal atrophy symptoms. Treatment can be continued indefinitely, although safety data for treatment beyond 1 year have not been established [40].

Lower dose estrogen therapy provides therapeutic efficacy while minimizing adverse effects. Literature supports the use of low dosages of estrogen therapy for effectively relieving symptoms and restoring healthy vaginal cytology in postmenopausal women with vaginal atrophy; nowadays, the tendency is to use the effective minimum dose that combines the biggest therapeutic effect with the lowest adverse effects.

A meta-analysis shows that local, low-dose vaginal therapy is preferred because lower drug doses can be administered to achieve comparable changes in the vulvovaginal epithelium while minimizing estrogen exposure to other organs. Lower drug doses are associated with fewer systemic side effects, such as breast tenderness, withdrawal bleeding, and endometrial stimulation. However, the low estrogen doses recommended for vaginal therapy usually do not achieve serum estrogen levels sufficient for relief of hot flushes or prevention of bone loss [41].

The systemic absorption of vaginal estrogen is conditioned to the vaginal epithelium and the estrogen dose. When the vaginal mucosa is atrophic, it decreases the vaginal epithelium cornified and the absorption is larger.

With the low-dose vaginal estrogen regimens systemic absorption is minimal; thus serum estradiol (E_2) concentrations remain within the normal postmenopausal range and no significant increases in endometrial thickness were observed.

A progestin is probably not necessary to protect against endometrial hyperplasia in women receiving low-dose local estrogen therapy.

A Cochrane review shows that creams, pessaries, tablets, and (E_2) vaginal ring appeared to be equally effective for the symptoms of vaginal atrophy [42].

Vaginal tablets with 25 μg and 10 μg E_2 provided relief of vaginal symptoms, improved urogenital atrophy, decreased vaginal pH, and increased maturation of the vaginal and urethral epithelium. Those improvements were greater with 25 μg than with 10 μg E_2. Both doses were effective in the treatment of GSM vaginitis [43].

The choice of modality for local estrogen administration should be guided by patient preference. A systematic review of 16 randomized trials investigating local estrogen treatment of vaginal atrophy found that creams, pessaries, and rings were all similarly effective in relieving the symptoms.

Vaginal ring is a device consisting of a silastic ring impregnated with (E_2). It is the lowest dose option for delivering estrogen locally to the vagina, 6–9 μg of (E_2) daily for a period of three months. It is estimated that only 10% is absorbed systemically; thus, the systemic effects would be expected to be minimal [44]. The efficacy of this method was similar to that of orally administered estrogen.

Therefore, the vaginal ring results in circulating levels of estrogens similar to the above mentioned vaginal tablets. These tablets follow an insertion protocol that is different to the ring, since they should be introduced into the vagina daily for 2 weeks and then twice per week thereafter. The ultralow-dose of 10 μg is effective for relief of vaginal symptoms [45].

Creams: Vaginal treatment with 0.625 g of conjugated estrogen cream daily for 21 days of two consecutive 28-day cycles resulted in beneficial changes in the vaginal tissues and induced an overall genital health pattern more characteristic of the premenopausal state. Promestriene used vaginally to relieve vaginal atrophy is a locally effective estrogen that has not shown systemic estrogenic effects. Thus, it could be a first-line option for those who necessitate a minimal or ideally no vaginal absorption, particularly in symptomatic cancer patients. After a long-term market experience (almost 40 years), in 34 countries, and millions of pieces prescribed, the side effects were very rarely reported in pharmacovigilance data, whereas the effectiveness to relieve atrophy was good [46].

Crystalline (E_2) can also be given by vaginal applicator at a dose of one-eighth of an applicator or 0.5 g (which contains 50 μg of (E_2)). It should be noted that the maximal doses indicated on the package insert (2.0 g) produce premenopausal plasma levels of (E_2), and should not be used long-term.

In order to obtain a prompt improvement in relieving urogenital symptoms, the association of local therapy acting on the genital epithelium to the systemic treatment should be considered. Adding vaginal estriol to hormone therapy (HT) may shorten the latency period for urinary symptoms [47].

Among women with a history of estrogen-dependent breast cancer who are experiencing urogenital symptoms, vaginal estrogen should be reserved for those patients who are unresponsive to nonhormonal remedies. The decision to use vaginal estrogen may be made in coordination with the patient's oncologist. Additionally, it should be preceded by an informed decision-making and consent process in which the woman has the information and resources to consider the benefits and potential

risks of low-dose vaginal estrogen. Data do not show an increased risk of cancer recurrence among women currently undergoing treatment for breast cancer or those with a personal history of breast cancer who use vaginal estrogen to relieve urogenital symptoms [48].

- Tibolone

Tibolone is a synthetic steroid that has estrogenic, androgenic, and progestagenic properties. Tibolone itself has no biological activity; its effects are the results of the activity of its metabolites on various tissues. The concentrations of tibolone metabolites and the metabolic regulation of hormonal activities vary depending on the tissue type. Tibolone has estrogenic effects on bone and vaginal tissue. In endometrial tissue the Δ4-isomer functions as a progestagen, whereas in the brain and liver it has androgenic effects. In breast tissue, the main actions of tibolone are strong inhibition of sulfatase activity and weak inhibition of 17ß-hydroxysteroid dehydrogenase activity, which result in blocking the conversion of estrone sulfate to E_2. Tibolone significantly reduces hot flushes and sweating and genital atrophy in postmenopausal women.

Tibolone has estrogenic effects on the vagina but not on the uterus. This drug has been associated with significant improvements in sexual function in postmenopausal women, reflecting both its estrogenic and androgenic properties. There were significantly greater increases in vaginal blood flow with tibolone in response to erotic fantasy but not film, suggesting two possible pathways of female sexual response.

A menopausal atrophic symptom questionnaire revealed that tibolone 2.5 mg significantly reduced nocturia compared with placebo and urinary urgency and increased the vaginal maturation value from baseline [49].

6.4.3.3 Alternative and Complementary Medicine

Alternative and complementary therapies have been proposed for the treatment of atrophic vaginitis, but data are not in agreement regarding efficacy.

Administration of the phytoestrogen genistein (54 mg/day) showed no significant difference in maturation value score compared to placebo, either at baseline or after 12 months [50].

Black cohosh, used alone or as part of a multibotanical product with or without soy dietary changes, had no effects on vaginal epithelium, endometrium, or reproductive hormones.

There is not enough information for its recommendation.

6.4.3.4 Selective Estrogen Receptor Modulator (SERM)

Ospemifene

Selectively targeted SERMs against GSM underlying physiopathology could be an alternative to local estrogen or systemic hormone therapy in the management of symptoms, apart from moisturizers and lubricants.

Ospemifene (a toremifene derivative) has an estrogenic agonist activity on the vaginal epithelium already noted in the first nonclinical studies and Phase I, II, and III studies [51]. This singular tissue selectiveness seems to be molecular structure related. It is the first nonhormonal selective modulator with multiple tissue-specific actions and, contrary to other SERMs, with an antagonist function in endometrial and breast tissue [52].

Ospemifene demonstrated efficiency in vaginal dryness and dyspareunia, regenerating vaginal cells, improving lubrication, and reducing pain during sexual intercourse. Symptoms improved in the first 4 weeks and endured for up to 1 year. Additionally, it demonstrated a good endometrial, cardiovascular system, and breast safety profile [53].

Ospemifene is the only marketed SERM which has demonstrated an estrogen agonist effect in the vaginal epithelium. It is the first nonhormonal, nonestrogenic drug indicated for moderate-to-severe GSM treatment in women not eligible for vaginal estrogen therapy [54].

Ospemifene treats the underlying cause of vaginal dryness and dyspareunia, regenerating vaginal cells, improving lubrication, and reducing pain during sexual intercourse [55]. Symptoms of GSM improve in most women receiving ospemifene, and they begin to revert following the first 4 weeks.

Physiological improvements endure for up to 1 year of daily ospemifene use, as well as those related to all sexual function aspects. Apart from its proven safety profile in the endometrium and the bone and cardiovascular systems, its safety in the breast makes it the first GSM oral treatment not contraindicated in women with a previous history of breast cancer who have completed treatment [56].

The association of SERM with estrogens (bazedoxifene and conjugated equine estrogens) has shown to have beneficial effect on the vaginal symptoms as well. The indication of this association, however, exceeds the treatment of GSM and because it adds systemic effects.

Table 6.7 shows the different therapeutic alternatives available for the treatment of the genitourinary syndrome of the menopause with available evidence level.

Table 6.7 Evidence level of treatments for vaginal atrophy

Lifestyle	Sexual activity	II-2B
	Avoiding obesity	III-C
	Exercise	III-C
	Quit smoking	II-3B
Vaginal hydrating	Regular use 2–3 times/week	I-A
	Recovery of symptoms	I-A
Vaginal lubricants	Use during sex relations	II-2B
Alternative and complementary medicine	Homeopathy	III-D
	Phytotherapy	III-D
	Phytoestrogens	II-3D
Systemic HT	Improvement of symptoms and trophism	I-A
Local HT	Improvement of symptoms and trophism	I-A
Ospemifene	Improvement of symptoms and trophism	I-A

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Sexual Health

7

Nicolás Mendoza Ladrón de Guevara and Ana Rosa Jurado

7.1 Introduction

Sexual health can be defined as a state of physical, emotional, mental and social well-being that is related to sexuality and not merely the absence of disease, dysfunction or infirmity. The sexual health of individuals requires them to have a positive and respectful attitude towards sexuality and sexual relations and the possibility of having sexual experiences that are pleasurable, safe and free of coercion, discrimination, and violence. Therefore, sexual health is not exclusive to the prevention of sexually transmitted diseases; it also entails a broader approach that is related to the full development of a person's welfare, health, education and love [1].

7.2 Changes in Sexuality Related to Menopause

The physical, psychological and sociocultural changes that occur in peri- and postmenopausal women people may favour sexual intercourse, but it is more common for them to harm or even completely interrupt sexual activity. Sexuality at this age is conditioned by previous sexual experiences and is often affected by health problems and the treatment of these problems with medications. Age and disease most often affect sexual desire in women (hypoactive sexual desire disorder), and erection most often affects men (erectile dysfunction) [2].

Age should not be considered a factor that is responsible for impaired sexual function. In the postmenopausal women, certain factors affect sexual desire:

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7.2.1 Hormonal Factors

The serum levels of certain hormones, including testosterone, oestrogen, oxytocin, beta-endorphins and prolactin, influence sexual activity. Testosterone is a hormone that stimulates sexual desire in both men and women, but from 40 years of age, testosterone levels decrease in the blood. Women of childbearing age have a peak secretion of testosterone and androstenedione for half of the ovarian cycle that coincides with ovulation that has been associated with an increase in spontaneous desire. Oestrogens help to maintain tropism and vaginal lubrication. Hence, they indirectly enable pleasurable sex. In postmenopausal women, a decrease in oestrogen levels results in atrophy and decreased vaginal lubrication. These changes may be responsible for less pleasurable or painful intercourse in women (dyspareunia), which could adversely affect their motivation and sexual desire [2].

Additionally, a progressive decrease in testosterone levels has been associated with decreased sexual activity. However, hormonal factors do not fully explain the changes that are observed in sexuality with increasing age.

Age fundamentally modifies the sexual response, just as it affects multiple other physical abilities in humans. Women are more likely than men to experience specific hormonal changes throughout their life that temporarily alter their sexual responses [3]. However, strong evidence has shown that neither age nor hormonal changes themselves are solely responsible for the decline of sexual health observed in individuals over 50. Rather, this decline is thought to occur in response to a number of other factors that are psychological, relational or sociocultural in nature [4].

7.2.2 Psychological and Relationship Factors

Different psychological problems can lead to decreased sexual desire. These include depressive syndrome or anxiety disorders. During menopause, changes in mood or sleep disturbances can influence desire in women. Additionally, decreased self-esteem or changes in body images that occur as a result of a disease or its treatment may lead to a deterioration in sexual health.

Relationship problems with partners can lead to decreased libido, especially in women. A good relationship is fundamental because a stable and harmonious relationship promotes the prompt and satisfactory resolution of any sexual conflicts that may arise. Conversely, a bad relationship itself can cause problems in a couple's sexual life [5]. Additionally, drugs can affect sexual experiences and lead to risky sexual behaviour and social conflicts within the couple [2].

Continued stressful situations facilitate the production of prolactin, and increases in serum prolactin levels decrease sexual desire [6].

In our society, models of education that do not encourage the acceptance of sexuality can have negative effects on sexual desire. Additionally, the false belief that older women do not have sex can unconsciously cause a loss of motivation and desire [2].

The sexual response of men progresses linearly and usually begins with desire. This desire can be triggered by sexual thoughts and fantasies or the urgency to experience sexual satisfaction. However, the female sexual response resembles that of males only occasionally, in particular at the beginning of romantic relationships, after which women require more stimulation. In general, spontaneous sexual desire decreases with women's increasing age [2].

According to Rosemary Basson, the progression of the sexual response in women is cyclical, and the phases of the female sexual response (desire, arousal, plateau, orgasm and resolution) do not necessarily follow this order but can overlap with each other or progress in an order that can vary according to the situation. Therefore, desire does not usually mark the start of the female sexual response. This entire cycle can be influenced by emotional intimacy, sexual stimulation and the woman's satisfaction with the relationship [7].

The human sexual response to exciting stimuli involves a cycle of motivation that is based on incentives and that comprises the physiological changes and subjective experiences of the individual. Psychological and biological factors influence the processing of sexual stimuli in the brain, causing it to allow or not allow the activation of the next phase of sexual response. The results obtained during both sexual and non-sexual intercourse influence an individual's future motivation to seek intimacy [8].

7.2.3 Cultural Factors

In our society, the belief that people do not have sex after a certain age is pervasive. This can unconsciously lead older adults to consider it to be normal to not have sexual relationships, motivation or desire. This myth is negated by studies showing that over 80% of people over 60 years of age continue having sex.

The cultural perception of sexuality in young people as a fiery and intense activity and attempts to enforce the social standards of youth and power could influence the sexual activity of the elderly. They leave no opportunity for a more leisurely and intimate sexuality, which could be the ideal type of sexuality for this population.

On the other hand, the physical factors and physiological changes that occur with ageing do not determine the sexual activity of older people because there are other factors that determine this behaviour, including the following:

- Previous sexual history: The level of sexual activity of each person during earlier life stages is very important to sexual activity in the second part of his or her life.
- The interest and existence of a partner in addition to the health of this partner have special importance in these stages of life. Older people discontinue sexual activities more as a result of a lack of available partners than a lack of interest.
- Physical and psychological health: Health problems can hinder sexual activity. If necessary and to avoid complications related to health problems, changing the usual recommended positions to perform sexual activity using a side or rear position may be advised. The use of a support pillow might also be advised.

7.3 Changes in Sexuality Related to Chronic Diseases

The existence of organic disease can decrease sexual desire, although it rarely fully prevents sexual activity. However, genitourinary diseases that require surgical treatment or are cancer based have a greater impact on people's sexual health. At this age, a frequent consumption of drugs may be responsible for decreased desire, including antihypertensives, antidepressants, and opioid analgesics [2].

Sexual health can deteriorate because of a variety of medical or psychiatric problems that become increasingly frequent over an individual's lifespan. This deterioration in sexual health results not only from the primary effects of the disease and its treatment on sexual responses but also from the negative psychological consequences that occur secondary to the development and pharmacological management of disease (i.e., decreased self-esteem, changes in body image or depression) [9]. However, evidence is scarce regarding the impact of disease on sexual health. Furthermore, much of the evidence that is available is heterogeneous and of low quality. Even the guidelines for clinical practice rarely mention sexual health unless the course of treatment directly targets sexual dysfunction.

Genitourinary pathology deserves special mention, especially if its treatment is surgical or the basis of the pathology is oncological, in which case sexual health can be compromised by alterations in the anatomy, physiology and psychology of the individual suffering from the disease [10, 11]. The same can be said regarding breast cancer: even if a condition does not directly affect the genital area, female sexual health can be greatly impaired due to the physical and psychological pain that results directly from the disease process itself or as an indirect consequence of various treatment regimens. For example, drugs with anti-oestrogen activity can compromise sexual health by greatly increasing vaginal atrophy [12].

7.4 Changes in Sexuality Related to Surgical Menopause

The uterus has historically been considered a regulator and controller of important physiological functions in addition to a sexual organ and a source of energy, vitality and maintenance of youthfulness and attractiveness in women. It is therefore not surprising that some women may feel that their sex life could be affected by the removal of the organ [13].

Female sexual responses are complex because they are influenced by physical and emotional factors and women's sexual experiences. Unlike what occurs in men, desire is not usually the beginning of the female sexual response. The female orgasm is also a complex process that is characterized by intermittent and rhythmic muscle contractions of the pelvic floor and the outermost portion of the vagina, anus and sometimes the uterus, which results in a more pleasurable feeling [14].

Women in stable relationships may be more concerned about emotional intimacy with their partners, and although in some cases the frequency of sexual intercourse

can be related to a better sex life, female sexual functions are more a matter of quality than quantity. Thus, the sexual well-being of women should not be defined as the mere absence of sexual dysfunction.

A hysterectomy may be necessary to treat tumours of cervix or body of the uterus or advanced endometriosis or prolapse, among other conditions. These conditions may be responsible for pelvic pain, painful intercourse (dyspareunia) or vaginal bleeding unrelated to menstruation, all of which can negatively influence the sexual health of women. Therefore, removing the uterus may improve the sexual relations of women who are affected by these problems.

When a subtotal or total hysterectomy is performed, it may affect the ligaments, blood vessels and nerves that are involved in sexual function. Moreover, following a total hysterectomy, the shortening of the dome of the vagina could be responsible for dyspareunia. However, there are currently conservative surgical techniques that can preserve the nerves that innervate the pelvic organs [15].

A hysterectomy does not adversely affect sexual health. Most women who have only their uterus removed will have equal or better sexual function after the surgery than before, probably because their symptoms and previous problems are relieved. In this sense, some authors claim that after a subtotal or total hysterectomy, women experience a decrease in abdominal pain and increased desire, excitability and frequency of intercourse. However, in women whose previous sexual experiences were not good, their sexual health is often worse after surgery [16].

In addition to hysterectomies, the removal of the ovaries may be necessary for the treatment of some benign, premalignant or malignant diseases of the internal genitalia [17]. In postmenopausal women, the removal of the ovaries causes no symptoms or major changes to their sexual health, but in premenopausal woman, it causes surgical menopause, with sudden and intense hormonal changes and subsequent consequences, mainly climacteric syndrome (hot flashes, sweating, psychological problems, insomnia, etc.) and impaired sexual function [18]. In this sense, women with surgical menopause show an increased risk of developing hypoactive sexual desire disorder and more emotional involvement than premenopausal women who experience natural menopause [19]. Additionally, a lower frequency of sexual intercourse, difficulty in lubrication, reduced sexual satisfaction, dyspareunia and difficulty achieving orgasm have been observed in women with surgical menopause [20].

The bilateral removal of the ovaries in premenopausal women causes a significant decrease in the levels of oestrogen and testosterone in the blood [17], which may explain some of the changes observed in these patients. Lower levels of oestrogen cause atrophy and decreased vaginal lubrication, which can cause less pleasurable or even painful sex in women, and this could negatively influence their sexual motivations and desire. The hypothesis in which a decline in blood testosterone causes hypoactive sexual desire disorder and sexual dysfunction in women with surgical menopause has not been supported. In all hysterectomy cases, it is recommended that women practice sexual self-stimulation 2 weeks after surgery because it allows them to experience pleasure without the pressure that can be exerted when in a relationship [6].

Some problems related to surgical menopause can be treated by oestrogen hormone therapy, which mitigates hot flashes and vaginal dryness and reduces dyspareunia, but it is less clear what effect this therapy may have on improving sexual function [21]. Testosterone replacement therapy patches seem to improve sexual desire and the frequency of intercourse and orgasms. In our experience, the use of tibolone has proved more effective in improving the sexual health of these women [2].

Moreover, psycho-educational therapy has been proposed to help women with surgical menopause to manage their sexual health problems. Short educational sessions on sexual health, body awareness and relaxation techniques seem to have a positive effect. Preoperative knowledge of the possible side effects decreased sexual distress after surgery [22].

In conclusion, removing the uterus does not adversely affect the sexual health of women. In most cases, the relief of symptoms and previous problems leads equal to or better sexual performance than they experienced before the surgery. In postmenopausal woman, removing the ovaries does not cause major changes. However, in premenopausal woman, it induces surgical menopause, which leads to sudden hormonal changes and impaired sexual functions and can be treated with hormone therapy and psycho-educational methods.

7.5 Hormonal Treatments

According to a Cochrane review, hormone therapy (HT) improves postmenopausal sexual function when used during the 5 years immediately following menopause [23]. The use of tibolone, a synthetic steroid with diverse actions in different tissues, has proven effective in the treatment of female sexual dysfunction, and its effectiveness is similar to that described for androgens. In some cases, tibolone is considered the best option for postmenopausal women with impaired sexual health [24].

Low-dose oestrogens are highly effective treatments for dyspareunia, low interest in sex and sexual dissatisfaction in women with atrophic vaginitis. Local oestrogen therapy is the treatment of choice for women with vaginal atrophy who do not have any other postmenopausal symptoms. In Spain, the most widely used product is the topical cream of promestriene [25].

Oestrogens and androgens can also be used in women with surgical menopause and HSDD. Women treated with 300 μg of transdermal testosterone per day had a statistically significant increase of the sexual events, orgasms and sexual desire, as well as a decrease in distress compared with women receiving placebo, although some of these values are not clinically meaningful [26]. However, considering the full hormonal deficit of these patients, the use of tibolone has been proven superior to promote improvements in the sexual health of women with surgical menopause [27].

Ospemifene is a selective oestrogen receptor modulator (SERM) with oestrogen agonist action in the vagina. It has been approved for the treatment of moderate-to-severe dyspareunia secondary to atrophic vaginitis. A recent meta-analysis indicates

Table 7.1 Recommendations of the Spanish Menopause Society about HT [2]

– Pharmacological treatments should be restricted to women with sexual dysfunctions for whom non-pharmacological interventions have proven ineffective
– A low dose of vaginal oestrogen is recommended for postmenopausal women with dyspareunia due to atrophic vaginitis (Grade 1A)
– The use of aqueous lubricants before or during intercourse is suggested for women with contraindications for oestrogen (Grade 2B)
– For postmenopausal women with sexual dysfunctions and vasomotor symptoms, the use of HT is recommended (Grade 1A). Tibolone can be an alternative to HT in the treatment of postmenopausal women with impaired sexuality (Grade 2B) and appears to be more effective than HT in women with surgical menopause (Grade 2C)
– For postmenopausal women with HSDD in whom pharmacological treatments have been unsuccessful, treatment with testosterone is suggested (Grade 2B). However, testosterone is not recommended for premenopausal women with sexual dysfunction (Grade 1B)
– The first line of treatment for vaginal atrophy symptoms in women with breast cancer includes non-hormonal options (i.e. lubricants or hydrating creams). Using vaginal oestrogen therapy is not recommended for women using aromatase inhibitors for breast cancer (Grade 2C). However, low-dose oestrogen therapy is a reasonable option for those who do not receive aromatase inhibitors or who present a low risk of recurrence
– For women with arousal or orgasm disorders associated with SSRI use, discontinuing the SSRI or changing to another antidepressant is not advisable; it is recommended to add a PDE-5 inhibitor (Grade 2B)
– Bupropion may be an effective treatment for sexual dysfunction in women with or without associated depression. However, no published data have proven the safety and effectiveness of phytotherapy in sexual dysfunction

that ospemifene is an effective and safe treatment for dyspareunia associated with postmenopausal vulvar and vaginal atrophy [28].

Although preclinical data and those from animal experiments suggest that ospemifene has a neutral or an inhibitory effect on mammary carcinogenesis, further studies are necessary to evaluate its safety in women with breast cancer. No thrombotic events have been reported either, although more data are necessary to rule out the complication that occurs with other SERMs. However, ospemifene use is contraindicated in women with breast cancer, endometrial cancer, venous thromboembolism, stroke, or myocardial infarction [29].

A summary of recommendations of the Spanish Menopause Society about these HT is shown in Table 7.1.

7.6 Sexual Dysfunctions in Menopause

We should not talk about a general sexual dysfunction in menopausal women, but it would be more appropriate if we consider different affections in the sexual response that can turn into abnormal sexual drive. It is very typical to have some difficulty, or variations, in the normal sexual response, due to aging, hormonal changes, chronic diseases, medications, surgeries and not turning into dysfunction. These are simply predisposing factors, which if the patient cannot adapt to could become pathological. Adaptability is related to attitudes, education, social myths, quality of the

relationship and several other factors that doctors should explore to help women during menopausal transition [2].

It is also typical that people cannot recognize what part of the sexual response was first affected. Main reason for consultation is low sexual desire, but if we diagnose correctly it will be presumably different. When a patient suffers lack of sexual arousal (erection, lubrication), uses to think that it is due to low desire, but it is more frequent that low desire is a consequence of repeated frustrations because of dissatisfaction during intercourse due to lack of sexual arousal.

Doctors should provide a correct diagnosis to prescribe the most optimum treatment and explore all involved factors to procure the best individual sexual counselling. The following pages will try to describe the diagnosis and therapeutic approach of the most frequent sexual dysfunctions around menopause.

7.6.1 Low Sexual Desire

There are different concepts of low sexual desire for women and men since DSM-V publication [30]. DSM criteria for sexual dysfunctions reflect new theoretical approach trying to explain sexual behaviour in women after linear model of sexual response proposed by Masters and Johnson was found to be inadequate [31].

Male hypoactive sexual desire disorder (MHSDD) remains similar to the prior concept for men and women hypoactive sexual desire disorder (HSDD), meaning lack or absence of sexual fantasies and desire for sexual activity, causing marked distress or interpersonal difficulties, and not being better accounted for by another mental disorder, a drug or some other medical condition [30].

New concept for women amalgamates female disorders of desire and arousal into a single diagnosis called female sexual interest/arousal disorder. This disorder is defined by a complete lack of or significant reduction of an interest in sexual activity, absence of fantasies or erotic thoughts, decline to initiate sexual encounters and no sense of pleasure during sexual acts. Three or more of these symptoms decide the diagnosis, if they persist more than 6 months, result in distress and are not better explained by drugs or another physical, biological and/or relational condition [30].

This new diagnosis approach has often been discussed, but in postmenopausal women could be adequate, because one of the main reasons for low sexual desire in these women comes from inadequate arousal due to age and hormonal physiological changes.

Knowledge about low desire after decades of research is based on prior HSDD. Thus, we know that prevalence of HSDD remains constant across age, because low desire can increase, but related distress decreases. This sexual dysfunction is present in 8.9% of women aged 18–44, 12.3% aged 45–64 and 7.4% over 65. Common associated factors to low desire are poor health-related quality of life, lower general happiness and satisfaction with relationship, and negative emotional states [32].

Around menopause, researchers find several specific factors to explain low desire in women [33]. They find general poor sexual function in older women; those

affected by menopausal symptoms; those suffering from anxiety/depress disorder; or those sharing sexual life with an alcoholic partner or with a man suffering from erectile dysfunction. Among women with low desire, inadequate intimacy, context or sexual stimulation are found to contribute to diagnosis in 85%, while hormonal related changes contributed only in 25% [34].

From a physiologic point of view, researchers have found that 87% postmenopausal women believed vaginal dryness a factor causing reduced libido; but only 46% had discussed it with health professionals and only half of them had received treatment [35].

However, it is rare to find a single cause for low sexual desire. So, with a view to be successful with the treatment, doctors need to help patient to initiate discussions and identify all associated factors. The correct treatment approach requires biological information to patients and psychotherapeutic and pharmacological interventions.

There is not too much approved medication for use in female with low desire. We had a label indication for testosterone patch for surgical postmenopausal women, and the new recently approved flibanserin. Testosterone has been demonstrated in several studies, not only for the development of the patches, that can be a good option for improving sexual drive in peri- and postmenopausal women and when adding to HRT has a beneficial effect on sexual function [36].

Flibanserin is indicated for the treatment of premenopausal women with acquired, generalized HSDD. It works as a serotonin 1A receptor agonist and serotonin 2A receptor antagonist, but its mechanism of action in the treatment of this sexual dysfunction remains unknown [37]. Is has been demonstrated an increase in the number of satisfying sexual events and sexual desire (FSFI desire domain score) over 28 days of use. In addition, it reduces distress associated with total sexual dysfunction and associated with low desire [38].

Other medical products have demonstrated slight improvement in sexual function: for example, DHEA, probably because of its conversion into oestrogen and testosterone in postmenopausal women [39], or phytoestrogens (soya, red-clover, black cohosh), perhaps by enhancing the quality of life. But they all still have an "out-of-label" indication for sexual desire.

By individualizing every treatment, most of the options could be considered, and should be used adding sexual education about how to optimize sexual response, ways to enhance intimacy with partner and recommendations for couples [2].

7.6.2 Sexual Pain

Before DSM-V publication, we used to talk about dyspareunia (genital pain associated with sexual intercourse, either a male or a feme) and the most related to psychosomatic concerns vaginismus (involuntary spasm of the musculature of the outer third of the vagina that interferes with sexual intercourse). They are both amalgamated into a new diagnosis called genitopelvic pain/penetration disorder [30]. Male dyspareunia is very infrequent and has been erased from the nomenclature.

To establish the diagnosis of genitopelvic pain/penetration disorder (GPPPD), one of these four conditions should persistently or recurrently occur:

- Difficulty in vaginal penetration
- Marked vulvovaginal or pelvic pain during penetration or attempt at penetration
- Fear or anxiety about pain in anticipation of, during or after penetration
- Tightening or tensing of pelvic floor muscles during attempted penetration

It could be difficult to evaluate if a patient is suffering from pain because of threat, or threat because of pain. Stronger automatic threat associations are related to lowered sexual arousal [40], but doctors need to be attentive during menopausal transition because the relationship between low hormonal level and changes in sexual response is well known (vaginal dryness, low lubrication, different vulvovaginal senses, delayed orgasm) [2]. Difficulty in penetration, dyspareunia and vestibulodynia are also frequently symptoms of the recently called genitourinary syndrome of menopause (GSM), due to lack of oestrogen, and these conditions could cause sex-related threats and avoidance.

Around menopause, the most frequent reason for sexual pain is, in different degrees, GSM. A correct examination should be enough to make the diagnosis (pale aspect of genital tissues, loss of vaginal folds …), and sometimes just the clinical interview about changes in sexual response. We often find that the patient experiences less pain during examination than intercourse. It is due to psychological factors (threats are sexual related).

First-line treatment for this condition should be low dose of oestrogens applied locally, because this improves genital tissue irrigation, vaginal ph, dryness and lubrication [41]. The efficacy does not differ between pharmacological presentations (pessaries, vaginal ring, creams, gels), but there is a consensus about using low dose of oestrogens in order to avoid high absorption to minimize side effects [41]. Low dose of local oestrogens does not need progestin neither endometrium control.

HRT and tibolone are also indicated, but women feel them less safe if vaginal problems are the only reason for their indication, and several studies have found symptoms of vaginal atrophy even when using them. If this happens in women on HRT or tibolone, we can add vaginal treatment.

Conjugated oestrogens/bazedoxifene development has demonstrated the effect of this tissue selective oestrogen complex (TSEC) on GSM. It improves vaginal epithelium cell maturation index, vaginal ph and dryness [42].

The same effects have been found during the development of the medication ospemifene. It is the first selective hormone receptor modulator with label indication in vulvovaginal atrophy and dyspareunia treatment, because it has demonstrated a benefit in dyspareunia by improving FSFI scale [43, 44].

Non-hormonal treatments have also shown to be effective. For example, intravaginal soya gel reduces vaginal dryness, ph and dyspareunia, by increasing epithelium maturation and thickness, and oestrogen receptor expression in postmenopausal women [45]. A topically and intravaginally administrated gel containing another

phytoestrogen (8-prenynaringenin) from *Humulus lupulus* L. reduces symptomatology in postmenopausal women with genital atrophy [46], and we have got some scientific evidence about another phytotherapeutics giving benefits over sexual arousal, as *Centella asiatica* (with a large traditional use) [47], Panax ginseng [48], *Tribulus terrestris* L [49], *Turnera diffusa* [50] and *Ginkgo biloba* [51].

The latest proposal is to treat GSM with laser, but we need more evidence to have guidelines for using it and to know the duration of its effect over epithelial tissues.

Personalized treatment leads us to provide sexual counsel to address psychological and couple issues, and to inform about physical changes; to use sex therapy if needed, to help women to see penetration in a more positive way; to add pelvic floor physical therapy to relax musculature if necessary; to recommend lubricants and moisturizers to be used as a part of sexual play; and to design strategies using combined or sequential options [52].

7.6.3 Female Orgasmic Disorder

This frequent dysfunction (prevalence 11–41%) [53] is diagnosed when some significant change occurs in orgasm, such as delay, reduction of intensity or cessation. Female orgasmic disorder (FOD) could appear after a period of normal sexual activity, but affect 75–100% of sexual attempts, during more than 6 months, and cause distress and/or relational problems [30].

No single cause is identified, but it is common to be associated with partner problems (health or sexual matters), relationship problems (poor intimacy or communication, abuse …), life stressors and personal vulnerabilities (self-esteem, body image, anxiety, attitude about sex, sexual education, sexual history …) [2, 53, 54].

Medical conditions can also be the cause: cardiovascular diseases; thyroid problems; chronic conditions affecting neurological aspect of sexual response, such as diabetes or multiple sclerosis; or use of several drugs that can inhibit the orgasm (antidepressants, antipsychotics, cancer treatment …) [2].

The association to other sexual dysfunctions is common, such as desire or arousal problems, and it is probably the most common reason for FOD during menopause. Hormonal changes can modify senses in genital tissues and hinder sexual arousal and orgasm. These variations can produce less sensation or even hypersensitivity, leading women to adapt their abilities for sexual stimulation.

Apart from the address of the found etiological factors, all hormonal and nonhormonal treatments proposed for arousal problems can help menopausal women with FOD, but this sexual dysfunction is specifically well treated with sexual therapy. Psychological interventions have the best results in desire and orgasmic disorders [55], and consists mainly of cognitive behavioural therapy, to reduce stress and promote relaxation; direct masturbation training (in which women are exposed to genital stimulation, and gradually incorporate sexual fantasies, role play and sexual toys to facilitate orgasm); couple therapy if necessary; and/or cooperation of the partner during the training.

Thus, in menopausal women affected by FOD, the best option for treatment is to associate hormonal treatment to sexual therapy [56].

Conclusions

In conclusion, even though sex may be constrained by the physical, psychological and social changes that accompany age, this should not disrupt sexual activity. Maturity can be an opportunity for a more intimate or relaxed type of sex. The acceptance of physical changes and a history of good sexual experiences can positively influence the maintenance of sexual health as the years pass. At any age, especially in long-term relationships, a good relationship is the most important factor that influences desire and sexual health. Pharmacological treatments could be reserved for cases in which couple therapy or changing lifestyles have not been effective in improving sexual health.

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Part III

The Impact of Estrogen Depletion on Disease Susceptibility

Postmenopausal Osteoporosis

8

Antonio Cano and Miguel Ángel García-Pérez

8.1 Osteoporosis and Women

Osteoporosis is a disease in which reduced bone mass and microarchitectural deterioration of bone tissue increase the risk for fragility fracture. Osteoporosis integrates one of the non-communicable diseases (NCD) with a higher impact in ageing population. Based on the densitometric reference established by the technical report of the World Health Organisation (WHO) in 1994 [1], osteoporosis emerged as a disease affecting 75 million people in Europe, North America and Japan. That prevalence was found by using bone mineral density (BMD) as diagnostic criterion, which in women establishes osteoporosis when reaching 2.5 standard deviations or more below the average value for young healthy population [2].

The more recent evidence that BMD is a strong, but insufficient, parameter to assess the risk for fragility fracture in many subjects has uncovered the role of clinical factors, like age or others, which have also emerged as strong risk factors (Fig. 8.1). Moreover, the availability of osteoporotic fracture data from cohorts at different geographical settings has made possible the integration of clinical parameters into the prediction of risk for fracture. New tools have been designed in which both clinical and densitometric factors are integrated and provide an absolute risk for fracture. It has been again the WHO that has issued the Fracture Risk Assessment Tool (FRAX) [3]. FRAX provides a 10-year absolute individual risk for fragility fracture and is sensitive to the varying conditions of different populations in the world.

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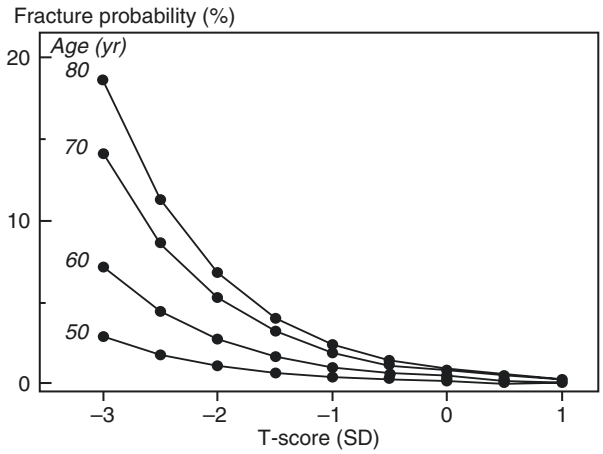

Fig. 8.1 Age is a strong risk factor for fragility fracture. The figure shows the 10-year hip fracture probability in a Swedish population according to age and bone mineral density (BMD) at the hip, which is presented as *T*-score. It is obvious that the lower the bone density (lower *T* value) the higher the risk for hip fracture. However, for a given *T* value, and particularly in ranges below −1 (osteopenia), age imposes dramatic differences in risk. With permission of Springer Verlag from Kanis et al. Osteoporos Int. 2001;12:989–95. Permission obtained through Copyright Clearance Center, Inc

Therefore, the emphasis is now fracture, instead of BMD, a most-needed approach to better identify those individuals that will suffer from the more than 8.9 million fractures occurring annually worldwide. Indeed, the lifetime risk for osteoporotic fracture, which moves between 30 and 40% in developed countries, approaches that for coronary heart disease. Complications of osteoporotic fractures include both increased morbidity and mortality, which translate into 2.8 million disability-adjusted life years (DALYs) annually. These figures are above those accounted by hypertension and rheumatoid arthritis [4].

One strong risk factor for osteoporosis is gender. Women have an increased vulnerability, since one in three women over age 50 will suffer from an osteoporotic facture vs. one in five men [5]. A more fragile habitus, with thinner bone constitution, is a variable influencing the higher risk of women. Another important variable is menopause, one unique endocrinological phenomenon of women. Albright already observed the impact of the abrupt fall in ovarian hormonal production on the risk for fragility fractures in women with surgical menopause [6]. The arrival of reliable densitometers confirmed that the fall in the circulating level of oestrogens at menopause was associated with an accelerated loss of bone density.

8.2 The Biological Basis

8.2.1 Structure of Bone

Bone is the system that maintains the body in an erect position. Against its static aspect, bone is a live tissue subjected to continuous change. The composition of

bone includes cells and inert material. Three main cellular types, osteoblasts, osteoclasts and osteocytes, distribute according to a framework provided by mineral, a calcium salt called hydroxyapatite, and a net of intertwined collagen fibres.

Two different forms of structures may be found in bone. Trabecular bone is a sponge-like design that fills up the vertebral bodies, where a network of trabecular plates determines a porous texture occupied by bone marrow. The transmission of tension through the trabeculae facilitates the flexibility required for energy absorption while maintaining a quite light fabric. Cortical bone, instead, is the basic component of long bones. Layers of bone are tightly overlapped to produce a thick structure most optimised to support loading. Cortical bone results from massive overlapping of osteons, structures composed of concentric layers of compact bone (lamellae) that surround a central canal (Haversian canal). The composition of lamellae is that of compact bone, i.e. the net of collagen fibres immersed into the hydroxyapatite mineral matrix.

8.2.2 Bone Cells

Osteoclasts, osteoblasts and osteocytes habit, and exert regulatory functions, in this apparently inhospitable environment. Both osteoclasts and osteoblasts are cells deriving from progenitors at the bone marrow, which occupies spaces close to the surface of mineralised bone. Their role is crucial for the renovation of bone while maintaining an adequate bone mass. The key system is the bone multicellular unit (BMU), in which osteoclasts and osteoblasts renovate bone at any location in the skeleton.

Bone resorption is the role of osteoclasts, which in this way eliminate areas that are damaged due to repeated loading. The formed cavities are then occupied by osteoblasts, which deposit osteoid, the proteinaceous matrix that will be slowly mineralised to produce new bone. One key duty of the BMU is the complete restitution of the digested bone, so that the balance is neutral and no loss of bone mass occurs.

Osteocytes derive from osteoblasts buried within the mineralised bone that they have contributed to create. Osteocytes occupy a network of hollow spaces (lacuna), which are communicated by a network of canaliculi through which cytoplasmic processes interconnect other osteocytes to form a full network. There is not a complete idea of the functional role of osteocytes, although there is growing consensus in that they constitute a finely tuned sensor system detecting the bone areas in which, because of material fatigue, damage or other reasons, remodelling is desirable. In this sense, osteocytes may be considered as the guardians of bone quality [7]. Recent studies have shown that this function seems mediated, at least in part, by the contribution of osteocytes to the pool of one cytokine, the receptor activator of NFkB ligand (RANKL) [8, 9], which is crucial in the differentiation of osteoclasts from progenitor cells [10]. The differentiation of osteoclasts is coupled, as previously mentioned, to that of osteoblasts, which refill the resorbed cavity and keep unaltered the structure of the bone. A scheme of the bone cells is presented in Fig. 8.2.

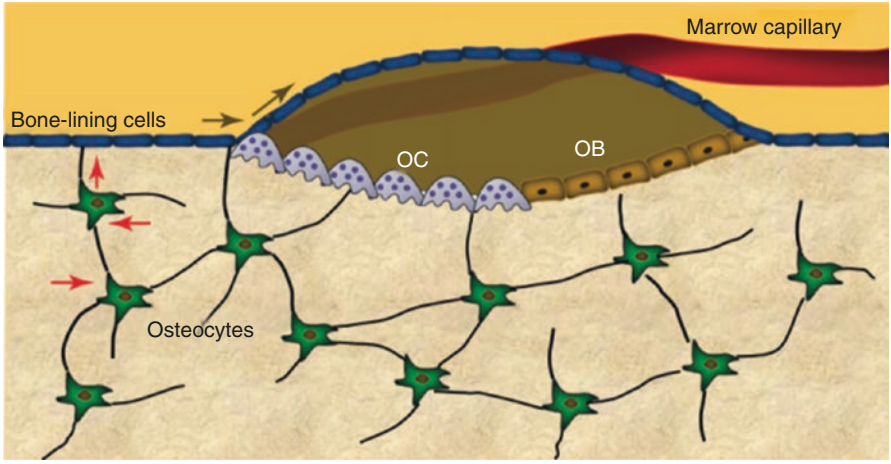

Fig. 8.2 The illustration shows a scheme of the basic multicellular unit (BMU), where the three main cellular types, osteoclasts, osteoblasts and osteocytes, are presented. The canopy of the bone-lining cells and one associated marrow capillary are also included in the figure. The network of the osteocyte canaliculi is well connected with every agent of interest, thus providing a stable structure for intercellular communication between the different cellular types in the BMU. With permission of Elsevier from Khosla S et al. Trends Endocrinol Metab. 2012;23:576–81. Permission conveyed through Copyright Clearance Center, Inc

8.2.3 Oestrogen Regulation

The initial observation by Albright that the loss of oestrogens in women increased the risk for osteoporotic fracture could only be adequately clarified in later years. Oestrogen receptors were initially described at the level of mRNA expression in cell cultures, experimental animals and human tissues [11–13]. Subsequent studies corroborated the presence of both alpha- and beta-ER in human cartilage and bone, this time at the level of protein [14, 15]. Both ER subtypes were detected in histological sections of the growth plate and in mineralised bone, and also in the three basic cellular types, osteoblasts, osteoclasts and osteocytes, although with different distribution patterns.

Parallel clinical observation confirmed that oestrogens behave as major regulators of bone metabolism not only in women, but also in men [16, 17]. Moreover, pioneer data from Lindsay et al. confirmed that treatment with oestrogens prevented the bone loss in ovariectomised women [18]. More refined work in the latter years has confirmed details supporting the role of oestrogens at different steps of bone metabolism (reviewed in [19]).

One first effect of oestrogens concerns the limitation of bone remodelling. Additionally, oestrogens have been demonstrated to limit bone resorption. This is consistent with the observation of net bone loss with oestrogen decline, which is already detected at early stages of perimenopause [20] and is maintained until late in the postmenopausal years [21]. The impact of oestrogen decrease is confirmed by the clear increment of biochemical markers of bone resorption, at rates of 79–97%

[21], in both blood and urine in postmenopausal women. The increase in resorption markers is accompanied by the concomitant increase in markers of bone formation, but in a lower magnitude. The biological basis of this observation is the acceleration in the activation of BMUs, in which the differentiation of both osteoclasts and osteoblasts from progenitor cells is increased, but with a deviation in favour of bone resorption in all cases. A net loss of bone, consequently, results.

One first effect of oestrogens concerns the reduction of bone remodelling through direct action on osteocytes, the main regulatory cells. Studies in humans have shown that increased osteocyte apoptosis, as demonstrated in bone biopsies, associates with depletion of oestrogens by GnRH analogues administered to premenopausal women [22], and that this effect is followed by the activation of BMUs.

Further experimental work has confirmed that there is a direct effect of oestrogens on osteoclasts too. For example, the selective deletion of ERα in mice is followed by loss of bone mass and the extension of the lifespan of osteoclasts in trabecular bone [23]. Vice versa, oestrogens have been demonstrated to suppress the differentiation of osteoclasts by several mechanisms, including the interference with RANKL [24], the overexpression of osteoprotegerin, the decoy receptor of RANKL or the own reduction in the production of RANKL and other pro-resorption cytokines by different cell types (for a review see [19]).

Together with the activation of bone resorption, the deficiency in oestrogens also determines defects in bone formation through a direct action on osteoblasts. Contrary to osteoclasts, oestrogens reduce apoptosis and increase lifespan of osteoblasts. The details of the mechanisms involved in this action of oestrogens are being investigated, although experiences in different models suggest that oestrogens might interfere with oxidative stress and reduce NF-κB, the latter being involved in impairing bone formation subsequent to bone resorption in BMUs [19].

As other NCDs, osteoporosis has a long subclinical period that is susceptible to risk reduction strategies. Menopause defines a period of particular interest because of two main reasons, the increased deterioration of bone mass that initiates at this period and the wide receptivity of women to health promotion during this phase of their lives. It is therefore important to design a most appropriate strategy, which should include both diagnosis and management.

8.3 Diagnosis

There are not specificities that make different diagnostic strategies for osteoporosis in the particular case of the menopausal woman. The basic principle that the main purpose of the action against the disease should be the reduction of the fragility fracture remains as a mainstay in the management plan.

8.3.1 Clinical Assessment

Also as for other stages in life, a detailed clinical anamnesis will provide whether there are clinical risk factors. They should be preferably integrated in the context of

any of the available tools for calculating absolute facture risk. The FRAX risk calculator, which provides absolute risk at 10 years, is supported by the WHO and by other scientific societies, like the National Osteoporosis Foundation (NOF) [25], International Osteoporosis Foundation [26], or others (Fig. 8.3). More risk calculators have been proposed, like the Q-fracture [27] or others, but they have not demonstrated clear advantages. The existence of a prior fragility fracture or parental history of hip fracture, for example, continues to be a strong risk factor, which should receive particular attention, as described in most guidelines [28].

8.3.2 Imaging

Additional diagnostic tools include imaging techniques, where bone densitometry is the main pillar. The status of bone tissue, not only its density, may be measured by several techniques, like quantitative computed tomography and quantitative ultrasound. Densitometry based on X-ray is, nonetheless, the universal priority and, therefore, we will focus on that technique. The basis of its utility resides in that the absorption of X-ray is very sensitive to the calcium content of the tissue. Dual-energy X-ray absorptiometry (DXA) is the most widely used technique, which is taken as a reference for the diagnosis of osteoporosis according to the WHO criteria (see above). Both areal and volumetric density may be measured, but areal BMD is

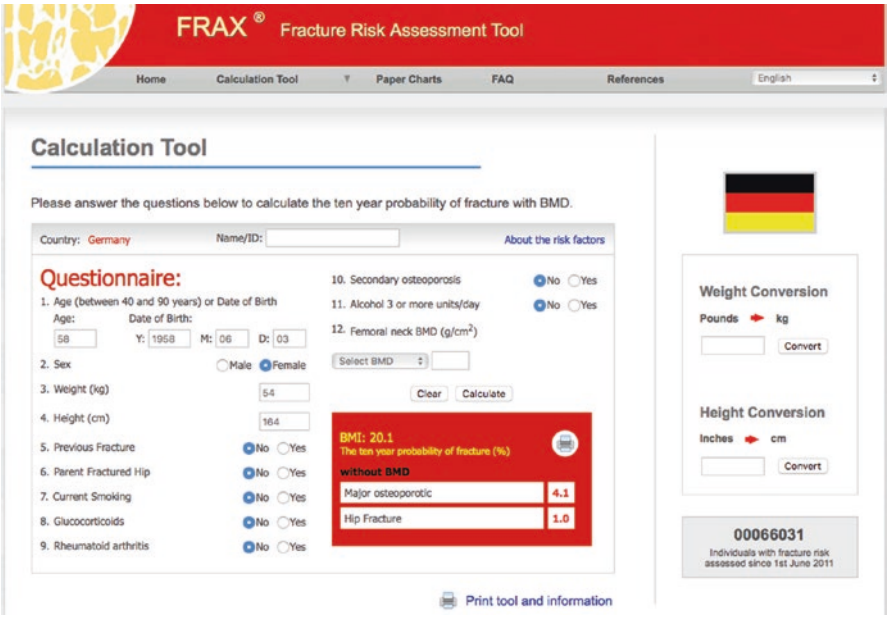

Fig. 8.3 The screen page of the FRAX tool German model (https://www.shef.ac.uk/FRAX), with permission of the World Health Organization Collaborating Centre for Metabolic Bone Diseases, University of Sheffield Medical School, UK

commonly used because it accounts for approximately two-thirds of bone strength and, consequently, is considered a strong risk factor for fracture. An additional advantage of DXA resides in its capacity to visualise deformities of the vertebral bodies, thus avoiding the additional use of conventional X-ray assessment.

In addition to its value to ascertain the risk for future fracture, the information obtained from DXA may also be used as a referent baseline to monitor the evolution of a particular patient. This is of interest in the case of postmenopausal women, because the rate of bone loss has an individual profile, and some women, those defined as "fast losers" in some studies, show a specific sensitivity to oestrogen drop. Also, observational studies have confirmed that the change rate of BMD in a treated patient is useful to determine the evolution of the future fracture risk [29]. The slow response of BMD to treatment is, however, a difficulty for taking advantage of this option of DXA. Moreover, the absence of BMD increase does not necessarily imply the absence of therapeutic response.

Trabecular bone score (TBS) is a novel method that, based upon the spine imaging provided by some specific densitometers, may give information that relates with bone texture and microarchitecture. A series of recent studies have suggested that TBS may improve fracture risk prediction over that provided by conventional DXA, particularly in some specific cases, like diabetes [30]. The potential of TBS, nonetheless, still needs investigation.

8.3.3 Biochemical Markers

Bone biochemical markers are analytes that result from the metabolic events in bone. Some of them are produced as a consequence of resorption by osteoclasts while others are released as a result of the osteoblastic activity. Since both cell types are coupled in the remodelling process because of the activation of the BMUs, both types of markers increase during raised resorption.

The great potential advantage of bone markers is that, if they are specific enough and the analytical method is sufficiently precise, a real-time report of the status of bone metabolism may be obtained. The magnitude of the treatment response, for example, might be assessed without waiting for the densitometric response.

Furthermore, their baseline value may be taken as an indicator of the magnitude of the resorptive process and, should this behave as a stable phenomenon, a certain prognosis of the fracture risk might be seized [31]. This is a very important feature to better detect the most abundant profile of fractured subjects, who have normal or only slightly decreased BMD for their age [32].

The choice of bone markers keeps increasing in parallel with the better knowledge of bone metabolism [33]. Resorption markers include collagen degradation proteins, noncollagenous proteins, osteoclastic enzymes and, more recently, osteocyte activity markers. Degradation products of type 1 collagen are produced by the activity of cathepsin K, an osteoclastic enzyme. Both the carboxy (CTX-1) and the amino-terminals (NTX-1) may be measured and are the most consolidated options. Indeed, CTX1 in serum has been recommended as reference bone resorption marker by IOF.

Formation markers have had less use. The list includes procollagen type I propeptides, osteocalcin and alkaline phosphatase. The procollagen type I propeptides are originating mainly from activated osteoblasts and result from the posttranslational cleavage of type I procollagen molecules by proteases. Both the N- and the C-terminal, PINP or PICP, are produced, but the most reliable and preferred is PINP, which is the reference formation marker in most studies. The practical value of PINP has increased considerably in the latter years.

In practice, the main limitation of bone markers is their variability, mainly due to the circadian and seasonal variation of bone metabolism. Even so, they may be taken as an adjunct to DXA for aspects like identification of fast losers in postmenopause, the above-mentioned prediction of fracture risk, and for monitoring the effect of anti-resorptive therapy. This latter advantage is of value only when using anti-resorptives capable of achieving a substantial reduction in bone turnover, like bisphosphonates or denosumab.

8.4 Management

The acceleration of bone resorption initiates prior to menopause [20], and the phenomenon keeps for many years, probably up to the end of life [34]. This means that, considering the global life expectancy, this state will last for 30 or more years. Moreover, it is known that most fragility fractures, including hip and vertebral, attain a significant incidence at relatively advanced age, not earlier than 70 years. Also important, most anti-resorptives have shown efficacy in clinical trials in which the median age of the participating women was advanced, far from the immediate postmenopausal period, and their prolonged use is not free of disadvantages [35]. Putting all these arguments together, it seems that most of the women that enter menopause should attend the reduction of osteoporosis risk with an armamentarium in which potent anti-resorptives are not a first option. Then, the identification of the optimal way to manage this long period of women's life raises several questions.

8.4.1 Assessment of Osteoporosis Risk

Osteoporosis should be an issue in the routine management of menopausal women. The purpose should be the identification and evaluation of high-risk individuals. A detailed clinical history is mandatory to disclose whether there are specific clinical risk factors, particularly the strong ones, a history of previous fragility fracture and parental history of hip fracture. The review of the list of clinical risk factors included in FRAX may help because it is quick and at the same time may be useful to position the woman in relation to her future (10 years) risk for fracture.

The option of a systematic DXA assessment is a matter of some debate. The majority of guidelines do not recommend its practice until the age of 65 years unless there are one of the strong risk factors mentioned above [36]. This is so because, even accepting that the proportion of women with osteoporosis at 50 years that will suffer from a fracture in the next 10 years is approximately 45%, a 96% of the

fractures will occur in women without osteoporosis [28]. One Australian study has added low body mass index as an independent risk factor, although the study referred to densitometric osteoporosis and not to fragility fracture [37]. There is no established recommendation on the use of biochemical markers.

8.4.2 Lifestyle as a Risk Reduction Strategy

Menopause is an excellent opportunity to implement healthy lifestyle in women who do not meet the criteria for DXA scanning. As mentioned above, they will be majority. This includes avoidance of toxics, mainly alcohol abuse and tobacco, good nutrition and regular practice of exercise. Regular physical activity may reduce the progression of ageing-associated sarcopenia, slow or even equilibrate the loss of bone mass and improve neuromotor coordination to decrease the risk of falls. Additionally, there is an impact on mood and wellness, which may translate into improvement of the quality of life, and on other organs and systems. So, it is a most appropriate option, which should be strongly recommended, to manage this period in the life of women [38].

Nutrition has received attention, particularly in what refers to the adequate intake of protein, calcium and vitamin D. The literature on the effect of calcium and vitamin D on the reduction of fracture is mixed, specifically in what refers to pharmacologic calcium. No discernible effect of calcium on hip fracture was detected in a meta-analysis pooling data from seven prospective cohort studies including 170,991 women. Moreover, data from Swedish women attending the mammography national programme and followed for 19 years showed that women with higher calcium intakes, well above the 1 g/day, had an increased risk for hip fracture [39] (Fig. 8.4). Moreover, some studies have shown that high dosages of pharmacologic calcium may be harmful in that there is an increase in kidney stones [40] and even myocardial infarction (24% increased risk in a meta-analysis pooling randomised studies) [41].

The possibility that high intakes of calcium, with or without vitamin D, may be harmful has moved scientific societies to strengthen a clear message. The recommended nutrient intake (RNI) of calcium is 1000 mg/day, which should slightly increase to 1200 mg/day in populations at higher risk, as postmenopausal women [42]. Dietary sources of calcium are the preferred option. The corresponding dose of vitamin D should be 800 UI/day, which may be acquired from diet and from fortified dairy products. Fortified yoghurts, for example, contain 200 UI vitamin D.

Some debate has also arisen about the potential of vitamin D to reduce the risk for falls. No definitive conclusion has been reached, particularly because some data have been published arguing that high dosages of vitamin D may even increase the risk for falls.

8.4.3 Hormone Therapy

The whole cascade of symptoms, quality-of-life deterioration and health threats presenting in women's lives at menopause is precipitated and caused by the drastic

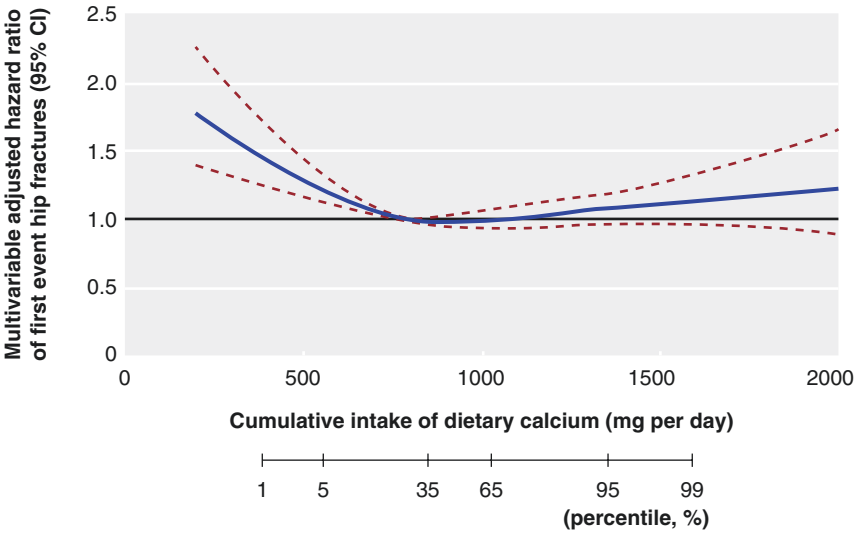

Fig. 8.4 Average intake of dietary calcium and time to first hip fracture as calculated by Swedish investigators working with the data from the Swedish Mammography Cohort. This database includes 61,433 women born between 1914 and 1948 and followed for 19 years. Models were adjusted for a series of confounding variables. Increases in calcium ingestion above 1000–1200 mg/day were associated with increased risk. Hazard ratio is indicated by the solid line and 95% confidence intervals by dashed lines. With permission of the bmjGroup from Warensjö E et al. BMJ. 2011;342:d1473

decline in hormone output, and more specifically, the fall of oestrogens. Consequently, it may be conceived that the reposition of the hormone should reinstate several, if not all, of the lost benefits.

In the case of osteoporosis, the pathophysiological features described above are clearly linked with oestrogen loss. Accordingly, oestrogen replacement should act to reverse every observed action, something consistently reproduced at each step. So, experimental data confirm that oestrogens impair osteoclast differentiation, and maintain osteocyte survival and osteoblast function [19].

At the clinical level, data obtained years ago with the most primitive densitometers clearly confirmed that oestrogens could prevent menopause-associated loss of bone mineral content, as described at the metacarpus in a landmark study by Lindsay et al. [18]. More than 20 years later, the same group performed a dose-dependent study showing that even low dosages of oestrogens were able to maintain, and even to slightly increase, BMD at the spine [43]. Similar results have been observed with low-dose transdermal oestradiol [44], and have been widely reproduced. The consistence of the findings confirms that the protective effect on the bone may be attained with dosages below those required for symptom control.

Hormones do not seem to have a significant residual effect after treatment withdrawal, with most of the BMD gain being lost in 1–2 years [45]. Interestingly, comparison with other anti-resorptives in osteoporosis prevention (BMD effect) in

menopausal women has shown non-inferiority of hormones, with advantages at some specific territories like the forearm [46].

More ambitious studies have taken the reduction of fracture as an endpoint. The clearest evidence was provided by the Women's Health Initiative (WHI) study, which clearly showed an increase in BMD and a reduction in fracture at the spine, the hip and the forearm, although only the hip effect was significant after adjustment for multiple comparisons [47]. Importantly, this effect was found in a population of healthy women.

The detrimental effects on other systems obscured the good performance of oestrogens on the bone in the WHI study. The rise in the diagnoses of breast cancer and the vascular effects, including increases in coronary heart disease, stroke and deep venous thrombosis, were the basis for recommendations of scientific societies and government institutions against the use of oestrogens to prevent chronic disease. This also applied to osteoporosis. Despite being the actor pathophysiologically entitled to restore the trigger mechanisms, and their excellent performance at both experimental and clinical level, the use of oestrogens to prevent or treat osteoporosis is discouraged, or taken as a last option, by most guidelines from scientific societies and governmental bodies.

8.4.4 Pharmacological Compounds

8.4.4.1 Selective Oestrogen Receptor Modulators (SERMs)

Advances in pharmacological chemistry together with the better knowledge of ER biochemistry have generated a number of synthetic compounds that have a molecular conformation distinct to oestrogens but share their potential to interact with the ER. The structural differences with oestrogens determine that their agonist/antagonist equilibrium changes as a result of the three-dimensional molecular configuration or the target tissue [48]. SERMs are grouped into families according to the root biochemical structure, and several of them have been approved for use with humans [49].

The most attractive property of SERMs is that molecules may be shaped to maintain the advantages of oestrogens, for example in osteoporosis, while getting rid of the disadvantages. This search of the perfect SERM keeps being a constant in the latter years.

Two compounds, raloxifene and bazedoxifene, have been approved for treating osteoporosis in several countries. Both raloxifene and bazedoxifene have demonstrated increases in BMD and effective reduction of vertebral, but not hip fractures [50, 51]. There was a protective effect against nonvertebral fractures in corresponding post hoc analyses [51, 52]. The size of the impact on the bone seems slightly lower than that achieved by oestrogens. Interestingly, raloxifene has demonstrated reduction in the risk for breast cancer [53], although as for oestrogens, an increase in deep vein thrombosis was apparent in the pivotal studies [50, 51]. Health economy analyses have shown acceptable cost/effectiveness of SERMs [54, 55].

Bazedoxifene has demonstrated a more antagonistic effect than raloxifene in endometrium, and this interesting property has been taken as the basis for development of new formulations in which bazedoxifene is mixed with oestrogens to counterbalance the oncogenic potential of oestrogens on the endometrium or the breast.

8.4.4.2 Other Anti-resorptives

The armamentarium of drugs with proved effectiveness against osteoporosis keeps increasing at good pace. The bone-forming agents emerge among the most recent novelties [56, 57], but the interest in the field of postmenopausal osteoporosis continues being focused in anti-resorptives. This is so because menopause favours bone loss since the fall of oestrogens increases bone resorption. Bisphosphonates and denosumab are two well-consolidated options that have proved effectiveness as anti-resorptives.

Bisphosphonates

These molecules are incorporated into the mineralised bone because of their affinity for calcium. Bisphosphonates are toxic for osteoclasts, so that they condition cellular demise when ingested in the course of the osteoclast-dependent resorptive action. In such a simple way, bisphosphonates drastically reduce bone turnover. Several compounds have been marketed and are now very good cost-effective options [58]. Alendronate, risedronate, clodronate, zoledronate and ibandronate have been those with higher popularity. They may be administered by oral and intravenous route. Oral bisphosphonates may be used in weekly and monthly doses with similar impact on BMD and bone markers as that of the daily administration. Randomised controlled trials including high-risk women have shown that oral bisphosphonates reduce vertebral fractures by approximately 40–50% and hip fracture by 51% (alendronate) [59], and by 30% (risedronate) [60] in some specific populations.

The highly effective reduction of bone turnover has become a difficulty in the long-term use of bisphosphonates. The lack of a minimal activity of the BMUs has favoured two rare but serious adverse events, osteonecrosis, particularly at the jaw [61], and atypical femoral fractures [62]. This has popularised the new strategy of drug holiday [63], which aims at intercalating periods without treatment in the course of long-term use of bisphosphonates.

Denosumab

The first biological treatment in osteoporosis is represented by denosumab, a human (IgG2) antibody that binds to RANKL, thus drastically reducing the differentiation of osteoclasts. The dose of 60 mg administered in the form of subcutaneous injection every 6 months achieved a reduction of vertebral fractures by 68% and hip fractures by 40% as compared with placebo [64].

Because denosumab is a powerful anti-resorptive, and similar to bisphosphonates, the antibody has been associated with increased risk for osteonecrosis of the jaw and atypical femoral fractures [65].

Conclusion

Osteoporosis is a disease with a strong gender profile. Menopause adds risk and therefore is a period of particular attention. Moreover, the age at menopause is still early enough to implement lifestyle measures that will provide benefit not only for bone but also for other systems, like the vasculature, the muscle, the central nervous system or others.

Fractures are rare at the age of menopause unless women suffer from additional risk factors. This is why the health exams at this period of the women's life should include a review of the risk factors for osteoporosis. Most women will be free of them and, consequently, should be advised healthy lifestyle only. This will include the avoidance of toxics, tobacco or excessive consumption of alcohol, a balanced diet in which the recommended amount of calcium (1200 mg/day) plus vitamin D (800 UI) is achieved, and regular physical activity. These measures will improve general health and quality of life and, again, should be the only recommendation to the widest majority of women.

Women with risk factors are fortunately very few, and should be studied adequately. This adds a bone densitometry and, if risk is sufficiently high, the use of anti-resorptive drugs. The selection of the drug should account that women living the early phases of menopause, usually aged less than 60 years, have a long life expectancy in front. Since one strong risk factor of osteoporosis is age, the indication for treatment will keep being stronger as years pass. This is why SERMs add two advantages, the reduction of the risk of breast cancer (raloxifene) and a smooth reduction of bone turnover, which discards the risks of jaw osteonecrosis or atypical femoral fracture. Also, SERMs reduce the risk of vertebral fractures, which rank prior to hip fracture in the chronologic sequence of osteoporotic fractures. After a certain number of years, SERMs may be changed for bisphosphonates [66]. This sequence, however, results from clinical judgement and has not been substantiated by any study. Therefore, initiation with bisphosphonates, for example, may be a good option as well. Denosumab, instead, should be left for women with higher risk of fracture [64, 65], which means women of more advance age, or with high risk for hip fracture.

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The Metabolic Syndrome in Mid-Aged Women

9

Faustino R. Pérez-López and Peter Chedraui

9.1 Introduction

The description of the metabolic alterations associated with diabetes mellitus and hypertension was independently reported at the end of the first quarter of the twentieth-century by Marañon (Spaniard) and Kylin (Swedish) [1, 2]. More than half of a century was needed in order to redefine the features that currently compose what today is known as the metabolic syndrome (METS) [3, 4]. Since the description of the first case of METS, the entity has been the focus of intense research involving many areas of knowledge and being linked to various diseases. On the other hand, being defined as a syndrome (not disease) generates overlapping and bidirectional relationships with diseases and medical conditions. The METS includes three of the following items: low high-density lipoprotein-cholesterol (HDL-C) levels, hypertriglyceridemia, hyperglycemia, hypertension, and obesity. It increases the risk of type 2 diabetes mellitus (T2DM), cardiovascular disease, and stroke among other conditions. The prevention and treatment of the METS is a health priority among mid-aged and older women [5, 6]. The importance of the syndrome increases as the prevalence of excessive weight and/or obesity does [7]. It has been estimated that its pernicious effects over cardiovascular health are very similar to those of smoking. Fortunately, changes in health styles and diet, promotion of exercise, pharmacological treatment, and support of qualified professionals may in fact control the entity.

The causes of the METS are not clearly identified, although they have been related to overweight and obesity, sedentary lifestyle, and insulin resistance. These

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associations are accompanied by oxidative stress, a pro-inflammatory status, and the risk of atherosclerosis which alter numerous cellular functions throughout the body. Despite this, other etiological possibilities have been sorted out such as alterations of the digestive microbioma, hypovitaminosis D, differences in epigenetic patterns, mitochondrial alterations, and activation of inflammatory pathways [8–11].

9.2 Diagnostic Criteria for the METS

Definitions of the METS have evolved throughout time, a fact that has been related to an improvement in the knowledge of its biology, and the consensus of various scientific organizations. For instance, while the World Health Organization (WHO) focuses definition on insulin resistance, the International Diabetes Federation (FID), and the consensus of various scientific societies, considers obesity the key diagnostic element of the syndrome, even after adjusting for ethnics (Table 9.1) [12–15]. The prevalence of the METS increases significantly as body mass index (BMI) and other indicators of obesity do. Therefore, the risk of the METS is higher among individuals with excessive weight or visceral adiposity as compared to those with normal anthropometry [16]. Despite this, even lean individuals could have the METS [17].

The prevalence of the syndrome is generally similar even when different classifications are used within a given population. However, each diagnostic criteria determines the inclusion of different subjects; hence, prevalence may vary: for instance, if diagnosis is centered on central obesity or abdominal obesity using various adiposity cutoff values or if based on insulin resistance or cardiovascular risk parameters.

9.3 The Metabolic Syndrome During Female Mid-life

The precise etiology of the METS has not been established, although it has been related to diet and lifestyle. Many characteristics of the syndrome are similar to impaired insulin sensitivity and hyperglycemia (and other metabolic alterations); indeed, the pancreas tries to overcome the metabolic dysfunction by producing more insulin (hyperinsulinism). The impairment of insulin sensitivity produces cortisol elevations which in turn creates an inflammatory reaction with concomitant negative effects upon all body tissues. Muscle fatigue is very common due to the lack of sufficient glucose in skeletal muscles. In addition, body weight gain (fat accumulation) potentiates the inflammatory status, leading to a vicious circle difficult to be broken. During the menopausal transition additional hormonal, sociological, and personal factors may enhance the severity and the risk of presenting the METS (Fig. 9.1).

The risk of the METS and hyperinsulinism is also increased by dietary and food components. Precooked foods, synthetic snacks and sodas, salad dressings, and many industrial foods may be linked to obesity, insulin resistance, and components

Table 9.1 Metabolic syndrome definitions by different organizations

Organizations	Insulin resistance or its subrogates	Obesity	Microalbuminuria	Fasting glycemia	Triglycerides	High-density lipoprotein cholesterol (HDL-C)	Hypertension (blood pressure)
WHO, 1998 [12] [insulin resistance plus 2 of other 4 findings]	Insulin resistance (glycemia >100 mg/dL) or its surrogates, impaired glucose tolerance or type 2 diabetes mellitus	Waist/hip ratio >0.9 in men or >0.85 in women, or BMI >30 kg/m^2	Albumin excretion ≥20 μg/min or albumin/creatinine ratio ≥ 30 mg/g	See insulin resistance	≥150 mg/dL (1.7 mmol/L)	HDL-C <40 mg/dL (1.03 mmol/L) in men or 0.50 mg/dL (1.29 mmol/L) in women	Systolic blood pressure ≥140 or diastolic blood pressure ≥90 mmHg
The NCEP ATP III, 2001 Panel [13] [3 or more findings]	Insulin resistance is not needed	Waist circumference >102 cm in men or >88 cm in women	–	≥110 mg/dL	≥150 mg/dL (1.7 mmol/L)	<40 mg/dL (1.03 mmol/L) in men or <50 mg/dL (1.29 mmol/L) in women	Systolic blood pressure ≥ 130 or diastolic blood pressure ≥ 85 mmHg

(continued)

Table 9.1 (continued)

Organizations	Insulin resistance or its subrogates	Obesity	Microalbuminuria	Fasting glycemia	Triglycerides	High-density lipoprotein cholesterol (HDL-C)	Hypertension (blood pressure)
International Diabetes Federation, 2006 [14] [abdominal obesity (according to ethnicity) and two or more others findings]	–	Caucasians: Waist circumference ≥80 cm in women, or ≥94 cm in men. It is assumed that if BMI >30 kg/m^2 subject has abdominal obesity (waist circumference not needed to be measured)	–	≥100 mg/dL (5.6 mmol/L) or previous type 2 diabetes mellitus diagnosis. If fasting glucose > 5.6 mmol/L or 100 mg/dL, is recommended to perform a glucose tolerance test (although not essential to define the syndrome)	≥150 mg/dL (1.7 mmol/L), or receiving specific treatment for this alteration	<40 mg/dL (1.03 mmol/L) in men or <50 mg/dL (1.29 mmol/L) in women, or receiving specific treatment for this alteration	Systolic blood pressure ≥130 or diastolic blood pressure ≥ 85 mmHg or receiving specific treatment for this alteration

International Diabetes Federation Task Force on Epidemiology and Prevention, National Heart, Lung, and Blood Institute, American Heart Association, World Heart Federation, International Atherosclerosis Society, International Association for the Study of Obesity, 2009 [15]	–	Waist circumference ≥88 cm in women, or ≥102 cm in men	–	≥100 mg/dL (5.6 mmol/L)	≥150 mg/dL (1.7 mmol/L), or receiving specific treatment for this alteration	<40 mg/dL (1.03 mmol/L) in men or <50 mg/dL (1.29 mmol/L) in women, or receiving specific treatment for this alteration	Systolic blood pressure ≥130 or diastolic blood pressure ≥ 85 mmHg or receiving specific treatment for this alteration

BMI body mass index, *NCEP ATP III* National Cholesterol Education Program Adult Treatment Panel III, *WHO* World Health Organization

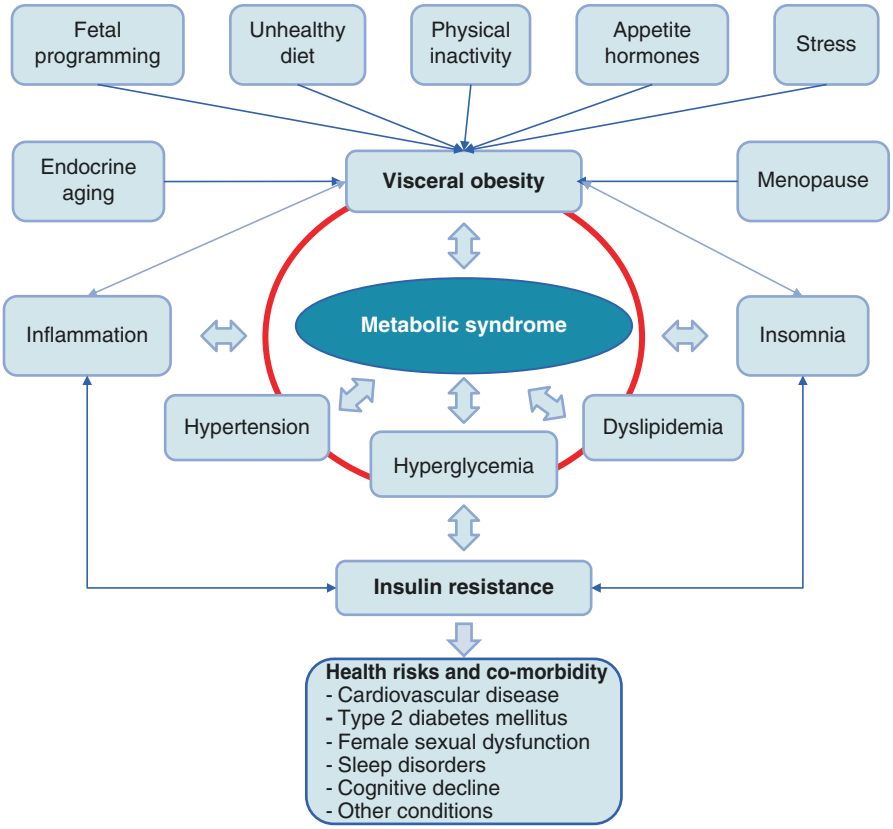

Fig. 9.1 Clinical, behavioral, and endocrine factors associated with the METS risk. Visceral obesity and insulin resistance and their relationships with health risks and comorbid conditions

of the METS. Interrupted sleep and insomnia may also alter hormonal circadian rhythms (growth hormone, cortisol) and insulin growth factors (IGFs). IGF-1 has protective effects against the deleterious pro-inflammatory changes that cause progression of insulin resistance and the METS. Inadequate nutrition may decrease insulin concentration in the portal vein system producing a reduction of hepatic IGF-1 synthesis [18].

Peri- and postmenopausal women are prone to reduce their physical activity where in addition to ovarian steroid hormone adjustments the net effect will be changes in body composition, fat mass infiltration in the muscle mass, and finally aggravation of insulin resistance and the pro-inflammatory status [19, 20]. The prevalence of the METS differs among pre- and postmenopausal women; but in general its increase is correlated to weight gain, changes in lifestyles, and endocrine adjustments. One study found that 41.5% of postmenopausal women (mean age 55.9 years) had the METS [21]. It has been estimated that the menopausal transition is related to an increase of 2–3 kg during a 3-year period with changes in body composition.

In a sample of Spanish mid-aged women (mean age 49.9 years), METS prevalence was 23.1%, with 66% having natural menopause and 38.9% obesity. Women with the METS were older, married in a higher rate, had altered glucose and lipid levels and had higher Kupperman Index scores as compared to those without the syndrome [22]. On the other hand, menopausal hormone therapy (MHT) for 10 years did not increase the risk of the METS in comparison to those not receiving hormones, although treated women had higher baseline glucose levels as compared to untreated controls [23].

In a series of postmenopausal women (mean age 55 years) it was reported that those with the METS had higher BMI than those without the syndrome, but similar interleukin 6 (IL-6) and tumor necrosis factor alpha. However, upon pooled analysis, those with abdominal obesity had higher IL-6 levels, and those with hypertension had increased levels of both cytokines. Moreover, there was a correlation between the number of positive components of the METS and levels of both cytokines [24]. In the same cohort, nitric oxide levels correlated inversely with HDL-C levels and positively with glucose and triglyceride levels and the number of positive METS items [25].

After the menopause the prevalence of the syndrome (and its components) increases and thus cardiovascular risk which could be explained, at least in part, due to changes in the secretion of sex steroids and cytokines [5, 26]. Postmenopausal women with the METS display higher adipsin, leptin, resistin, and insulin levels, and homeostasis model assessment of insulin resistance (HOMA-IR) values, together with lower adiponectin levels. Lower adiponectin levels correlated to lower HDL-C, triglyceride, and glucose levels. In this series, women with the METS displayed higher IL-6 (inflammation marker) and lower urokinase-type plasminogen activator levels (a marker of endothelial dysfunction) [27, 28].

Irisin is a myokine that produces the conversion of white adipose tissue into brown-fat-like tissue and mediates the beneficial effects of exercise on metabolism. Irisin is associated to an increased risk of the METS and cardiometabolic endpoints. Circulating irisin is increased in subjects with the METS correlating with its components, high fasting glucose, high triglycerides, and increased BMI, blood pressure, and HOMA-IR values [29]. The METS has been related to various diseases and comorbid conditions with negative interrelationships in terms of health (Fig. 9.1).

9.4 Female Sexual Dysfunction

Female sexual dysfunction is a multidimensional problem related to several biological, psychological, and social determinants. During the pre- and postmenopause the METS affects sexuality negatively, with impact on several of its domains such as satisfaction, pain, and desire as determined with the Female Sexual Function Index (FSFI) [30]. In postmenopausal women, sexual dysfunction has been related to hyperglycemia [31]. Maseroli et al. [32] have studied the pulsatility index of the clitoris using Doppler. Women with obesity or the METS have high pulsatility

indices, which are higher as are the number of positive components of the syndrome. Moreover, indices negatively correlated with the arousal and satisfaction domain scores of the FSFI. The authors conclude that the vascular resistance of the clitoris positively correlates with the METS, and especially with insulin resistance.

Postmenopausal women of the Rancho Bernardo cohort have been studied with the FSFI. These women had a mean age of 73 years, 39% were sexually active, and 41.5% had the METS. Total FSFI scores did not significantly differ between sexually active and inactive women, although the number of METS components was significantly associated with lower sexual activity, desire, and satisfaction. In addition, waist girth, diabetes, and hypertension were related to decreased sexual activity and elevated triglycerides to low desire. Also women with coronary heart disease had limited sexual activity [33].

9.5 Hyperinsulinism, Type 2 Diabetes, and Cardiovascular Risk

Many symptoms and changes related to the menopause, such as weight gain, fatigue, weakness, irritability, thirst, increased appetite, sexual dysfunction, or polyuria, are in fact associated to disorders of carbohydrate metabolism and hyperinsulinism [34]. In the postmenopausal period, sex hormone-binding globulin serum levels have an inverse correlation with insulin resistance and the risk of T2DM [35]. Within this scenario, one should add the age-related increased risk of T2DM. Other contributing factors for insulin resistance are obesity, sedentary lifestyle, sleep disorders, unbalanced diet, excessive tobacco and alcohol consumption, and vitamin D and calcium deficiency. In addition, the presence of the METS increases T2DM risk and has a predictive value for insulin resistance which can be increased fivefold [36].

Low estradiol levels after the menopause increase cardiovascular disease risk [5, 26, 37]. Postmenopausal dyslipidemia is characterized by an increase in LDL-C and a decrease in HDL-C. The antiatherogenic effects of HDL-C decrease after menopause onset, possibly in relation to the profile of subclasses of lipoproteins that has a clear negative impact, accelerating the atherosclerosis process [38].

A BMI above 30 kg/m^2 has a negative effect on all cardiovascular risk indicators. Indeed, it increases insulin resistance, blood pressure, blood glucose, and triglyceride levels, and decreases HDL-C values [39]. The digestive hormone ghrelin influences insulin sensitivity but also has negative effects on blood pressure, lipoprotein metabolism, coagulation, immunity, and inflammation [26, 40].

The link between the METS and increased cardiovascular disease risk has repeatedly been reported, regardless of the criteria used to define the syndrome. The increased risk of cardiovascular disease and mortality due to coronary heart disease ranges from 1.5 to 3 times higher in several prospective cohorts [41]. One meta-analysis has reported that the METS doubles cardiovascular disease risk while increasing 1.5 times the mortality rate due to all causes [42]. These higher risks have been related to the criteria used to define the METS. Nevertheless, a multiethnic,

large-scale international research study called the INTERHEART reported that the risk of myocardial infarction is 2.5-fold higher in the presence of the METS as compared to its absence, yet similar for cardiovascular disease, using WHO definition and that of the International Diabetes Federation [43].

9.6 Insomnia

During sleep, growth hormone is released while cortisol secretion is inhibited. Conversely, sleep disturbances are associated with cortisol release that mobilizes glucose stores and stimulates insulin secretion. Thus, repeated sleep loss becomes a risk factor for obesity and T2DM. The relationship between increased obesity risk and sleep impairment is pivotal for the regulation of hormones that control appetite and energy expenditure, such as leptin and ghrelin [27]. Hence, control and quality improvement of sleep are desirable interventions aimed at reducing obesity, the METS, hyperinsulinism, and T2DM.

In a sample of postmenopausal women, 33% displayed insomnia according to the Athens Insomnia Scale, with no differences observed if the METS is present or not. Multiple regression analysis found that higher total insomnia scores correlated with the use of psychotropic substances, the intensity of hot flashes and female depressive symptoms or anxiety, and partner premature ejaculation, but not the METS [44].

The most frequent features of insomnia, such as difficulty in initiating sleep (DIS), difficulty in maintaining sleep (DMS), early awakenings (EA), and excessive daytime sleepiness (EDS), may be associated with the METS and cardiovascular disease risk. In a cross-sectional study, Lin et al. reported that the METS was related to DIS and DMS. In addition, after stratifying sleep duration into <7, 7–8, and ≥9 h/night, the prevalence of METS was associated with short sleep duration regardless of insomnia symptoms. Despite this, there is no association between the combination of insomnia symptoms and sleep duration and the prevalence of the METS [45].

Prospective results of lifestyle intervention (diet and exercise) among individuals with a recent diagnosis of T2DM (with high obesity rates at baseline) indicate that after 6 months loss of sleep is associated with obesity and insulin resistance, and after 12 months of sleep impairment insulin metabolism was also severely impaired. It is estimated that for every 30 min of sleep loss per day, after 1 year the risk of obesity and insulin resistance increases by 18% and 41%, respectively [46].

In the cross-sectional Three Cities study, symptoms of insomnia in older people have several manifestations: DIS, DMS, EA, and EDS. EDS increases the risk of the METS and this association was independent of a previous history of cardiovascular disease, insomnia symptoms, obesity, and snoring [47]. Given the bidirectional possibilities of this relationship, prospective studies are needed to clarify the results.

On the other hand, sleep disturbances may be accompanied by alterations in the digestive microbiota that can aggravate the METS and have negative metabolic consequences in terms of weight gain and an increase of insulin resistance [48].

9.7 Genitourinary Pathology

The presence of the METS has been associated in postmenopausal women with endometrial and breast cancer, as well as non-gynecological neoplasms [49]. Some METS components have been linked to cancer risk, although this is not a universal phenomenon or relationship. The influence is not the same, when it comes to insulin resistance and the risk of female genital cancer (e.g., endometrial or ovarian cancer) [50–52].

The METS is associated with an increased risk of uterine fibroids which may be due to shared predisposing factors. Some studies suggest similar risk factors for uterine fibroids and atherosclerosis such as obesity, hypertension, and metabolic alterations [53]. In the North Finland Birth Cohort, a population-based long-term study, women born in 1966 were followed up and studied again at the age of 46. It was found that the METS was associated with a hospital discharge-based fibroid diagnosis (OR = 1.48 [95% CI 1.09–2.01]). In addition, every one unit increase in the waist-hip ratio was also related with fibroids (OR = 1.48 [95% CI 1.09–2.01]) [54].

The components of the METS have been linked to the presence of endometrial polyps in young postmenopausal women. Several variables were studied in a cross-sectional study of postmenopausal women. Those with histologically diagnosed endometrial polyps were compared to those with no bleeding and an endometrial thickness <5 mm (controls). A higher percentage of women with polyps were obese as compared to controls (72% vs. 39%). In addition, abdominal perimeter and the incidence of diabetes, hypertension, and dyslipidemias were higher in women with polyps than in the control group. Prevalence of the METS was also higher (48.5% vs. 33.3%). The data suggest that in postmenopausal women obesity, dyslipidemia, hyperglycemia, and the METS are predictive factors for endometrial polyps [55].

The METS is associated with an increased prevalence of stress urinary incontinence (SUI) in both pre- and postmenopausal women as compared to those without the syndrome. Furthermore, in women with the METS, the prevalence of SUI is higher among postmenopausal as compared to premenopausal ones. In addition, when components of the syndrome are taken into account separately, waist circumference and increased glucose levels were associated with SUI [56]. On the other hand, a systematic review has found links between the overactive or neurogenic bladder and the METS and obesity as a component of the syndrome [57].

9.8 Osteoporosis and Fracture Risk

Among individuals with the METS, bone mineral density (BMD) and fracture risk are determined by the balance of the dominant factors of the syndrome. Hyperglycemia and diabetes tend to decrease BMD, while hypertriglyceridemia and lower HDL-C levels related to obesity seem to protect against fracture risk. A meta-analysis of 17 very heterogeneous studies reported that the METS is associated with a non-significant reduction of fracture risk; and the analysis of 16 studies shows no differences in vertebral, femoral, or calcaneus BMDs compared to individuals without the syndrome [58].

The Rotterdam Study provides some information regarding the relationship between the METS, hip bone geometry, femoral BMD, and risk of osteoporosis and incidental fractures. After adjusting for age, BMI, and consumed drugs, women with the METS have a lower risk of osteoporosis; and fracture risk is not increased by the syndrome [59]. In a meta-analysis of eight prospective epidemiological studies, the METS was not explicitly associated with prevalent or incidental fractures [60]. In addition, no significant correlations between the METS and BMD or bone metabolic variables have been demonstrated [61].

9.9 Cognitive Decline

The METS has a negative influence on cognitive ability as it persists over the years, especially when it coexists with T2DM and cardiovascular disease and if the necessary therapeutic precautions have not been taken. In a cohort of individuals with normal cognitive status at age 55, it has been reported that those with cardiovascular risk factors or diabetes have higher chances of presenting cognitive problems and, more importantly, the determinants are the METS components: abdominal adiposity, hypercholesterolemia, hyperglycemia, hypertension, and hypertriglyceridemia [62]. Subjects with the METS have a 4.4 likelihood ratio (95% CI 1.30–14.82) of progressing to mild cognitive impairment in less than 4 years as compared to those without the syndrome [63].

The inflammatory status caused by increased adipose mass in subjects with the METS is the common pathway that favors insulin resistance [8]. The early identification and treatment of the METS is a promising way to reduce cognitive disorders, including dementia, which are to date inexorably related to aging.

9.10 Clinical Interventions for the Management of the Metabolic Syndrome

Engaging to healthy habits is pivotal for the prevention and treatment of the METS. Taking into account that obesity and insulin resistance are the central elements of the syndrome, educational measures should be implemented that encourage engaging with a balanced diet and physical exercise. Interventions intended to maintain estrogen protection may delay endocrine changes and body composition during the menopausal transition. On the other hand, treatment of specific components of the METS seems to benefit several parameters and comorbid conditions.

9.10.1 Mediterranean Diet

Healthy diets can maintain the physiology of digestion and prevent the onset and progress of insulin resistance and obesity which ultimately reduce METS risk. The Mediterranean diet (MD) has generated a huge amount of information in recent

years. Ingredients include (1) vegetables (cereals, fruits, vegetables, legumes, nuts, olives), and virgin olive oil as the main source of fat; (2) moderate consumption of fish and shellfish, eggs, dairy derivatives (cheese and yogurt), and mild consumption of red meat; and (3) moderate consumption of alcohol (wine) during meals [8, 64, 65].

In recent years, it has been repeatedly shown that the MD reduces the risk of the METS and has benefits over its components. In addition, the consumption of olive oil, legumes, and red wine is related to a lower prevalence of the METS [66]. The meta-analysis assessing the effect of the MD on the METS confirmed (after adjusting for age, sex, total caloric intake, smoking, and physical activity) that the quartile of maximum adherence to the MD has protective effects on METS components such as HDL-C, glucose and triglyceride levels, blood pressure, and waist circumference as compared to the quartile of lowest adherence [67].

Consuming the MD for 3 months is accompanied by favorable metabolic changes, and a decrease in abdominal perimeter, blood pressure, triglycerides, and homocysteine levels. In addition, it reduces the atherogenic lipoprotein profile [68]. A meta-analysis of observational studies indicates an inverse relationship between the MD and the METS risk (with a relative risk of 0.81, confidence interval 0.71–0.92), and also benefits over its components such as waist circumference, blood pressure, and HDL-C levels [69]. In addition, the comparative meta-analysis of different "prudent" diets, from the major to the lesser category, confirms that the risk of the METS is significantly lower for MD types [70]. On the other hand, adherence to the MD is also associated with a reduced hip fracture risk in postmenopausal women [71].

Beneficial components of the MD modify the gastric microbiome, including metabolic changes in probiotics, prebiotics, omega-3 polyunsaturated fatty acids, and polyphenols [72]. A diet low in fat and high in carbohydrate, but especially the MD, influences the gastric bacterial flora by changing the microbioma composition in different ways. In addition, the changes produced by the MD are more effective in reducing insulin resistance and the risk of developing T2DM [73]. *Roseburia* and *F. prausnitzii* bacteria that produce butyrate may also generate short-chain fatty acids that contribute to the reduction of oxidative stress and inflammation [74]. The impact over gastric microbioma has been studied after 2 years of following a MD, confirming changes in the bacterial profile depending on the presence or not of METS. Thus, the most abundant bacteria in subjects with the METS have an inverse correlation with glucose, triglycerides, and HDL-C levels, whereas those changes do not occur in individuals without the syndrome [75].

9.10.2 Physical Activity and Exercise

Physical activity and exercise produce numerous metabolic and endocrine changes. Prescribing physical exercise is many times more important than medication: exercise is medicine and each personal circumstance has a particular and customizable form [76, 77]. Exercise and training have an important effect on reducing visceral

obesity, METS risk, and changes caused by adipose mass accumulation [78–80]. In addition, moderate to vigorous daily exercise is very effective at reducing insulin resistance and indirectly the METS. Insulin sensitivity increases by 25% by doing 60 min of daily exercise as compared to not exercising [81].

9.10.3 Ovarian Function and Menopause Hormone Therapy

There is an increase of blood triglycerides, total cholesterol, and LDL-C with a slight decrease in HDL-C 6 months after women are treated with hysterectomy and bilateral oophorectomy. In addition, after surgical menopause the carotid pulsatility and resistance indices are increased as compared to women with natural menopause. At the same time, the Kupperman Index is higher among women who had surgical menopause as compared to those having natural menopause [82]. For these reasons, it would be desirable to attempt to replace oophorectomy by salpingectomy as a preventive intervention of ovarian cancer during genital surgery for benign pathology [83].

MHT is currently not recommended for the prevention of metabolic alterations. However, it can be considered within the framework of a broad strategy of prevention of chronic diseases considering a balance between benefits and risks. For instance, estrogenic oral therapy, in postmenopausal women with the METS, is associated with increases in leptin and resistin levels, and decreased ghrelin. Transdermal estrogen therapy increases adiponectin levels and decreases ghrelin levels [84].

Women with absolute contraindications should not use such therapy. MHT is beneficial in reducing several of the METS components, with the transdermal rather than the oral route being preferred. In general, women with the METS can improve various inflammatory parameters with MHT, with the exception of C-reactive protein and metalloproteinase 9, which increase with oral treatment, but not transdermal. However, the benefits of MHT are minimal among women with the METS compared to those who do not have the syndrome [85].

9.10.4 Other Interventions

Given the links between the METS and cardiovascular risk and T2DM, it is advisable to treat the components of the syndrome in an individualized manner, even if the number of positive items does not complete full criteria for the definition of the syndrome. This will provide benefits and prevent health complications [86].

As indicated before, shortening of the sleep period exacerbates the METS and insulin resistance, so it is advisable to encourage educational programs that promote restorative sleep and to correct its fragmentation. This would neutralize the progression of obesity and insulin resistance [46].

Experimental studies have shown that the digestive microbiome has the ability to cause or prevent the METS and can be transplanted to treat obesity and the METS

[10, 87]. The so-called fecal transplantation of the microbiota with butyrate-producing bacteria from individuals without the METS is a new therapeutic opportunity that increases insulin sensitivity and improves metabolism by increasing mitochondrial activity, eliminating endotoxemia, and activating glycogenesis. These may become future specific interventions against obesity and T2DM [88].

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The Impact of Estrogen Decline on Other Noncommunicable Diseases

10

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10.1 Introduction

The ovary is the main source of estrogens in women from menarche to menopause. Besides the key role in reproduction, estrogens have effects on several organs in the body, as confirmed by the identification of estrogen receptors (ER) in multiple tissues. This is not only a biochemical incident without an impact, because there are obvious

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clinical manifestations, like hot flashes, which eloquently show the effect of estrogens on the central nervous system. Therefore, the key question is whether the fall in the estrogen levels in blood will have an impact on the health of women. There is the obvious case of postmenopausal osteoporosis, which is described in a separate chapter, but also important questions in relation with other chronic noncommunicable diseases, among them, those related with the central nervous system, particularly in the area of cognition and mood, cardiovascular disease, or a highly prevalent disease as it is osteoarthritis.

10.2 Cognitive Decline and Mood

10.2.1 Introduction

Basic neuroscience studies have provided evidence that estrogens influence aspects of brain chemistry and morphology known to be important for cognitive functions [1]. That consistency, maintained during decades, has translated with difficulty to specific neural functions because there is no unanimity on the effects of hypogonadism on measures of attention, concentration, or memory in clinical studies [2]. Thus, one issue of interest is the influence of estrogen depletion on cognition across and after menopause and, if confirmed, the mechanism through which it occurs. Moreover, brain function also includes mood states, mainly depression and anxiety. This is why, as proposed by Greendale et al. [3], the potential association of menopausal hormonal changes with brain function may be approached in two ways, directly, i.e., effects on neural cells and systems, and indirectly, i.e., effects of hormonal changes on the brain functions, mainly cognition and mood.

The interest on the action of hormones may also extend to other systems with an impact on brain functions, specifically the vascular tree, which determines the adequacy of cerebral blood perfusion [4, 5]. This area is receiving particular attention because of the changes in perfusion observed during hot flushes, a very frequent symptom of menopausal women. Indeed, recent data suggest that vasomotor symptoms might represent a female-specific risk factor for memory declines during the menopausal transition [6].

Overall, memory complaints are the most frequent claim in people older than 50 years, but the cognitive issue in menopausal women is much broader and affects cognitive functioning in general. As detailed below, not only memory (especially some subtypes as verbal recall and working memory) but also processing speed, cognitive performance, difficulty in concentrating, and, therefore, learning processes are specific functions of interest. With regard to emotional aspects, mood stability and mood disorders are the main issues (Fig. 10.1).

10.2.2 Psychobiological Feasibility

The conception that women have an increased risk of developing cognitive decline (CD) and Alzheimer's dementia (AD) compared to men is widespread in

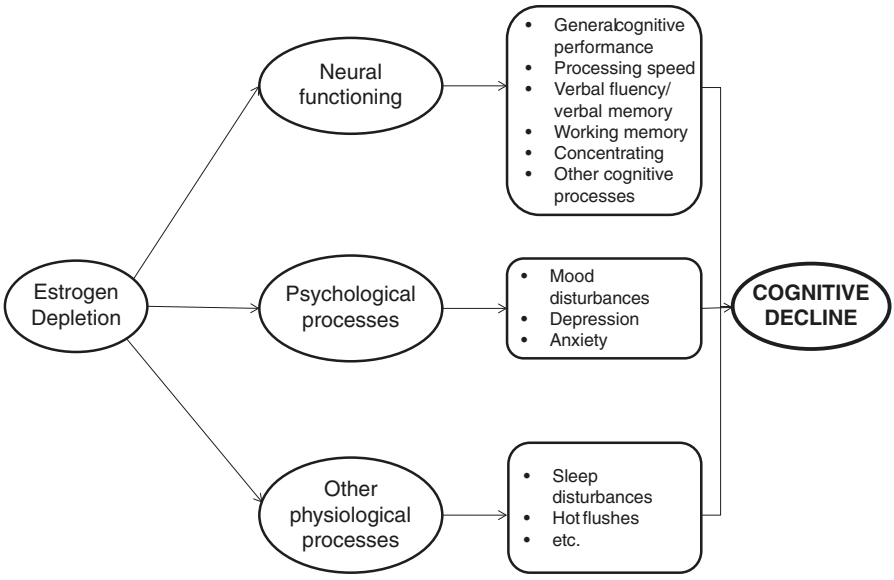

Fig. 10.1 Schematic view of ways and effects of estrogen depletion on cognition

literature [7]. Moreover, it has been postulated that this higher risk may be due to a reduction in the neuroprotective effects of estrogen on the brain in the early postmenopausal period. This view is supported by, for example, some findings suggesting that ovariectomy in premenopausal women significantly increases the risk for the development of memory problems and AD in later life [8]. In the same way, other studies have consistently shown that induced hypogonadism is accompanied by a decline in cognitive test performance [2].

Among the biological mediators underlying the changes, a possible direct role of the raised levels of gonadotropin-releasing hormone (GnRH) on neurodegeneration has been postulated [9]. But interest has focused mainly on estrogens. There is plenty of data about a direct action of estrogens on some brain areas related with memory, mainly prefrontal cortex and hippocampus, which are rich in estrogen receptors (ER). This action may be conveyed through a modulatory effect on the levels of neurotransmitters, which may enhance neuronal growth and formation of synapses [10, 11]. The rationale, therefore, has been that if estrogens benefit the hippocampal and prefrontal cortical functions, the drop of estrogen in perimenopause could negatively impact the cognitive performance. In consistence with that hypothesis, data in rats show effects of estrogens on stress-induced neuroplasticity and activity changes, which has been taken to sustain the assertion that the female brain has a different innate strategy to handle stress. The pathways followed by estrogens have been described in rat models [12].

The biochemical mechanism underlying estrogen neuroprotective effect has to be elucidated considering that there are two subtypes of ER, α and β, as well as a growing number of ER splice variants. For example, recent work has described the pathways

implicating ERα in the pathogenesis of AD [13]. Furthermore, a meta-analysis has found that single-nucleotide polymorphisms of the ERα might favor AD. There is also considerable information on the role of ERβ. For example, selective modulators of ERβ have been demonstrated capable of altering Alzheimer's pathology in transgenic models, and ERβ polymorphisms have been associated with the risk for AD [14].

It is unclear whether the actions of ERα and ERβ are overlapping or independent of each other. There is some information obtained from immunocytochemical studies on brain from AD patients, which have suggested specific roles for each receptor subtype, but the issue is still pending clarification [15].

There is also evidence showing that insulin and insulin-like growth factor 1 (IGF1) play major roles as regulators of growth and regeneration in the central nervous system (CNS) in rodents. It has been hypothesized, for example, that exposure to estradiol may favor the action of IGF1 that, in turn, increases performance of ERα for extended periods, thus favoring protection of hippocampal functions (Fig. 10.2) [16]. Important roles for insulin, which may require the involvement of ER, have been described in spatial memory processing. Specifically, estrogen regulates different insulin-related processes with cognitive correlates (glucose transport, aerobic glycolysis, and mitochondrial function). Accordingly, decline in circulating estrogen during menopause is coincident with decrease in brain bioenergetics and shift towards a metabolically compromised phenotype [17].

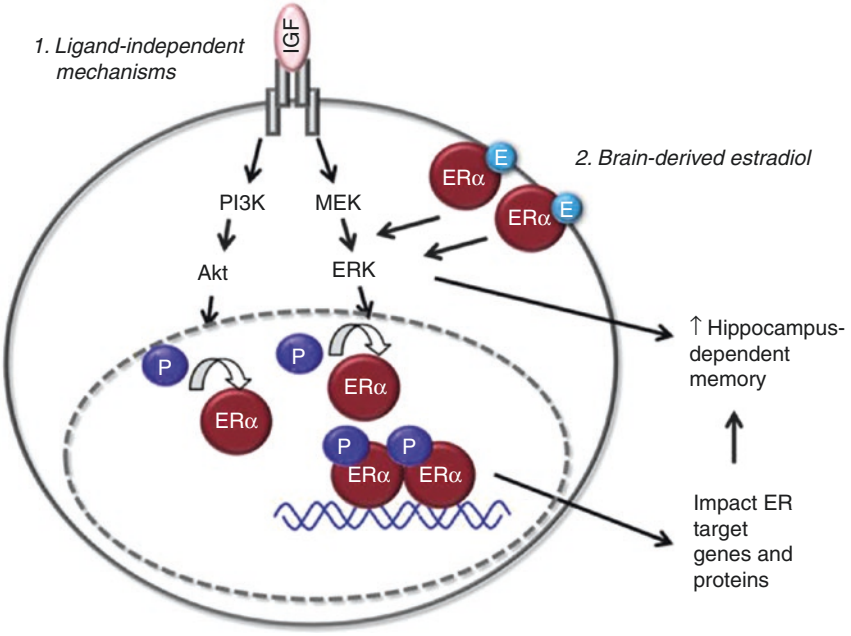

Fig. 10.2 Interactions of activated ERα with intracellular signaling cascades of IGF1 at the hippocampus. With permission of Elsevier, Daniel, Witty, Rodgers. Horm Behav. 2015;74:77–85. Permission conveyed through Copyright Clearance Center, Inc

10.2.3 Studies in Animals

Some studies go back to the hypothesis of effects mediated by GnRH. The point is of interest, because it constitutes an alternative to the role of sex steroids. Some support is obtained from studies showing that luteinizing hormone (LH) is elevated in AD [18]. To disclose whether the elevated level on gonadotropins has an effect on the risk of AD, GnRH analogues (GnRHa) were used in an aged transgenic mouse model. GnRHa produced an acute decline in ovarian hormone output leading to a status similar to menopause. The decrease in LH by GnRHa resulted in an attenuation of amyloid-beta deposition as compared to placebo-treated animals. Also, this reduction correlated with improved cognition [19].

Despite the data in support of gonadotropins, most evidence accumulates with regard to an estrogen-mediated protective effect. So, estradiol increased the synthesis of choline acetyltransferase (ChAT) in the medial septal nucleus, nucleus basalis of Meynert, and frontal cortex [20], as well as high-affinity choline uptake (i.e., the rate-limiting step in acetylcholine synthesis) in the cortex and hippocampus of ovariectomized rats [21]. Also, estradiol has been shown to promote the release of acetylcholine in the cortex and hippocampus following potassium stimulation [22] and during place learning [23].

Together with the effects on cognition, there is interest on the potential effect of estrogens on mood. Animal models are also useful to improve knowledge in emotional issues. For example, depressive-like behaviors in animals are detected by an increase in immobility time and immobile behavior, and a decrease in exploratory and active behaviors. Ovarian hormone withdrawal has been associated with these features in rats [24] and macaques [25]. Thus, increased risk of affective disorders appears to be related with hormonal changes also in animal models, something which overlaps the observations in humans [26]. Other investigators have confirmed that ovariectomy influences affective and, of interest, also somatosensory processing in rats [24]. Further data in pain control are being awaited.

10.2.4 Clinical Studies

The issue of whether the menopausal transition affects cognition in women has been investigated in several trials. The Kinmen Women-Health Investigation (KIWI) [27, 28] is a longitudinal population-based study of rural women in Taiwan. During a follow-up period of 18 months, 114 out of the 495 followed women progressed to perimenopause. Interestingly, all cognitive scores slightly improved except verbal fluency, which was slightly worse. The Seattle Midlife Women's Health Study (SMWHS) explored memory functioning and, in consistence with the KIWI observations, found that perceived memory functioning was more closely related to perceived health, depressed mood, or stress than to perimenopause [29]. The positive correlation of depressed mood with nearly every indicator of memory functioning raises important questions and opens the door to indirect actions of estrogens through their well-known relationship with mood states.

The Study of Women's Health Across the Nation (SWAN) study provided a further step in terms of sophistication, since investigators performed a cross-sectional analysis of a consistent cohort of 1657 women in which menopausal status was assessed together with hormonal levels, estradiol, and FSH. Again, no relationship was found between menopausal status and the cognitive performance tests when adjusting for covariates. This did not change when either estradiol or FSH levels were included in the analysis [30].

10.2.5 Mood and Cognition

The influence of ovarian function on mood states has been claimed in the literature for years. The issue is interesting in itself, but also in what it may affect cognition, which would then be an indirect effect. Indeed, higher levels of depressive and anxiety symptoms are directly related to slightly poorer cognitive performance because both disorders are often accompanied by attention and concentration-deficit symptoms. Specifically, depression can be both a risk factor for dementia and an early indicator of incipient dementia [31]. Thus, cognitive complaints during perimenopause may result from adding perimenopausal anxiety or depressive symptoms to the brain [3].

The role of ovarian hormones on the regulation of affective disorders has been addressed in different ways. Research has demonstrated that the lifetime prevalence rate of mood disorders is significantly greater in women than in men, approximately two times more frequent [12, 32]. Data suggests that estrogen, or its absence, is strongly implicated in the regulation of mood and behavior, as well as in the pathobiology of mood disorders [33]. The interaction of estrogens with the serotonergic systems [34] has been taken to propose estradiol as a protective agent against mood changes related with serotonin withdrawal [35].

Clinical observation also confirms that estrogens play a vital role in the precipitation and course of mood disorders in women. Gender differences in mood disorders first appear after menarche, and continue through reproductive age. Periods of hormonal fluctuations or estrogen instability (i.e., premenstrually, postpartum, perimenopausally) have been associated with increased vulnerability to mood disorders among susceptible women [33].

10.2.6 Possible Actions Through the Vascular System

There is, finally, the potential vascular deterioration as another issue that should be considered when assessing the impact of menopause on cognition. One main point relates to the vascular changes associated with vasomotor symptoms occurring across and after menopause. Again, the SWAN study evaluated whether the decrease in cognitive processing speed detected across perimenopause might have been influenced by the presence of hot flashes. Anxiety and depressive symptoms were also included in the analysis. Investigators only found a small effect

associated with anxiety and depressive symptoms, but no interaction with vasomotor symptoms [30].

A possible long-term effect has been raised as well. The hypothesis that menopause might accelerate atherosclerosis and therefore future cardiovascular risk has a correlate in terms of cognitive function. Vascular factors are involved in approximately half of all dementia cases, probably because they show the cumulative impact of very different factors along life span [36–38].

10.3 Cardiovascular Diseases

Cardiovascular diseases (CVDs) are the number one cause of death globally, both for men and women. It is well documented that morbidity and mortality rates from CVD are higher in men than in women; however this gender gap narrows after the menopause suggesting a role of female sex hormones and aging. In fact the incidence of cardiovascular disease in women increases substantially with aging, probably because the menopause diminishes the gender protection contributing to an adverse impact on cardiovascular risk variables. Nevertheless, whether this higher cardiovascular risk is a function of aging or a consequence of the loss of endogenous estrogen due to the menopause or both has been debated in the literature for many years.

There is a wealth of data about the effect of estrogens on the vasculature or on cardiovascular risk factors, like lipids, or others. The analysis of that information will facilitate the understanding of the clinical observations.

10.3.1 Effects of Estrogen on the Cardiovascular System Physiology

Estrogens and the other sex hormones regulate some of the fundamental cardiovascular functions including blood pressure, blood flow, vasodilatation and vasoconstriction, vascular inflammation and remodeling, and atherosclerosis [39]. These actions of endogenous estrogens on the cardiovascular system can be mediated directly on the vessels or indirectly through the modulation of cardiovascular risk factors.

Estrogen exerts pleiotropic functions on the cardiovascular system through both genomic and non-genomic effects [40, 41]. Traditionally, ERs act as transcription factors regulating the expression of target genes by directly binding to specific DNA sequences, the estrogen response element (ERE). Non-genomic effects are rapid responses that occur too quickly to be mediated by gene transcription, instead involving modulation of membrane and cytoplasmic proteins.

At this level, estrogen triggers rapid vasodilatation, exerts anti-inflammatory effects, and regulates vascular cell growth and migration, leading to a protective action on vessels [42]. These rapid and non-genomic effects are reached by complex interactions with membrane-associated signaling ERs leading to the activation of downstream cascades such as mitogen-activated protein kinase (MAPK) and phosphatidylinositol

3-OH kinase (PI3K). These cascades are responsible for important cardiovascular actions of estrogens, for instance, the activation of nitric oxide (NO) synthesis or the remodeling of the endothelial actin cytoskeleton. Moreover, these cascades play crucial roles in regulating the expression of target proteins implicated in cell proliferation, apoptosis, differentiation, movement, and homeostasis [43].

Furthermore, estrogens have also systemic effects that could have influence on cardiovascular risk altering the serum lipid concentrations, the coagulation and fibrinolytic systems, and the antioxidant system. In fact, through ER estrogens regulate hepatic expression of apoprotein genes and several coagulation and fibrinolytic proteins. The net effect of these changes is to improve lipid profile, and promote vasodilatation and antioxidant activities. By contrast, the menopause leads to an overturn of all these effects increasing the cardiovascular risk.

Recent advancements in the characterization of the molecular basis of estrogen's actions help us to understand the biological functions of estrogen and would be beneficial in elucidating current controversies on estrogen's clinical efficacy in the cardiovascular system.

Estrogen can regulate the level and activity of ion channels and can modulate cardiac repolarization. There are male-female differences in calcium and potassium channels and these differences are attributable, at least in part, to estrogen. The mRNA levels of potassium channel components, Kv4.3 and Kv1.5, are decreased with estrogen [44]. These data illustrate that estrogen can alter ion channels and transporters that can alter cardiac contractility, contractile reserve, repolarization, and susceptibility to arrhythmias. Several studies have suggested that female mitochondria generate less reactive oxygen species (ROS) when exposed to estrogens [45, 46]. Female mitochondria exhibit increased phosphorylation of mitochondrial α-ketoglutarate dehydrogenase, which leads to less ROS generation by this enzyme under conditions of increased NADH. How much the effects of estrogen on mitochondrial function are mediated by nuclear ER versus acute signaling pathways versus mitochondrial localized ER will require further study. ROS at low levels is a signaling messenger, whereas at high levels it contributes to cardiovascular disease. Estrogen-mediated differences in ROS production therefore could account for some of the male-female differences in cardiovascular function and disease. Figure 10.3 presents a scheme of the different actions of estrogens.

10.3.2 Estrogen and Vascular Injury and Atherosclerosis

Endothelium represents an elective cellular target for estrogens. It is well established that estrogen improves vascular function, maintaining and repairing endothelium, and reduces atherosclerosis. Estrogen receptors (ERs) are expressed in endothelial cells and have an athero-protective effect. Through the recruitment of ERs, estradiol increases endothelial nitric oxide (NO) and prostacyclin synthesis, thus slowing early atheroma formation. Estradiol also decreases synthesis of pro-inflammatory cytokines by circulating or resident immune cells. In addition, estradiol facilitates endothelial vascular healing and neo-angiogenesis. While many of these effects are

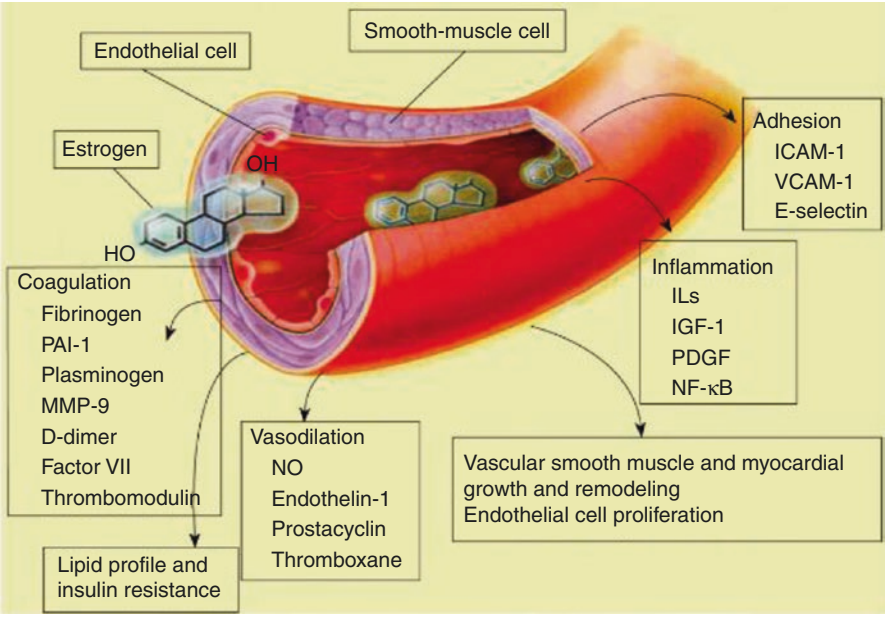

Fig. 10.3 Multiple effects of estrogen on the cardiovascular system. From Vassalle et al. World J Cardiol. 2009;1:26–30

regulated by either ERα or ERβ, ERα is found to be dominant at vascular level. Emerging evidence suggests that estradiol also exerts vascular actions through other receptors, and particularly through the recently identified G-protein-coupled receptor dubbed GPR30. Protective effects exerted by estrogens on endothelium include multiple cellular mechanisms, as evidenced by a number of experimental and clinical data. Estrogen has been demonstrated to activate calcium-dependent potassium channels and induce a rapid increase in NO release [47]. These non-genomic effects of estrogens on NO production are paralleled by their genomic actions exerted by activation of endothelial NO synthase (eNOS) through a receptor-mediated system [48]. Estrogen has antioxidant and anti-inflammatory properties, acting through multiple effects. Among them, estrogen may upregulate prostacyclin synthase and the expression of vascular endothelial growth factor. Conversely, it inhibits endothelin-1 release, and modulates adhesion molecule and tumor necrosis factor α (TNF-α) expression and endothelial cell apoptosis [49, 50]. Moreover, estrogen can act by upregulating superoxide dismutase in the vascular district, which contributes to increased superoxide ion clearance [51]. In addition to this genomic effect, estrogen can detoxify superoxide ions through binding with the proton in the hydroxyl group of its aromatic ring. Most of the experimental studies suggest the protective role of estrogen in terms of the oxidative stress status that may improve the oxidative balance in the vascular sites, improving local NO bioavailability and consequently enhancing endothelium-dependent dilatation. Estrogen may also influence the redox balance through modulation of mitochondrial enzyme activity. Thus, the

antioxidant effects are regarded as one of the main mechanisms by which hormones protect women during their fertile life, when they are at lower risk of cardiovascular events with respect to men. In fact, oxidative stress is generally higher in men compared to premenopausal women. After menopause, when hormonal levels markedly fall, the risk to experience cardiovascular events rapidly rises in women, in parallel to a rapid increase of oxidative stress biomarker levels [52].

10.3.3 Estrogen and Cardiac Hypertrophy

The details of the mechanism by which estrogen reduce cardiac hypertrophy are still undergoing investigation. One clarifying study shows that the beneficial effects of estrogen in limiting cardiac hypertrophy are attributable to estrogen-mediated degradation of calcineurin A [53]. It is likely that estrogen alters the expression of additional genes that are important in the response to cardiac hypertrophy.

10.3.4 Diabetes, Lipid Profile, and Obesity

Insulin resistance and diabetes have been associated with greater cardiovascular risk among women in different clinical trials. Moreover, data from a meta-analysis suggest that the risk for fatal coronary artery disease associated with diabetes is 50% higher in women, whereas diabetes and hypertension represent the two most important cardiovascular risk factors in women, especially when they occur in association [54]. Estrogen seems to contribute to glucose homeostasis through increased glucose transport into the cell, whereas lack of estrogens has been associated with a progressive decrease in glucose-stimulated insulin secretion and insulin sensitivity as well as insulin resistance increase [55]. Hormone replacement therapy has been found to exert a beneficial effect on glycated hemoglobin levels in postmenopausal women.

Early after menopause women begin to gain weight and their body fat is redistributed from a gynecoid to an android pattern. The increase in body mass index (BMI) and proportion of visceral fat is strongly correlated with the development of hypertension, insulin resistance, and a number of metabolic risk factors for CVD. It is otherwise known that menopause is associated with an increase in triglycerides (TGs), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C) and lipoprotein (a) [Lp(a)]. Levels of high-density lipoprotein cholesterol (HDL-C) gradually fell after menopause, although concentration remained always significantly higher in women with respect to men, this finding being considered a protective factor for female subjects.

10.3.5 Clinical Impact of Menopause

The impact of natural menopause on CVD risk is a matter of current research. The significant fall in the circulating levels of estrogens, however, takes some years in

many women. This smooth decline may perhaps obscure the cardiovascular impact of natural menopause. So, it has been considered that artificial menopause is a good model for showing the clinical impact of hormonal deprivation, because the fall in the levels of estrogens is both rapid and acute. Primary ovarian insufficiency, in which women are exposed to longer hypoestrogenic periods in their lives, may also be illustrative.

The data are not uniform, since some studies focusing on cardiovascular risk factors have found unfavorable changes in women with surgical menopause [56–58], while others have not [59]. Of interest, the incidence of cardiovascular events, coronary heart disease, and stroke seems to be increased by early menopause [60, 61]. Reviews about the topic also conclude accordingly [62, 63].

The impact of natural menopause has been thoroughly investigated too, and interest has focused on the menopausal transition.

10.3.5.1 The Menopausal Transition and Cardiovascular Risk

With regard to this, it is worth mentioning the results of the Study of Women's Health Across the Nation (SWAN). SWAN is a multicenter, multiethnic longitudinal study designed to characterize the physiological and psychosocial changes that occur during the menopausal transition and to observe their effects on subsequent health and risk factors for age-related diseases. A total of 3302 women were enrolled at seven clinical sites between 1996 and 1997. At the time of enrollment, women were premenopausal, not taking hormones, and between 42–52 years of age. Participants self-identified as African-American (28%), Caucasian (47%), Chinese (8%), Hispanic (8%), or Japanese (9%). SWAN has a multidisciplinary focus and thus has repeated measures of bone health, cardiovascular risk factors, psychosocial factors, and ovarian hormones [64].

In this set, Matthews et al. [65] evaluate the change in CHD risk factors in relation to a very particular and critical period of women's life, that is, the final menstrual period (FMP). Women who experienced a natural menopause (1054 out of the total) were analyzed independent of age and other confounders. The results showed significant increases in total cholesterol, LDL-C, and Apo B within a year of the FMP; importantly, the rate of change relative to FMP did not vary by ethnicity, suggesting that menopause had a uniform influence on lipids. The other risk factors changed in a linear pattern consistent with chronologic aging: triglycerides, lipoprotein (a), insulin, factor VIIc, and systolic blood pressure increased; diastolic blood pressure, tissue plasminogen activator antigen, fibrinogen, and high-sensitivity C-reactive protein did not change.

10.4 Osteoarthritis

10.4.1 Introduction

Osteoarthritis (OA) is the most common degenerative joint disease. The process consists of breakdown of cartilage that affects the surfaces within the joints (Fig. 10.4). The cartilage covering the ends of the bones gradually roughens and

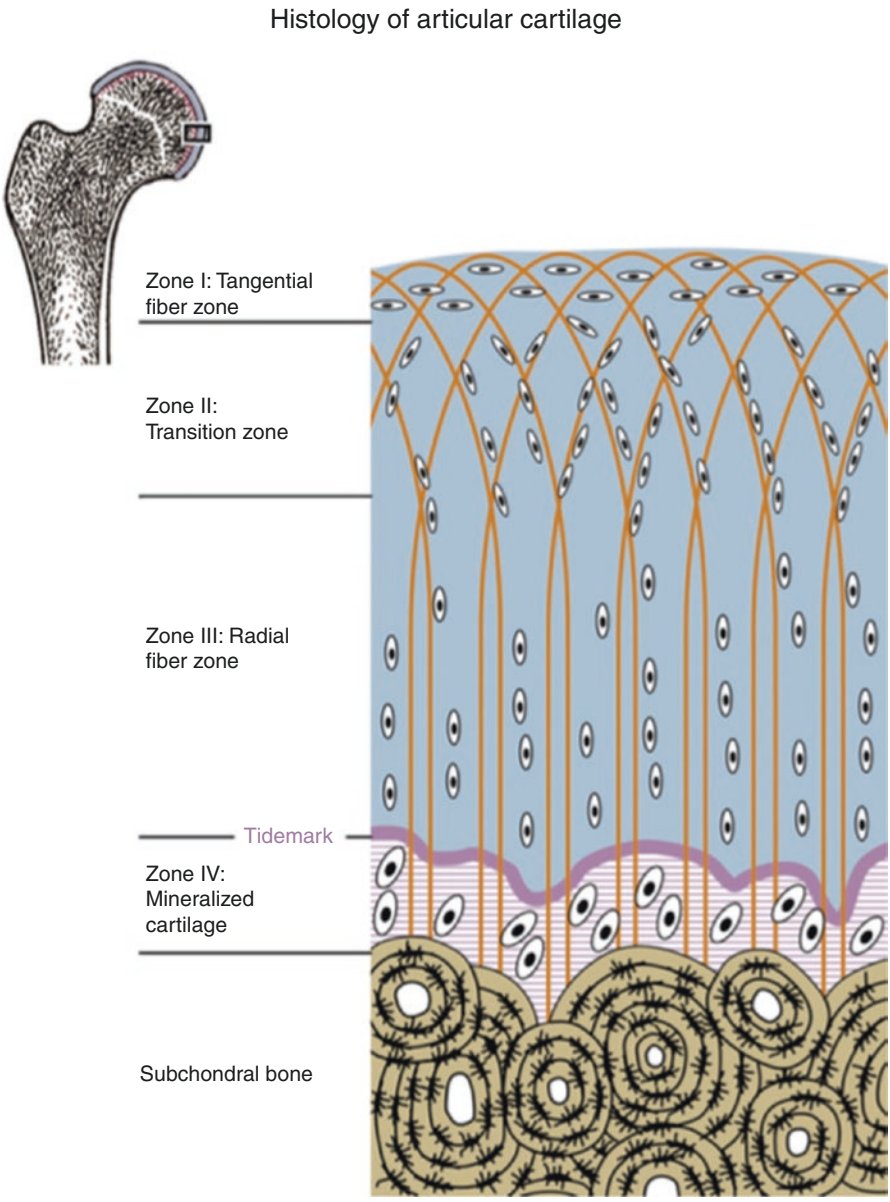

Fig. 10.4 The articular cartilage is composed of different histological layers, as shown in the figure. The mineralized cartilage (Zone IV) constitutes the transition to the subchondral bone. With permission of Elsevier from Prog Histochem Cytochem. 2011;45:239–93. Permission obtained through Copyright Clearance Center, Inc

becomes thin, while the underlying bone surface becomes thicker. A reparation process initiates at the joint so that the bone edges grow outwards, forming bony spurs called osteophytes; the synovium becomes thick and produces extra fluid; and both capsule and ligaments slowly thicken and contract. The consequence is that a joint affected by OA does not move as smoothly as it should. The most common symptoms are stiffness, particularly first thing in the morning or after resting, and pain. Moreover, affected joints may get swollen after extended activity. The whole picture may severely impair the quality of life.

The pathogenesis of OA is complex because its development involves the interaction of multiple factors, and estrogens have been claimed to be one of them. The association with menopause derives from direct epidemiological observation [66, 67], together with a higher prevalence among women and the expression of estrogen receptors (ER) in joint tissues [68, 69]. Estrogens are involved in several biological processes through different molecular mechanisms. Their final actions consist of a combination of both direct and indirect effects. In general, acute estrogen deficiency increases the production of both pro-inflammatory cytokine and reactive oxygen species, and activates nuclear factor-κB. Pro-inflammatory cytokine expression, in turn, attenuates with estrogen replacement [70, 71].

10.4.2 Evidences from In Vivo and In Vitro Experiments

The proposal that estrogen deficiency is involved in the onset and progression of OA is limited by the incomplete understanding of the underlying molecular mechanism [72, 73]. Deletion of ER in female mice results in cartilage damage, osteophytosis, and changes in the subchondral bone of the joints, supporting the hypothesis that estrogens play a role in the maintenance of the structural integrity of articular cartilage. Experiments performed in OVX mice have shown that acute loss of estrogens induces joint damage, and ERα knockout animals develop more and larger osteophytes, as well as a thinner lateral subchondral plate [74, 75], all observations suggesting that the presence of ER in the cartilage is important for joint cartilage homeostasis. However, the fact that estrogen deficiency also increases subchondral bone remodeling, which has been suggested to promote osteoarthritis changes [76], has brought some concern about whether the phenotypes obtained from the models described above are either only due to the effects of estrogen deprivation on joint cartilage or due to an indirect effect derived from the subchondral bone loss induced by the hormone decline [77].

In order to overcome the indirect effects of the lack of estrogen signal on the joint cartilage through the subchondral bone, different experimental approaches have been proposed. It is known that OVX rabbits do not suffer bone loss as much as mice; because of this feature, this animal model has been proposed to better disclose the effect of estrogens on joint cartilage [78]. Mild abnormalities in the joint structure have been reported in 22-week-old OVX rabbits, as well as higher Mankin scores, while no significant changes in subchondral bone mineral density were developed as compared to their controls, indicating that estrogens have a protective effect on joint cartilage through a direct mechanism [77].

Another approach used to provide evidence about the relationship between estrogen and joint cartilage has consisted of the ex vivo experiments performed in OVX rats. Ovariectomy induced a rapid increase in serum type II collagen (CII), indicating cartilage degradation, which was correlated with microstructural cartilage damage [79]. Other authors have investigated the effect of estrogen deficiency on the synthesis of glycosaminoglycans (GAG), which are an important component of the connective tissue. A significant decrease in GAG from knee joints was found in both cryo- and paraffin sections of OVX animals compared with sham controls, indicating that loss of estrogens has a detrimental effect on cartilage tissue [80].

Therefore, evidence obtained from animal models with either estrogen depletion or lack of ER supports the hypothesis that estrogen has a chondroprotective role. In line with the data observed in the experiments performed in animals, there are also clinical observations, which have contributed to gain knowledge on this potential action of estrogens.

10.4.3 Clinical Evidence

The possible relationship between the hormonal changes of menopause and OA was already proposed in 1925, when Cecil and Archer described the "arthritis of the menopause," which affects the hands of women around the time of menopause [81]. Sometimes the process occurs in a more generalized form, as reported by Kellgren and Moore, who were first in describing a form of "menopausal arthritis" of rapid onset, with Heberden's nodes [82]. This form, which they baptized as "generalized primary osteoarthritis," was characterized by a rapid initiation of symptoms and multiple affected joints (hands, spine, and knees). Although there is controversy on the existence of this syndrome, the increase in the prevalence of OA in the perimenopausal woman is generally acknowledged [83].

10.4.4 Epidemiological Studies

The prevalence of OA increases with age and is similar in men and women up to the age of 50 years, when the disorder becomes more prevalent, severe, and generalized in women [84]. Moreover, OA changes are more pronounced in the hand than in the hip or in the knee, and this pattern reproduces, although maintaining prevalence differences, between women and men. So, symptomatic OA affected the hands of 26% of women and of 13% of men, and the knees of 11.4% of women and 6.8% of men in the Framingham cohort [85]. Also, more than 40% of women reported to have received the diagnosis of OA in the Women's Health Initiative (WHI) Study, which included postmenopausal women from the general population. As in other studies, women who were older or overweight had a higher risk [86].

The increase in the population of middle-aged women with polyarticular symptoms has further nourished the hypothesis that a relationship exists between the onset of OA and menopause, although there is no specific clinical feature in the disease that

differs between pre-, peri-, and postmenopausal women or between women and men [87]. But, as previously mentioned, symptomatic disease becomes more frequent in women since 50 years, the age at natural menopause. In support of a role for hormones, some studies have found that hysterectomized women suffer from higher rates of OA at the knee or at the first carpometacarpal joint [88]. Also, an inverse association has been observed between premenopausal status and patellofemoral OA [89]. The same authors also reported that women with artificial menopause, who undergo a more drastic reduction of circulating estrogens, suffer from a significantly higher rate of OA in hands and knees [88, 89]. Also, a study in a population of women aged 25–45 years found that, even after adjusting for age, hand OA was more frequent in those who had already passed menopause [90]. More recently, a similar observation reproduced in the case of users of aromatase inhibitors, since younger women, with the FMP within the latter 5 years, report a higher rate of arthralgia than women in whom the FMP occurred more than 10 years ago [87].

The association of OA with estrogen, however, has not been unanimous in the literature. For example, one study could not confirm an effect of the duration of the exposure to estrogens, as measured by the age at menarche or menopause, rate of hysterectomy, parity, or use of oral contraceptives, with the onset of OA [91].

So, and although the trigger for the onset of OA in middle-aged women is unknown, a relationship with the hormonal changes at menopause has been claimed by some investigators. The issue, however, is controversial, as it is whether the potential relationship applies to all forms of OA in women or only to any of the two subsets, generalized OA or OA of the menopause [92].

10.4.5 Endogenous Sex Steroids in Women with Generalized OA

Low levels of testosterone were described in women with hand OA [90], and low levels of serum estradiol and urine 2-hydroxy-estrone were predictive of radiographic signs of knee OA [93]. However, no trend in the sex hormone concentrations was found when contrasted with the severity or radiographic hand OA in a study on 229 Caucasian women [94]. The comparison of the age- and obesity-adjusted sex hormone concentrations by the worst Kellgren-Lawrence score revealed little difference in the same study. Moreover, a systematic review of 16 studies examining the association between OA and hormonal exposure, including the fertile period (duration, hormone levels, age at menopause, and menarche) and the postmenopause (years since menopause, surgical menopause), concluded that the assumed relationship between the female hormonal aspects and OA could not be clearly observed [95].

10.4.6 Radiologic Imaging Studies of the Articular Cartilage

The loss of the articular cartilage is a significant feature of OA progression. There is therefore interest in using the level of damage of articular cartilage as an indicator

of either the progression of OA or the impact of therapeutic interventions [96]. There is very sparse evidence on the structural damage of the articular cartilage and fine radiological methods, as for example, magnetic resonance [97]. A study on 325 subjects showed that the rate of the articular cartilage loss was higher in women than in men, and that the difference started to become evident from the age of 50 years [98].

Conclusion

OA is more prevalent in women, and the difference increases after menopause. The molecular mechanisms determining the effect of menopause are still unknown. However, both experimental data in transgenic animals devoid of estrogenic signals and observations in the human suggest that hormonal deficiency may be a determining factor in the process. Despite the progression in the knowledge of the disease, details of the interaction of estrogen deficiency with other factors to induce or influence the progression of OA remain to be clarified.

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Part IV

Management of Menopause

Hormone Therapy (I): Estrogens, Progestogens, and Androgens

11

Francisco Quereda

11.1 Introduction

Hormonal deprivation is related to a variety of symptoms and to negative changes in the risk profile of some chronic diseases in women. Although a great variability in severity exists, this situation constitutes a negative impact on present or future health and/or quality of life for many women. Thus, perimenopause is an important period to evaluate the following aspects:

Identification of climacteric symptoms and quality-of-life alterations related to hormone deprivation
Estimation of the level of risk for pathologies that may arise in the future, like osteoporosis or cardiovascular disease
Evaluation and discussion with the woman whether it is or not appropriate the use of hormonal therapy (HT)

These topics have been extensively reviewed in other chapters. Next step now, if the decision to start HT is taken, is to decide what type of HT might be most suitable. This is not always an easy decision, given the great number of different alternatives and their implication in compliance, undesirable effects, and efficiency.

In TH prescription, the selection of formulation, schedule, doses, and route of administration are important issues because different alternatives have different effects, and perhaps different benefit/risk profiles [1]. Also, a great number of options are available, so that prescription might be done in a suit-tailored way, looking for the best formulation for the specific woman that is going to be treated [2].

Effectively, after evaluation of menopause-related quality of life, health status, and health risks at the perimenopausal period of a particular woman, and once the suitability and acceptance for HT use are agreed, the identification of the best HT

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alternative is important. For that, this chapter reviews the role of different hormones in HT, the alternatives in each group, schemes of treatment, dosages, and their differences. Altogether, this constitutes an important background that a menopause health-care provider should consider to get the best final impact on his/her patients.

So, the final selection of HT for a woman will depend on her context and preferences, as well as on the targets to cover [3, 4]. In addition, reasons to treat or scenarios may change with time leading to adjustments of treatment. So, a good knowledge of alternatives in the HT components is of great value for prescription, appropriate adherence, and good effectiveness/risk ratio [5].

11.2 HT Composition and Objectives: Role of Estrogens, Progestogens, and Androgens

The purpose of HT prescription is never to achieve premenopausal hormonal levels. Instead, the objective is to suppress or alleviate the clinical symptoms of hormonal deprivation [6], and this is achieved with doses and schemes that simulate ovarian function, but also with lower doses and even with non-physiologic treatment schemes.

Therefore, once the preferences of a woman have been identified, the target of treatment should be defined, and then, the best suited compound, dose, route, and scheme for this woman should be chosen. In addition, possible collateral effects of a particular form of HT can lead the selection, in order to get or to avoid them, because in some cases they could be pursued while in others avoided [7, 8]. Table 11.1 shows

Table 11.1 Variables to consider about prescription of hormonal treatment

Composition
– Estrogens
– Estrogens and progestins
– Androgens
– Estrogens and androgens
– Estrogens, progestins, and androgens
– Tibolone
– T-SEC compounds or other combinations
Scheme of treatment
– Cyclic or continuous
– Sequential or combined
– Cycle-sequential
Route of administration
– Oral
– Transdermal
– Subcutaneous implants
– Vaginal
– Intramuscular
– Combination of routes
Dosage of treatment
– High
– Standard
– Medium
– Low
– Ultralow

the variables to keep in mind for HT prescription. They should be considered under the perspective of the following *general guidelines*:

Most objectives of HT are achieved by estrogens.
The inclusion of progestogens in HT leads to protection of endometrium against the risk induced by estrogens use. Therefore, they should not be used when treating women without uterus, unless there is a specific reason to do so.
In general, progestogens partially reduce some of the beneficial effects of estrogens, like the impact on cardiovascular risk profile.
Progestogens have remarkable differences, which generate a variety of effects that can be desirable for some women, but undesirable for others.
The inclusion of androgens adds a specific profile of effects, such as improved sexual function and mood.
The overall risk profile of androgens is not well defined, but it is known that, for example, they worsen the lipid profile.

11.2.1 Estrogens: Objectives and Alternatives

Estrogens define the etiological treatment for climacteric syndrome. Several randomized clinical trials have demonstrated that estrogens are effective in the reduction or suppression of hot flushes and most of the other symptoms related to menopause [6]. Thus, they are the main component of HT.

At present, the evidence-based objectives for estrogens in HT are the following:

To avoid, suppress, or alleviate vasomotor, urogenital, and other symptoms related to hormonal deprivation, especially when they affect quality of life: This includes psychological alterations, sexual dysfunction, well-being perception, sleep disturbances, etc.
To maintain or recover the beneficial effects on multiple targets, among them bone, endothelium, lipid profile, or skin.

Because high estrogenic potency is not required to achieve those objectives, natural estrogens are preferred to synthetic estrogens in HT.

Table 11.2 shows the molecular types of estrogens more frequently used in HT. Among them, estradiol is the most commonly used estrogen in Europe while conjugated equine estrogens (CEE) are so in the United States. In some countries, weaker estrogens like estriol have been frequently used, but it seems that the molecule is advantageous mainly when used for local vaginal treatment. Promestriene is another weak estrogen used for topical vaginal treatment in some countries.

At the beginning of HT treatment, the thinking was that the estrogen dose should reproduce, or even overcome, the usual physiological levels of estradiol during the reproductive age. But it soon became clear that much lower doses reached the goal [9, 10]. A standard dose was then defined (see Table 11.3), which in general afforded the estrogenic blood levels of a 6th–8th days of the physiological menstrual cycle.

Table 11.2 Alternatives for hormonal treatment composition

Estrogens
– 17-beta-Estradiol
– Estradiol valerianate
– Micronized estradiol
– Conjugated equin estrogens
– Estriol
– Promestriene
– Others
Gestagens
– Micronized natural progesterone
– Dydrogesterone
– Medrogestone
– Medroxyprogesterone acetate
– Levonorgestrel
– Norgestrel
– Norethisterone acetate
– Drospirenone
Androgens
– Testosterone
– Methyl-testosterone
– Others
Tibolone
– T-SEC combinations

Table 11.3 Doses of estrogens used for HT

	High dose	Standard dose	Intermediate dose	Low dose	Ultralow dose
Oral estradiol (mg)	4 or 3	2	–	1	0.5
Transdermal estradiol (μg)	100 or 75	50	37.5	25	–
Conjugated equin estrogens (mg)	1.25	0.625	0.45	0.3	–

More recently, the Health, Osteoporosis, Progestin, Estrogen (HOPE) trial showed that lower dosages are effective for many targets in women, so that HT might become a woman-tailored selection among different therapeutic possibilities and goal adjusted [11, 12]. The higher chance for non-desirable effects with higher hormone doses was another reason to search for the lower dose able to achieve the wanted effect [13]. Of interest, the accomplishment of the target does not always correlate with the blood levels of estrogens. Therefore, the achievement of a concrete level of serum estrogens should never be the goal of HT nor, against the case of, for example, thyroid hormones, should be taken as the way to control the treatment effect.

11.2.2 Progestogens: Objectives and Alternatives

It is now well recognized that the use of estrogens without progestogens induces endometrial proliferation, hyperplasia, and even carcinoma. And there is also good evidence about the efficacy of progestogens in the prevention of that adverse effect.

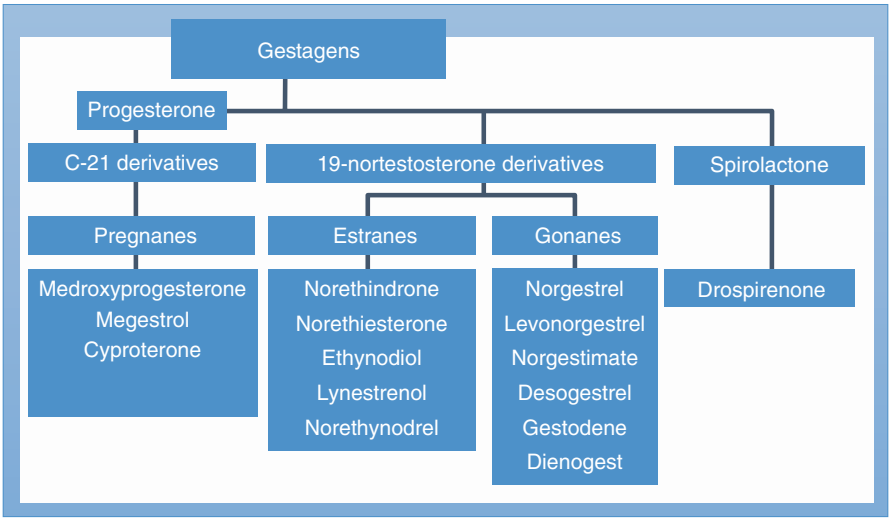

Fig. 11.1 Classification of gestagens used for HT between chemical structure

So, at present, the main target for using progestogens in HT is the induction of endometrial secretory changes, even atrophy, to counteract the estrogen-induced proliferative effects [2].

Because progestogens reduce the beneficial effects of estrogens on the lipid profile and other targets, they are only recommended for HT in women with uterus; thus, estrogen-only is the appropriate therapy form for hysterectomized women. However, when there is risk of recurrence or reactivation of any estrogen-dependent disease, like endometriosis or early-stage endometrial cancer, progestogens are recommended despite the user being hysterectomized.

It is important mentioning that progestogens have different molecular forms that group them into families, and that there are important pharmacologic differences between them, with subsequent physiological impact. Therefore, the selection of a progestogen always results from an array of possibilities. Figure 11.1 shows that there is a variety of synthetic progestogens besides natural progesterone. All of them protect the endometrium against the proliferative effect of estrogens [14], but their different potency and other effects, metabolic or of other nature, should be considered in the choice. Those alternative effects sometimes are not desired, but other times they could be secondary objectives for treatment, and all of that may influence the selection.

The diversity of progestogens is in part the translation to HT of years of research in the field of contraception, which has searched for a lower neutralizing impact on the beneficial effects of estrogens. Progestogens from the same family share some characteristics, but some differences exist even inside each group, and those specificities should be known.

Some general guidelines and considerations are the following [2]:

Natural progesterone has lower potency and more mineral-corticoid blocking effect.

A certain diuretic effect has been shown for progesterone, although this is not

necessarily reproduced with all of its derivatives, for example, medroxyprogesterone acetate.

Nor-derivative progestogens, which could exert some positive effect on sexuality throughout a certain androgenic effect: Also, they show higher capacity of endometrial protection, although less favorable lipid profile impact than estrogen-only HT.

Cyproterone acetate, and less drospirenone, has antiandrogenic effect which may be especially desirable for some women. Drospirenone characteristically adds a weak diuretic effect that contributes to a slight decrease in weight, very much valued by some women.

11.2.3 Androgens: Objectives and Alternatives

Androgen production basically takes place in adrenal glands, ovaries, and testicles, and decreases along the life in men and women after 30s. But in women, ovarian failure determines an accelerated decrease throughout the perimenopausal and postmenopausal periods, although postmenopausal ovaries maintain some androgen production many years afterwards. In fact, when ovaries are removed, the decline in androgen levels is greater than after natural menopause.

Androgens have been related to energy, mood, well-being, self-perception, and some parameters of sexuality (libido, activity, arousal, excitability, and satisfaction) [15]. Androgen deficiency has been related to adynamia, sexual dysfunction, and minor depressive states, altogether included in the so-named androgenic deficiency syndrome [16, 17]. It is remarkable that this is a clinical diagnosis, and cannot be defined by serum androgenic levels, although it is more frequent after surgical menopause.

In consistence with above, the main potential goal for the inclusion of androgens in HT is the improvement of libido, especially when sexual desire is hypoactive, and mood and well-being perception are altered. Additionally, androgens may help estrogens in the reduction of vasomotor symptoms, the increase of anabolism effect on bone, and overall the increase of sexual activity and satisfaction [18, 19].

However, androgens may induce some adverse effects, like hirsutism, acne, or virilization, particularly when used over physiological threshold. For example, methyl-testosterone (5 mg/day) was satisfactorily used to improve sexuality in women, but the mentioned adverse effects and potential risks discouraged its use at those dosages.

Other concerns about androgens include a negative impact on lipid profile added to a possible increase in cardiovascular and breast cancer risk [20]. Androgens are metabolized to estrogens in a variable degree, so they may contribute to cancer risks by themselves or be mediated by induced increases of estrogens. In any case, evidences for impact on breast cancer risk are scarce, controversial, and inconclusive.

The field in which androgens are specifically appropriate is that of women with androgen deficiency syndrome and/or hypoactive sexual desire, in which lower doses have demonstrated a significant improvement of those aspects, clearly related

to quality of life. Two decades ago, randomized clinical trials demonstrated that the use of transdermal testosterone, at doses inside the physiological premenopausal range, effectively improved sexuality of women with that profile [21]. Testosterone patches afford transdermal administration achieving serum levels within the physiological premenopausal range.

The lack of commercial availability of transdermal testosterone in some countries has increased the interest on nor-derivative progestogens, which may be an alternative option providing some of the mentioned effects for androgens.

11.3 HT: Dose, Route, and Schemes of Administration

Once we have reviewed the different alternatives and objectives for HT, it is necessary to analyze other aspects that contribute to individualize the selection and make it target directed. Once composition is decided, dose, route, and scheme of treatment should be selected from a diversity of possibilities. Some general guidelines for this purpose are the following:

The dose of estrogen should be chosen firstly.

The lower possible dose of progestogen is preferred, and for that, both dose and duration of treatment are main variables. This will depend on the estrogenic dose, so that the higher the estrogen, the higher the progestogen dose.

There is an individual variability and some women may need higher doses to get the goal. For example, smokers have an accelerated hepatic metabolism of estrogens.

11.3.1 Dose

The goals for HT are achieved in most women with doses that lead to serum estrogenic levels similar to a 5th–8th days of a normal ovarian cycle. Those are referred to as standard doses (Table 11.3). However, some randomized clinical trials in the latter years have shown that lower doses get the goals for many women. These findings reinforced the potential of low-dose HT, which is roughly understood as half the standard dose. Even more, it has been shown that even lower doses (ultralow dose of HT) have positive effects, for example on bone metabolism in older women [22]. The ultra-low doses are so low that they do not induce endometrial proliferation in most cases, although the addition of a progestogen is recommended in some countries.

11.3.1.1 Selection of the Dose of Estrogen

Different approaches can be used to select the appropriate dose of HT. In general, the tendency is to use standard dose of estrogens for younger women. Low-dose HT is more used for women between 50 and 55, and especially over 55 years of age. But the dose should always be adjusted in order to get the pursued objectives, at the beginning and also later, during the follow-up.

Nowadays, the rule is to give the minimal dose to get the goal [23]. The strategy to reach that stage may be to start with a low dose and then increase step by step when necessary, or either begin with standard dose and introduce changes afterwards if required.

Ultralow-dose HT is an opportunity for older symptomatic women or long-term HT users. It may also be a useful strategy for women either old or with comorbidities but with potential benefits from HT because, for example, bone metabolism has shown sensitivity to ultralow estrogen dose. Patients' acceptance to such a low dose may improve as well.

11.3.1.2 Selection of the Dose of Progestogen

The endometrial protection of progestogens against the proliferative estrogenic stimulus depends on total dose and duration of progestogen per cycle, although the potency of the molecule also has an effect [24]. For example, natural progesterone at a dose of 200 mg/day is needed for at least 10–12 days each cycle for a standard dose of estrogen. Lower doses of estrogen require half-dose (100 mg) progesterone.

Some combinations have tried to reduce the dose of progestogen, as shown later in another section.

It is also of interest that commercial preparations of progesterone may be used by oral or vaginal route. The vaginal route avoids first liver step, and so some secondary effects are reduced or avoided. But this vaginal route is not well accepted by some women, and compliance uses to be worse.

11.3.1.3 Selection of the Dose of Androgens

The dose of testosterone approved for HT in Europe is 300 μg/day delivered by a twice-a-week transdermal patch. Randomized clinical trials demonstrated that these patches lead to serum concentrations of testosterone within physiological range and were effective with a good benefit-risk balance. The main indication for this treatment is androgen deficiency and related symptoms (hypoactive sexual disorder or complete androgen deficiency syndrome with adynamia, low well-being status, etc.).

Testosterone may be used in combination with estrogens because so was done in the trials, and especially when symptoms persist in spite of estrogenic treatment.

Testosterone is not available in some countries. This is why some similar effects can be partially got with the use of nor-derivative progestogens, tibolone, or androgen gel formulations, which were designed for men and therefore require dose correction. These gels have lower reliability and blood level stability than patches.

11.4 Routes of Administration for HT

HT may be administered by different routes (Table 11.1). This variety perhaps translates that a perfect universal route does not exist. The available alternatives have differences in comfort, posology, acceptance, and consequently in adherence. But, besides, there are pharmacokinetic differences that are clinically relevant when considering side effects, either beneficial or adverse. And those different

characteristics may be used to select one or the other while considering women's desire, potential risks, and/or for secondary goals of treatment.

11.4.1 Oral HT

This route of administration has the first pass through the liver as a characteristic. Therefore, there is partial steroid metabolism before systemic bioavailability, which requires a higher daily dose and induces some metabolic hepatic changes. The result is a specific serum estrogenic profile, which differs from the physiological pattern in that there are higher estrone levels and proportions, even when the administered steroid is oral estradiol.

The disadvantage of the estrogenic induction of liver enzymes is that the thrombotic and/or hypertensive risk may increase in some women. But, now as an advantage, oral estrogens favorably change the lipid cardiovascular risk profile, promoting a decrease in total and LDL cholesterol, as well as in lipoprotein (a). In contrast, HDL cholesterol and triglycerides increase.

This route affords simplicity but also an increase in missing doses, and requires constancy.

11.4.2 Transdermal Route

This is a route broadly used in Europe, and overall in South European countries. The following aspects characterize this route of administration [25, 26]:

Estrogenic serum levels are uniform and sustained.
The first pass through the liver is avoided and logically its related effects. Consequently a very lower dose is required, and the serum estrogenic profile is dominated by estradiol, more similar to the premenopausal profile.
Some evidences suggest a lower risk for this route of estrogenic associated venous thrombosis and/or hypertension.
However, cholesterol levels are less reduced than in the oral route, and triglycerides do not change.
In the case of patches, some women show a variable local intolerance with erythema, eczema, and/or pruritus.
Detachment of the patches in some women leads to variable estrogenic levels.
The use of gel is associated with lower adherence, lower reliability of dose, and daily variability of estrogenic levels. Together with efficacy, gels share the characteristics of the transdermal route.

11.4.3 Transvaginal Route for HT

This route can be used for systemic treatment but requires high doses. This route shares with transdermal systems the avoidance of the first-pass hepatic effect,

but its use is restricted to few countries. However, vaginal formulations are broadly prescribed for local vaginal treatment using weak estrogens or very low doses of estradiol. The main indication is maintenance and improvement of trophic vulvovaginal properties to limit symptoms like dyspareunia and dryness. In fact, vaginal HT is sometimes used associated to systemic HT when the latter is not enough to solve these problems. And of course, the vaginal route is indicated for women who do not desire or do not need systemic HT but suffer from local problems.

The transvaginal route with the used formulations has reduced systemic absorption and shows no evidence of endometrial proliferation. So, it is considered local HT. It is available in the form of pills, ovules, creams, and gel, which suffer of low compliance as main difficulty and of pruritus as main adverse effect.

11.4.4 Other Routes of Administration of HT

Other routes of administration have been used and deserve some comments.

Intrauterine device (IUD) for delivery of HT only exists for progestogen administration.

Intramuscular depot formulations were broadly used for HT in the past, but nowadays this route is only used for very specific patients, like those with poor compliance with other routes.

Transrectal route does not seem to add advantages vs. vaginal and is not available in most countries.

Nasal and sublingual are singular routes that developed the concept of pulse therapy, but are only available in some countries [27]. They have some pharmacokinetics differences and lower general bioavailability. Briefly, the "pulse therapy" concept is based on a quite specific genomic effect induced throughout a quick and short peak of estrogenic serum concentration. A low dose is absorbed but is enough to induce nuclear intracellular estrogenic effects, which are sustained for some time while the concentration in serum declines quickly. It has been presumed that the adverse effects might not be induced so rapidly and therefore might be of lower level, but evidence for that is limited.

11.5 Schemes of Treatment for HT

HT is administered following some specific treatment regimes. Although there is some confusion and controversy, perhaps the clearest terminology to denominate the more usual schemes of treatment is the following:

Cyclic or continuous HT, based on whether there are, or there are not, periods without treatment.

Combined or estrogen-only HT, based on whether progestogens are, or are not, associated to estrogen.

Sequential HT, when a combined HT includes periods of changing doses of progestogen, or without progestogen. And because there is a very low use of cyclic HT nowadays, the frequently used "continuous combined HT" nomenclature denotes a regime in which both estrogen and progestogen are used without changes in dose and without interruption. In contrast, triphasic formulations are those in which the doses of one or both estrogen and progestogen change during the cycle [28].

The cyclo-sequential regime aims at reducing the progestogen dose while maintaining amenorrhea. Estrogens are administered daily while progestogens are given in alternating phases of 1–3 days separated by 3–4-day phases [29, 30].

Those schemes differ sufficiently to justify the selection or one or another in order to get some goals. Concerning the endometrial protection, 12 days of progestogen and an adequate dose related to estrogenic dose are needed in cyclic regimes.

Figures 11.2 and 11.3 graphically show different schemes of associations for HT. Finally, looking for a decrease in total progestin dose and long periods of amenorrhea but accepting a pre-planned bleeding, the long cyclo-sequential schemes are used, when progestin is associated for 12–14 days at higher doses every 2 or 3 months with estrogen-only HT until this moment. This last regime requires more strict endometrial control because a small increase in endometrial hyperplasia rate has been found.

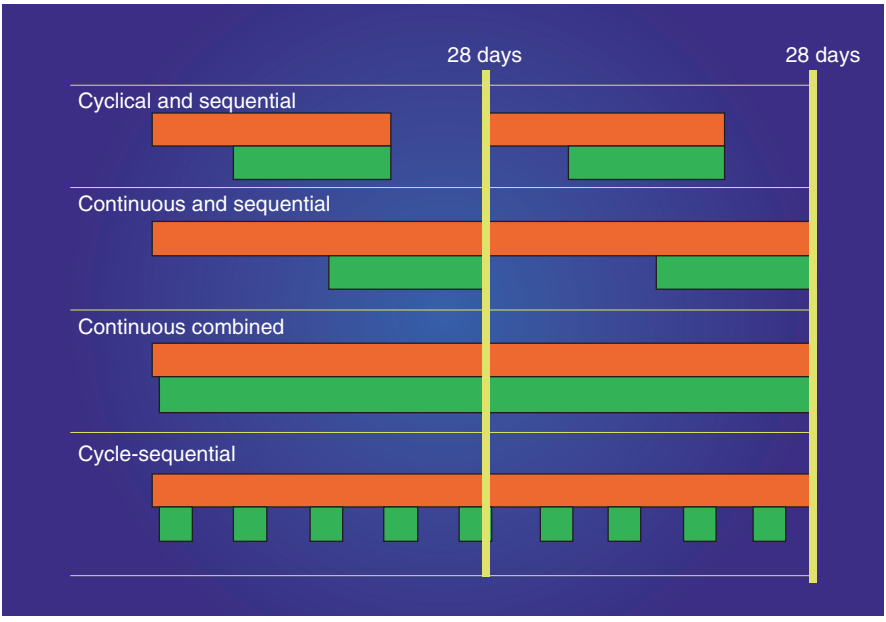

Fig. 11.2 Schemes of HT (*red* for estrogen and *green* for progestin administration)

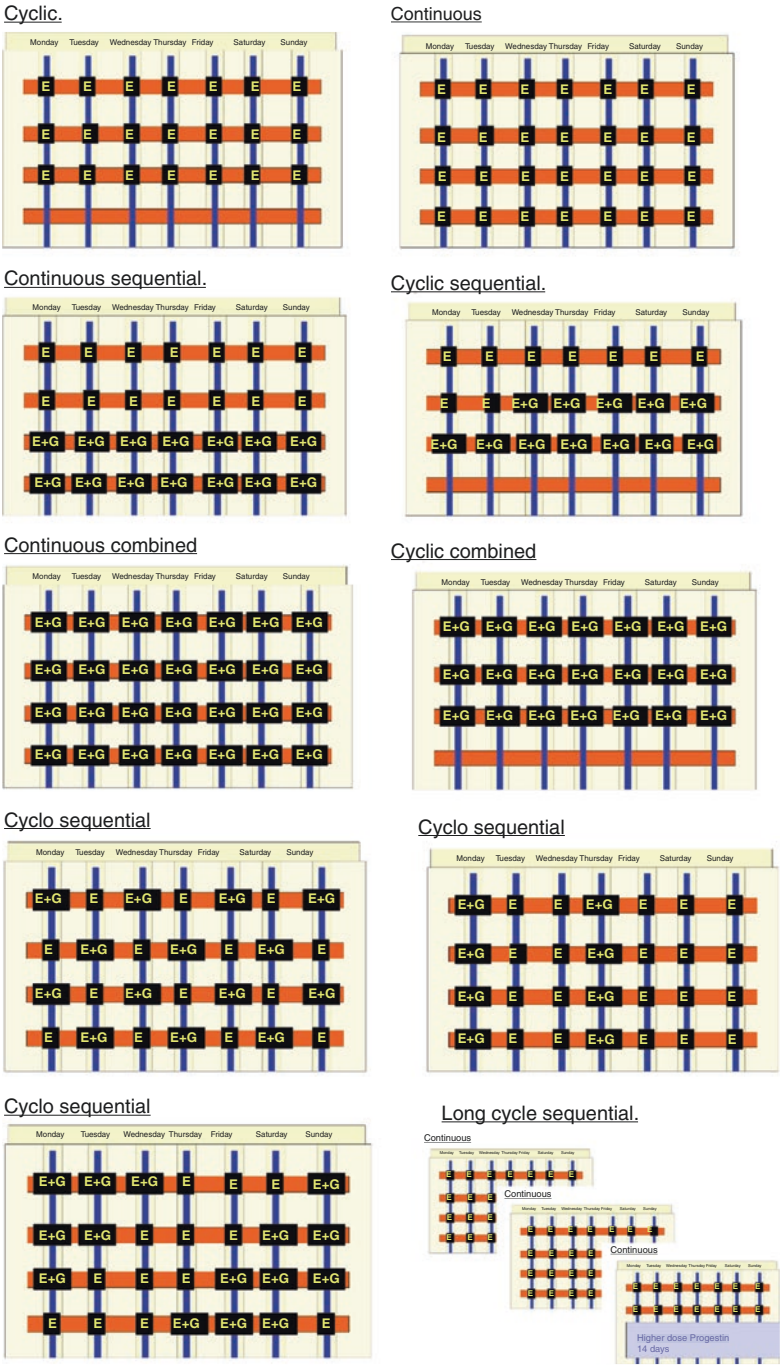

Fig. 11.3 Graphical representation of most usual schemes of treatment for HT (*E* estrogen, *G* gestagen)

Table 11.4 Characteristics and objectives for different schemes of HT

Scheme of treatment	Characteristics and objectives
Cyclic	To reduce monthly dose of estrogen
	Hormonal variation
	Deprivation bleeding
Continuous	To avoid possible symptomatic periods
	To simplify treatment
	Nonhormonal variations
Sequential	Reproduction of physiology
	Hormonal variation
	Deprivation bleeding
Combined	Amenorrhea
	To reduce total progestin dose
	To avoid hormonal variation
	Endometrial atrophy more frequent

Table 11.4 summarizes the main characteristics and goals for the different schedules for HT. For example, it can be noticed how in some cases the induction of a deprivation bleeding may be an objective (especially in perimenopausal period), and to avoid it may be the goal in other cases. Sometimes, it could be useful to maintain a certain hormonal variation along the cycle of treatment (in case of low libido or depressive tendency, for example), and exactly the opposite could be better in other occasions, as when there are premenstrual symptoms.

Therefore, different doses, routes of administration, and schemes of treatment lead to substantial differences that may constitute a main reason for its selection and recommendation for a concrete woman, in order to increase acceptance and compliance, and to minimize collateral and adverse effects. And it is clear that an individual and changing approach and adjustment to woman's desire and requirements might be used. For those instances it is very useful to know the different strategies with proven efficacy and safety.

11.6 HT Follow-Up

Once HT is initiated, a visit in the short term is useful and a plan for the long-term follow-up may be convenient.

11.6.1 Short-Term Follow-Up Visit

A first visit between the 3rd and the 6th months is not mandatory, but it is useful for verification and reinforcement of compliance. Special attention should be given to detect efficacy and tolerance, absence of adverse effects, and, sometimes, adjust or change the dose or scheme according to results and desires of the user.

Although determination of serum levels of estradiol sometimes may support any decision, a specific threshold never is the target nor is guarantee of good control with HT. Thus, it is relevant that confirmation of efficacy and adjustment requirements focus on clinical effects, most of them referred by the woman herself. Clinical experience has shown that this visit and adequate adjustments improve compliance.

11.6.2 Long-Term Follow-Up

The follow-up of women on HT basically includes the following aspects: prevention and diagnosis of organic pathology, verification of compliance, confirmation of efficacy, reevaluation of indication and acceptance of HT, and woman's desires and requirements at any time. And, after those aspects have been evaluated, a decision based on discussing benefit-risk balance should be taken. This may result in continuation of HT, modification of dose, route or scheme of treatment, or interruption of treatment.

Each one of those topics deserve some commentaries:

With regard to *prevention and diagnosis of organic pathologies*, women using HT may be followed as untreated women. HT users in general do not require any different strategy, although usually they follow a stricter pattern consisting of higher frequency of regular exams and mammograms, especially women younger than 55 years. In any case, only duration of treatment for longer than 5 years for those over 55 years of age might be considered a discrete risk factor for breast cancer and influence the respective screening.

Of course, any abnormal uterine bleeding in HT users must be investigated as in non-users. In this sense, both the health-care provider and the woman should be aware that continuous combined and some cyclo-sequential schemes, despite pursuing amenorrhea, induce occasional bleeding episodes, mainly during the first months of use.

And also, it should be kept in mind that endometrial thickness ultrasound image will be modified depending on the treatment regime and the dose used, and the limits for alert may be higher and more similar to reproductive age.

With regard to *confirmation of efficacy or adjustment of dose and/or scheme* of treatment to women's requirements and desires, it is in general appropriate to choose the more suitable type, dose, route, and scheme of HT for each particular woman. The target must be total control of symptomatology, so, when it is not obtained after some months of treatment, the option of modifying treatment should be considered. Once the objective is gotten, and often after years of use, the target should be to maintain the control with the minimal effective dose. The gradual decrease of dose is a good strategy to prolong the treatment while maintaining a good symptomatic control.

The *review of the indication and acceptance of HT* requires the awareness that a clinically relevant climacteric symptomatology will persist for longer than a few months, and often for years. So, the use of HT use should be considered as a long-term treatment. However, the benefit-risk ratio should be reevaluated more or less annually during the follow-up of each woman. The appearance of a contraindication makes it mandatory to withdraw HT, but leaving this aside, it is convenient to inform and discuss benefit-risk at each visit. So, the decision about the persistence of the indication and acceptance to follow HT should be shared between health-care provider and user: this will require specific information, and the acceptance to continue should account the necessities and desires of each woman. In this context, adjustment of dose and/or scheme of treatment may be done along the time. And in case of doubt, a temporal withdrawal of treatment will clarify if symptoms recur with enough severity to justify the continuation of treatment.

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Hormone Therapy (II): Tibolone, The TSEC Concept

12

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12.1 Tibolone

12.1.1 Introduction

Tibolone ((7α 17)-17-hydroxy-7-methyl-19-norpregnen-5(10)-en-20-In-3-onA, OD14) is a progestin structurally related to norethynodrel. It was developed at the end of the 1960s, initially focused on osteoporosis, and since then has been shown to have significant effects on other organs and systems, so its use is currently approved primarily for the treatment of vasomotor symptoms in postmenopausal women in more than 70 countries [1].

It is considered that its mechanism of action is tissue specific. This concept has originated as a consequence of three physiological processes:

- Active conversion of molecules leads to differences in the affinity of the metabolites to bind specific receptors.
- As a consequence, physiological tissue or organ responses to a compound are highly dependent on active (local) metabolism, especially when the enzymatic conversion leads to the production of a specific active metabolite.
- A specific response may be expected at the cellular or tissue site.

After oral ingestion, tibolone is converted to three active metabolites: a Δ4 isomer (especially in endometrial tissue), a 3α-hydroxy metabolite, and a 3β-hydroxy metabolite, which have different binding affinities to the various sexual steroid receptors, which allows them to deploy estrogenic actions, as well as progestational and androgenic actions, from both a basic and clinical point of view [2].

The different metabolites, as well as the original compound, have been tested for their affinity for binding to estrogen, progesterone, or androgen receptors located in

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the MCF-7 cell nucleus. It has been shown that native tibolone has an affinity for binding to estrogen receptors, as well as progestogen and androgen receptors. Hydroxy metabolites have only affinity to bind to estrogen receptors, whereas the Δ4-isomer has no affinity for the estrogen receptor [3].

These specific metabolite affinities for binding to sex hormone-specific receptors have led to the prediction of the physiological response of a tissue to a given treatment if known specific tissue metabolism occurs.

For tibolone, this means that if the tibolone precursor compound is specifically converted to any of the hydroxy metabolites or the Δ4-isomer, specific tissue hormone activity can be predicted [2, 4].

The main tissue in which the absence or presence of an estrogenic or progestational activity can be demonstrated is, of course, the endometrium. The mechanism, following tissue-specific action (TSA) of tibolone in this tissue, appears to be due to its intrinsic binding properties, in combination with specific endometrial metabolism. In other tissues, such as bone, breast, or cardiovascular system, different and more complex mechanisms may be involved.

The sum of all these tissue-specific mechanisms of action may explain the interesting clinical profile of this hormone [5], which, like other progestins, can modulate the activity of different enzyme complexes that may influence the in situ production of estradiol, for example, in the breast [6].

We can, however, understand that binding to the receptor is not synonymous with the physiological activity of the product. For example, the binding affinity of a pure anti-estrogen to the estrogen receptor is extremely high [7].

Tibolone has been used in the treatment of climacteric symptoms and in the prevention and treatment of osteoporosis for more than 20 years with several trials done (Table 12.1). It effectively controls climacteric symptoms including neuroendocrine,

Table 12.1 Most important tibolone studies: summary

Study	Primary objective	*N*	Main result
Opal (2006)	Changes in mean common carotid intima-media thickness (CIMT)	866	Both tibolone and CEE/MPA showed increased progression of common CIMT
THEBES (2007)	Confirm endometrial safety of tibolone	3240	Tibolone does not induce endometrial hyperplasia or carcinoma
Total (2007)	Compare bleeding, efficacy, and tolerability of tibolone vs. E_2/NETA	572	Tibolone as effective as E_2/NETA but induces less bleeding and breast tenderness
Lift (2008)	Test hypothesis that tibolone reduces risk of vertebral fractures	4538	Tibolone reduces the risk of fractures
Step (2008)	Compare effects of tibolone vs. raloxifene on lumbar spine BMD in osteopenic women	308	Tibolone increases BMD significantly more than does raloxifene
Lisa (2008)	Compare effects of tibolone vs. E_2/NETA on sexual dysfunction	403	Tibolone and E_2/NETA improve sexual function; significantly better effects with tibolone on FSFI
Liberate (2008)	To demonstrate non-inferiority of tibolone compared to placebo regarding breast cancer recurrence	3058	Tibolone increases risk of breast cancer recurrence vs. placebo

such as hot flashes (HF) and night sweats, as well as urogenital symptoms including vaginal dryness and atrophy, but without stimulating the endometrium [9].

As for the breast, it is known that extracellular estrone sulfate (E1S) is the main precursor of estrogen in cancerous mammary cells. E1S reaches the membrane of the tumor cell where it is converted by the action of estrone sulfatase into estrone (E1). Within the cell, E1 is converted to estradiol (E2) by the action of 17β-hydroxysteroid dehydrogenase (17β-HSD). On the other hand, sulfotransferase, on the cell membrane of the tumor cell, converts nonconjugated intracellular estrogens (E1, E2, and estriol) into sulfated estrogens that are secreted into the extracellular medium. Tibolone and its metabolites appear to act via inhibition of enzyme systems, such as sulfatase and 17β-HSD, or via stimulation of cell differentiation and apoptosis. It has been shown that with tibolone these processes occur in both normal and cancerous mammary cells [10–12].

Noting the clinical profile of tibolone, its activity as Selective Tissue Estrogenic Activity Regulator (STEAR) is based through the various mechanisms of action mentioned and opening a new therapeutic category.

We know from clinical studies and experience that tibolone is as effective as 1.5 mg of 17β-estradiol, 2 mg of estradiol valerate, or 0.625 mg of conjugated estrogens to control climacteric symptoms, as well as for effects on the bone and in the urogenital tract [13, 14]. However, in a recent systematic review it was found to be slightly less effective than conventional hormone therapy (HT) in the control of vasomotor symptoms [15].

12.1.2 Tibolone and Vasomotor Symptomatology

The main indication for the use of HT of menopause, whether estrogenic, conventional combined, or tibolone, is the relief of vasomotor symptoms, which has a direct impact on the quality of life of women.

Tibolone has demonstrated more or less the same percentage of efficacy over vasomotor symptoms as standard doses of estrogen and progestogen therapy [13–15].

Several authors have shown that the benefits offered by tibolone are not only comparable to those of conventional HT but are in some respects better. This is reflected in mood, fatigue, or lack of energy and also in improvement in quality of life, probably mediated by its light androgenic effects [15].

12.1.3 Tibolone and Sexuality

There are several aspects of sexuality that have been improved with tibolone, when compared both with placebo and with conventional HT, which have been well pointed [1, 16, 17, 26].

In relation to placebo: Increase in blood flow and vaginal lubrication, increase in sexual fantasies, desire and arousal, no differences in coital frequency, sexual activity without penetration or initiation or rejection of sexual activity, and increase in plasma testosterone and sex hormone binding globulin (SHBG).

In relation to conventional HT: Increase in sexual desire, orgasms, coital frequency, response and excitation or satisfaction, and increase in plasma testosterone and decrease of SHBG.

12.1.4 Tibolone and Bone

The prevention and treatment of osteoporosis by estrogens is conveyed at different levels. At the skeletal level, estrogens maintain bone mass; at the tissue level, bone remodeling decreases, mainly due to a reduction in bone resorption; at the cellular and molecular level, estrogens modulate the functionality of osteoblasts and osteoclasts, directly and indirectly affecting the paracrine mechanisms between these cell strains [18–24].

Because of the importance of the loss of estrogen production in triggering the factors that lead to the development of osteoporosis, it is important to recall the consensus statement published in 1991, which clearly states that osteoporosis can be prevented. The treatment of choice to prevent bone loss in postmenopausal women or with altered ovarian function is HT at menopause [25].

Tibolone has shown indirect actions on bone, modifying the balance of both calcium and vitamin D3 when compared to non-intervention [26].

Tibolone has an estrogenic effect on bone and prevents postmenopausal bone loss. By selectively blocking the androgen receptor and progesterone receptor in ovariectomized rats, the effect of the drug on bone mineral density (BMD) is not altered, but is lost when the blocking receptor is estrogen [8]. It has been used in clinical trials for the treatment of climacteric symptoms and in the prevention and treatment of osteoporosis for more than 20 years [27].

In October 2004, a multidisciplinary and international expert panel on menopause management met at the 4th Menopause Symposium in Amsterdam to determine the specific place for tibolone, a synthetic steroid with a unique clinical profile, among the wide range of therapeutic options for postmenopause available to date [28]. It was concluded that as regards prevention of bone loss, tibolone is as effective as Estrogen Therapy (ET)/HT, with a level of evidence Ia [28, 29]. Subsequently, in the STEP study [30], its superiority to raloxifene (RLX) was demonstrated in relation to bone mass increase.

Tibolone is able to prevent the development of osteoporosis and also to reduce the risk of fracture, both vertebral (relative risk 0.55, 95% CI 0.41–0.74, $p < 0.001$) and non-vertebral (relative risk 0.74, 95% CI 0.58–0.93, $p < 0.001$) in osteoporotic women as demonstrated in the Long Intervention Fracture Trial (LIFT) study at a dose of 1.25 mg daily. The LIFT study [31] was designed as a prospective, randomized, double-blind, placebo-controlled, 3-year (+2 extension), multicenter (worldwide) study. The predictions were intended to include 4000 women with fractures (2000 tibolone and 2000 placebo), and all included patients received between 400 and 800 IU/day vitamin D and 500–1000 mg/day calcium. The main objective of the study was to detect the occurrence of new vertebral fractures. Secondary endpoints included non-vertebral fractures, BMD, bone turnover markers, quality of life, changes in patient height, cognitive function, and economic impact of the intervention.

For a median of 34 months of treatment, the tibolone group, compared to the placebo group, had a decreased risk of vertebral fracture, with 70 cases versus 126 cases per 1000 person-years (relative risk, 0.55; 95% confidence interval (CI): 0.41–0.74, $p < 0.001$), and a lower risk of non-vertebral fractures, with 122 cases compared to 166 cases per 1000 person-years (relative risk, 0, 74, 95% CI, 0.58–0.93, $p = 0.01$). The tibolone group also had a reduction in the risk of invasive breast cancer (RR 0.32, 95% CI, 0.13–0.80, $p = 0.02$) and colon cancer (relative risk, 0.31; 95% CI, 0.10–0.96, $p = 0.04$). However, in the tibolone group, there was an increased risk of stroke (relative risk, 2.19, 95% CI, 1.14–4.23, $p = 0.02$), whereby the study was stopped in February 2006 by recommendation of the data and the safety advice. There were no significant differences in the risk of coronary heart disease (CHD) or venous thromboembolism events (VTE) between the two groups.

The conclusion of the study was that tibolone reduced the risk of fracture and breast cancer and colon cancer but increased the risk of stroke in elderly women with osteoporosis [31].

12.1.5 Tibolone and Cardiovascular System

Although tibolone decreases high-density lipoprotein (HDL) cholesterol, unlike the lipid effects of oral estrogens, it also induces a significant decrease in triglycerides, which are an independent risk factor for insulin resistance and for heart disease, and does not modify C-reactive protein. It also decreases the concentration of lipoprotein (a), which has both atherogenic and thrombotic properties [32, 33].

In the OPAL study [34], annual carotid intima-media thickness (CIMT) values were significantly higher in the tibolone and CE/medroxyprogesterone acetate (MPA) groups compared to placebo.

As regards carbohydrate metabolism in women with and without diabetes mellitus, it has been observed that tibolone does not modify blood levels of glucose, insulin, C-peptide, or glycosylated hemoglobin, nor does it modify the glucose tolerance curve [35].

The results of the OPAL study [34] and the increased risk of stroke demonstrated in the LIFT study [31] point to tibolone as a hormone with the similar cardiovascular risks as estrogen and progestogen therapy.

12.1.6 Tibolone Safety

Endometrial

Tibolone has been shown to produce no estrogenic effect on the endometrium, either by selective conversion to the Δ4 Tibolone metabolite or by its affinity for progesterone receptors. This leads, from the clinical point of view, to a lower tendency for spotting/bleeding (especially in the first months) than conventional combined HT, which in the long run is at least as safe as traditional regimens [36, 37], as demonstrated by the THEBES study, comparing face-to-face with the fixed combination of CE + MPA [36].

Mammary

Although there are discordant results among epidemiological studies, the Million Women Study [38] found that among the 828.923 postmenopausal women included in the main analysis, the risk of breast cancer was significantly higher among HT users than among nonusers (RR = 1.43, 95% CI, 1.36–1.50). This increased risk was largely confined to current users, rather than to users in the past. The RR of breast cancer was significantly higher in current users of estrogen alone (1.30, 95% CI, 1.22–1.38), estrogen + progestogen (2.00, 95% CI, 1.91–2.09), and tibolone (1.45, 95% CI, 1.17–1.76). The magnitude of the increase in risk is very different in these three types of HT and was significantly higher in the current users of estrogen + progestogen ($p < 0.0001$).

These data are extracted from another study in the same English population [39], showing an increase similar to the use with estrogens alone. However, the Women's Health Initiative (WHI) study has shown that the use of estrogens alone decreases the risk of breast cancer, so these data should be questioned.

As any preparation with estrogenic action, tibolone is not indicated in the treatment of climacteric syndrome in survivors of breast cancer, as shown by the LIBERATE [40] study. The LIBERATE study [40] was a randomized, controlled, double-blind, multicenter study between tibolone 2.5 mg/day vs. placebo, with a mean follow-up of 3.1 years. The study population was 3058 women with surgical treatment for breast cancer and vasomotor symptoms (mean time of surgery 2.1 years). The results showed a significantly higher rate of recurrence of breast cancer with tibolone than with placebo (RR 1.40). So the study was stopped 6 months earlier than planned.

12.1.7 Conclusions

Tibolone, with its different mechanisms of action, has unique characteristics that allow it to approach what has traditionally been considered a good profile of HT in menopause, since it allows controlling the climacteric symptoms, improving mood, sexual response, and the state of the genitals, and protecting the bone, but without stimulating the endometrium. Also it has a beneficial effect on several intermediary indicators of cardiovascular risk, although it increases the risk of stroke and its behavior in the breast is similar to estrogen/progestogen HT.

Tibolone is the first of a new class of compounds, the STEAR, which describe molecules with Selectively Tissue Estrogenic Activity Regulators activity.

12.2 TSEC

12.2.1 Introduction

Tissue-selective estrogen complex (TSEC) is a combination of Bazedoxifene (BZA) with CE, and it is a therapeutic option for the management of menopausal symptoms and prevention of postmenopausal osteoporosis [41].

The rationale for TSEC development was that the SERM component would minimize adverse estrogenic effects on the endometrium and breast while maintaining the beneficial effects of estrogens on menopausal symptoms [42]. BZA was specifically selected because this SERM showed favorable preclinical effects on the skeleton, vasomotor activity, and lipid metabolism, as well as mammary and uterine safety [43]. Gene expression profiling of CE in combination with three different SERMs [BZA, RLX, and lasofoxifene (LAS)] showed differential patterns of gene expression, indicating that different SERM/CE combinations may have distinct clinical activities [44].

BZA is a third-generation SERM with phenyl rings which act as binding sites for the alpha and beta estrogen receptors but with greater affinity for alpha [45]. This SERM has been extensively studied in preclinical [45, 46] and in clinical studies [45, 47]. In addition to the CE, sex steroid hormones derived from cyclopentanoperhydrophenanthrene also have a great experience with both preclinical [46, 48–51] and clinical studies [52–54].

The efficacy and safety of the combination of BZA/CE for menopausal symptoms and prevention of postmenopausal osteoporosis have also been evaluated in preclinical models. The two points to evaluate for safety were endometrium and breast. Preclinical data have shown that whereas CE alone stimulates proliferation of MCF-7 and T47D human breast cancer cells and reduces cell apoptosis, the addition of BZA at an adequate dose level abrogates these effects [55]. BZA, but not RLX or LAS, antagonized CE-induced increases in uterine wet weight to levels similar to vehicle control [56]. Several studies in rats and monkeys found a safety and efficacy profile while using BZA/CE, different for the one found with estrogen alone, SERMs, and other SERMs with estrogens [48–50].

12.2.2 Clinical Studies

The combination of BZA/CE has been evaluated in different multicenter, randomized, double-blind, placebo and active-controlled trials called Selective Estrogens, Menopause, and Response to Therapy (SMART) (Table 12.2).

Study 303, SMART 1 with 3397 patients in 94 sites in the United States, Europe, and Brazil, included healthy postmenopausal women between 40 and 75 years, with uterus, BMI $\leq$32.2 kg/m^2, and normal endometrial biopsy before admission. Its main objective was to evaluate the efficacy of multiple doses of BZA/CE (combination of BZA 10, 20 or 40 mg and CE 0.45 or 0.625 mg) in endometrial protection, HF, vulvovaginal atrophy, and osteoporosis prevention. The study duration was 24 months [52, 53, 57, 58].

The study 305, SMART 2 with 318 patients at 43 sites in the United States, included healthy postmenopausal women aged 40–65 years with a uterus and BMI $\leq$34 kg/m^2. All should have seven or more hot flashes a day of moderate to severe or a minimum of 50 a week before starting the study and wishing to start handling them. This study evaluated the effects of BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg in the improvement of HF compared with placebo at 12 weeks of treatment. The main result was to see the decrease in the intensity and frequency of

Table 12.2 Selective estrogens menopause and response to therapy (SMART) trials: summary

Studies	Duration of treatment	Primary endpoint	Treatment arms	Number of subjects
303 Smart 1	24 months	Dose range	BZA 10, 20 40/CE 0.45 mg	3397
		Endometrial hyperplasia to 12 months	BZA 10, 20 40/CE 0.625 mg	
		BMD to 24 months	Raloxifene 60 mg	
		Vasomotor symptoms	Placebo	
		Vaginal maturity		
305 Smart 2	3 months	Vasomotor symptoms	BZA 20/CE 0.45 mg	318
			BZA 20/CE 0.625 mg	
			Placebo	
306 Smart 3	3 months	Vulvovaginal atrophy	BZA 20/CE 0.45 mg	652
			BZA 20/CE 0.625 mg	
			BZA 20 mg	
			Placebo	
304 Smart 4	12 months Ext. 1 year	Endometrial hyperplasia	BZA 20/CE 0.45	1061
		BMD	BZA 20/CE 0.625 mg	
		Supportive safety study	CE 0.45/MPA 1.5; placebo	
3307 Smart 5	12 months	Endometrial hyperplasia	BZA 20/CE 0.45 mg	1843
		BMD	BZA 20/CE 0.625 mg	
		Breast density	CE 0.45/MPA 1.5 mg	
			BZA 20 mg	
			Placebo	

BMD bone mineral density

HF and secondary were the effects on sleep, quality of life, and satisfaction with treatment [53, 59].

The study 306, SMART 3 with 652 patients in 66 sites in the United States, included healthy postmenopausal women aged 40–65 years with a uterus and BMI ≤34 kg/m^2. All had to have vaginal cytological smear with no more than 5% of superficial cells, vaginal pH >5, and HF at least moderate to severe before admission. This study evaluated the effectiveness on vulvovaginal symptoms in women with vulvovaginal atrophy over a period of 12 weeks [60, 61].

SMART 4 (304) study with 1061 patients was a multicenter, double-blind, placebo- and active-controlled phase III study in non-hysterectomized postmenopausal women. This study evaluated the effects of BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg compared with CE/MPA, BZA, and placebo on endometrium and BMD. It lasted 12 months [62].

The study 3307, SMART 5 with 1843 patients in 166 sites in the United States, Europe, Latin America, Australia, and New Zealand, included healthy postmenopausal women aged 40–75 years with a uterus and BMI ≤34 kg/m^2 with normal endometrial biopsy result before admission. The study evaluated the efficacy of

BZA/CE on endometrial protection and osteoporosis prevention as well as the effects on breast density. Two TSEC combinations, BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg, were compared with CE/MPA, BZA, and placebo. It lasted 12 months [54, 63].

12.2.3 Effects on Vasomotor Symptoms and Quality of Live

Two clinical studies, the SMART 1 and 2, assessed the efficacy of BZA/CE for the treatment of moderate to severe HF. Both combinations of BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg were associated with a marked improvement of HF compared with placebo [53].

The SMART 1 showed a decrease in perception of intensity ($p < 0.05$ vs. placebo) and frequency ($p < 0.001$ vs. placebo) of HF at 4 and 12 weeks with BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg, which indicates the effectiveness for treating HF [53].

SMART 2 showed that using BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg, there was a significant decrease ($p < 0.001$) at 2 and 4 weeks in the number of moderate to severe HF per day compared with placebo. A reduction of 5–6 HF per day with the use of this therapy compared to a decrease of three flushing with placebo, representing a significant improvement in BZA/CE treatment [53].

Data from these two randomized, double-blind, placebo- and active-controlled, phase three studies were pooled for non-hysterectomized postmenopausal women with moderate/severe HF given BZA 20 mg/CE 0.45 mg, BZA 20 mg/CE 0.625 mg, or placebo for 12 weeks. HF frequency and severity were assessed by daily diary [64]. The pooled analysis included 403 participants. At 12 weeks, BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg significantly (all $p < 0.001$) decreased moderate/severe HF frequency versus placebo (−7.9, −8.2, −4.1), reduced adjusted average daily HF severity score vs. placebo (−1.0, −1.3, −0.3), and increased the percentage of women who had a ≥50% (81.2, 87.1, 50.6%) and ≥75% (62.4, 74.8, 26.4%) reduction from baseline in daily frequency of moderate/severe HFs. Significantly improved Menopause-specific Quality Of Life questionnaire (MENQOL) vasomotor function versus placebo (adjusted mean change −3.08, −3.69, −1.37). BZA/CE was significantly more effective than placebo irrespective of time since menopause, with some evidence of a lower placebo response in women in later menopause (>5 years) versus early menopause (≤5 years) [64].

Another analysis of these two studies concluded that BZA/CE affected the MENQOL vasomotor domain both directly and indirectly, whereas effects on other domains were fully mediated via HF severity reductions [65].

12.2.4 Effects on Vulvovaginal Atrophy

The decrease in estrogen in postmenopausal women can also lead to vulvovaginal symptoms that may be associated with sexual dysfunction and alter quality of life. These aspects were evaluated in the SMART 1 and 3 [52, 60].

The SMART 3 study evaluated the efficacy of BZA 20 mg/ CE 0.45 mg and BZA 20 mg/CE 0.625 mg on vulvovaginal symptoms in women with vaginal maturation index with no more than 5% superficial cells, pH >5, with moderate to severe vulvovaginal symptoms. Both combinations of BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg showed an increase in superficial cell compared to placebo ($p < 0.001$) and a decrease in vaginal pH ($p < 0.001$) as well as an improvement in annoying vulvovaginal symptoms for women compared to placebo ($p < 0.05$). Those include dyspareunia, vaginal dryness, and itching [60].

The SMART 1 showed similar results in terms of increased superficial cells compared to placebo ($p < 0.001$. These changes on epithelial maturation had had a significant relationship with decreased dyspareunia compared with placebo during 9–12 weeks of therapy ($p < 0.001$) and improved lubrication compared to placebo ($p < 0.05$) in the Arizona Sexual Experience Scale (ASEX), which positively impact on quality of life measured by the MENQOL [52].

12.2.5 Effects on Bone Mass

The effect on bone was evaluated by three studies. The impact of TSEC on bone was evaluated in two studies, SMART 1 and SMART 5, separately. As compared with placebo, both studies confirmed moderate increases in BMD at both the spine and the hip after 12 months of treatment. SMART 1 showed a greater increase in BMD than RLX at 24 month [54, 57].

Those two studies, SMART-1 and SMART-5, were pooled for BMD and turnover marker over 12 months [66]. There were 1172 women, mean age 54.9 years, mean 6.21 years since menopause, mean lumbar spine, and total hip *T* scores −1.05 and −0.58; 58.8% had a Fracture Risk Assessment Tool score less than 5% indicating low fracture risk. At 12 months, adjusted differences (vs. placebo) in BMD change in the groups taking conjugated estrogens 0.45 or 0.625 mg plus bazedoxifene 20 mg were 2.3 and 2.4% for lumbar spine, 1.4 and 1.5% for total hip, and 1.1 and 1.5% for femoral neck (all $p < 0.001$ vs. placebo). These increases were unrelated to baseline Fracture Risk Assessment Tool score, age, years since menopause, body mass index, or geographic region. Both doses reduced bone turnover markers ($p < 0.001$) [66].

In the third study, SMART 4 (304) with 1061 patients, both BZA/CE doses (20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625) significantly increased lumbar spine and total hip BMD, versus placebo ($p < 0.001$) [62].

In conclusion, BZA/CE significantly improved BMD and turnover in a large population of younger postmenopausal women at low fracture risk and is a promising therapy for preventing postmenopausal bone loss.

12.2.6 BZA/CE Safety

Based on the SMART studies, doses of BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg are not only well tolerated but also have a good safety profile which approves its use in healthy postmenopausal patient with uterus [52, 53, 60]. Adverse

events and discontinuation of the treatment secondary to these events were similar in all groups.

Endometrium

Endometrial protection is the main objective to keep in mind in postmenopausal patients with uterus receiving estrogens. The combination of BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg showed a low incidence (<1%) for endometrial hyperplasia and cancer similar to placebo during 24 months of treatment. Therefore, the selective activities of SERMs in the combination of BZA/CE are the key to the endometrial protection [52]. At 12 months, in SMART 5, endometrial hyperplasia incidence was low (<1%) and similar to CE/BZA or placebo [54].

Reports obtained from transvaginal ultrasound examinations showed that the use of BZA/CE achieved an almost neutral effect on the endometrium at 12 months of treatment (less 1 mm) very similar to what was observed with placebo [52].

Women using CE/MPA in the SMART 5 had a greater increase in endometrial thickness >5 mm compared with BZA/CE or placebo. Both the SMART 1 and 5 evaluated vaginal bleeding and found that BZA 20 mg/CE 0.45 mg and 0.625 mg were associated with higher cumulative amenorrhea, similar to placebo, in proportion >83, >87, >85%, respectively [54, 67]. In SMART 4 (304) study with 1061 patients at 1 year, no cases of endometrial hyperplasia were identified in the BZA 20 mg/CE 0,45 mg group, while three cases (1.1%) were confirmed for the BZA 20 mg/CE 0.625 mg group [62].

Breast

Although the number of patients and the time of treatment were insufficient to draw conclusions across studies, no difference was observed in the incidence of breast cancer after 2 years between groups of BZA/CE and placebo (BZA 20 mg/CE 0.4 5 mg, $n = 1$, BZA 20 mg/CE 0.625 mg, $n = 0$, placebo, $n = 1$) [68].

The effects of BZA/CE on the incidence of pain and breast tenderness were studied in the SMART 1, 2, and 5. The pain was evaluated by diaries filled up by the patient. The use of BZA 20 mg/CE 0.45 mg and 0.625 mg showed no significant difference in pain and breast tenderness compared to placebo, RLX, or BZA 20 mg alone [52].

In SMART 5, the incidence of pain and tenderness using BZA/CE was significantly lower compared with women treated with CE 0.45 mg/MPA 1.5 mg ($p < 0.001$). BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg did not show inferiority compared to placebo in terms of changes in breast density, different from what was found in patients using CE/MPA [52, 59]. The results show that BZA 20 mg/CE 0.45 mg and BZA 20 mg/CE 0.625 mg have a neutral effect (similar to placebo) in breast density [54].

Cardiovascular Disease

In a recent study [69], cardiovascular adjudicated safety data from healthy, non-hysterectomized, postmenopausal women who received ≥1 dose of CE 0.45 mg/BZA 20 mg ($n = 1585$), CE 0.625 mg/BZA 20 mg ($n = 1583$), any CE/BZA dose ($n = 4868$), or placebo ($n = 1241$) were pooled for up to 2 years in five trials. CHD, cerebrovascular events, and VTE were reviewed using a meta-analytic approach.

The rate of VTEs per 1000 woman-years (95% confidence interval, CI) was 0.3 (0.0–2.0) in women taking BZA 20 mg/CE 0.45 mg, 0 (0.0–1.5) in those taking BZA 20 mg/CE 0.625, 0.7 (0.0–1.5) among women taking any BZA/CE dose, and 0.6 (0.0–2.9) with placebo. The incidence of stroke per 1000 woman-years (95% CI) was 0.4 (0.0–2.4), 0.2 (0.0–1.9), 0.44 (0.0–1.1), and 0.0 (0.0–1.7), respectively. The CHD rate per 1000 woman-years was 2.6 (0.0–5.6), 1.4 (0.–3.9), 2.4 (1.00–3.7), and 2.0 (0.0–5.2). Compared with placebo, relative risk (95% CI) with any BZA/CE dose was 0.5 (0.1–1.8) for VTE, 0.5 (0.1–2.6) for stroke, and 0.63 (0.23–1.74) for CHD [69]. Up to 2 years, BZA/CECE had an acceptable cardiovascular safety profile, with rates of stroke and CHD comparable to placebo in healthy postmenopausal women. VTE risk was low [69].

Lipids and Coagulation Factors

Lipid (n = 1843) and coagulation (n = 590) variables were assessed in women receiving daily BZA 20 mg/CE 0.45 mg, BZA 20 mg/CE 0.625 mg, BZA 20 mg, CE 0.45 mg/medroxyprogesterone acetate (MPA) 1.5 mg, or placebo for 12 months in the SMART.5 trial[70].

At 12 months, BZA 20 mg/CE 0.45 mg, BZA 20 mg/CE 0.625 mg, BZA 20 mg, and CE 0.45 mg/MPA 1.5 mg decreased total cholesterol and low-density lipoprotein cholesterol compared with placebo ($p < 0.01$ for all). Both BZA/CE doses and CE/MPA increased high-density lipoprotein cholesterol compared with placebo ($p < 0.05$ for all). BZA 20 mg/CE had a neutral effect on triglycerides. Both BZA/CE doses were associated with small but significant effects on hemostasis variables, including reductions in antithrombin, plasminogen activator inhibitor-1, and fibrinogen activity and an increase in plasminogen activity relative to placebo at 12 months [70].

This study provides that BZA/CE does not adversely affect lipid metabolism or hemostatic balance [70].

Conclusions

The TSECs are a new therapy for the management of menopausal symptoms and bone loss with a protective effect up to 2 years in breast and endometrium.

Treatment with BZA/CE has been shown a safety profile and tolerability in preclinical and clinical studies, thus making a significant improvement in HF, vulvovaginal atrophy, and osteoporosis prevention in postmenopausal women as well as providing security in lipid and cardiovascular profile. Thrombotic events do not show a higher incidence compared to placebo, being able to compare them with estrogens or SERMs.

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The Impact of Hormone Therapy on the Clinical Symptoms of Menopause

13

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13.1 General Principles

Many women experience a range of symptoms during the menopause and perimenopause, and these symptoms are often short-lived and lessen or disappear over time. The most common include vasomotor symptoms (e.g., hot flushes and sweats), effects on mood (e.g., low mood), and urogenital symptoms (e.g., vaginal dryness). Postmenopausal women are at increased risk of a number of long-term conditions, such as osteoporosis, cardiovascular disease, and changes in the vagina and bladder. These occur because of natural aging as well as estrogen depletion [1].

During the latter part of the last century, hormone replacement therapy (HRT), also known as hormone therapy (HT) and menopausal hormone therapy (MHT), was advocated for both symptom relief and chronic disease prevention. Menopausal hormone therapy (MHT) is the broad term used to describe unopposed estrogen use for women who have undergone hysterectomy or combined estrogen–progestin therapy (EPT) for women with an intact uterus who need a progestin to prevent estrogen-associated endometrial hyperplasia. By convention, unopposed estrogen therapy is known as ET, combined estrogen–progestin therapy as EPT, and menopausal hormone therapy as MHT [2]. For menopausal women 60 years of age or 10 years past menopause with bothersome vasomotor symptoms (with or without additional climacteric symptoms) who do not have contraindications or excess cardiovascular or breast cancer risks and are willing to take MHT, we suggest initiating ET for those without a uterus and EPT for those with a uterus.

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Variations in consultation patterns for menopausal symptoms depend on many factors, including cultural, ethnic, educational, and psychosocial factors, as well as the impact of the symptoms on the women. However, it is thought that more than one-third of all women want more support for managing menopausal symptoms from their GP or practice nurse [1].

13.1.1 Goals of Therapy

The goal of MHT is to relieve menopausal symptoms, most importantly hot flashes (vasomotor symptoms). Other symptoms associated with perimenopause and menopause that respond to ET include mood lability/depression, vaginal atrophy, sleep disturbances (when related to hot flashes), and in some cases, joint aches and pains.

Women being treated for menopausal symptoms such as hot flashes require systemic estrogen; women being treated only for vulvovaginal atrophy (now referred to as "genitourinary syndrome of menopause" [GSM]) should be treated with low-dose vaginal estrogen rather than systemic estrogen.

In the past, MHT was also used by some clinicians to prevent coronary heart disease [CHD] and osteoporosis. However, we do not recommend MHT for prevention of disease given the results of the Women's Health Initiative (WHI), a set of two large randomized trials that demonstrated an unfavorable risk–benefit profile of MHT.

13.1.2 Importance of Patient Age

While the WHI clearly demonstrated adverse effects of MHT in older postmenopausal women (over age 60 years), this is not the age group that presents with new onset of menopausal symptoms. Almost all women who seek medical therapy for menopausal symptoms do so in their late 40s or 50s. Women in this age group should be reassured that the absolute risk of complications for healthy, young postmenopausal women taking MHT for 5 years is very low [2].

13.2 Benefits of Menopausal Hormone Therapy

13.2.1 Vasomotor Symptoms

Hot flashes are the classic symptom of the menopausal transition, experienced by more than 70% of women at some point during the menopausal transition. Hot flashes are associated with impairments in quality of life (QOL), depressed mood, reported sleep disturbance, and possibly even poorer memory function. Despite their prevalence and impact on women's lives, the understanding of the physiology of hot flashes remains incompletely understood. Leading models conceptualize hot flashes as originating in the central nervous system, yet there has been limited data

investigating relations between the brain and hot flashes. Some data support changes in the brain regions associated with awareness of bodily sensation, such as the insula and prefrontal cortex, acutely during hot flashes and the involvement of brainstem areas in the triggering of hot flashes [3, 4].

Hot flashes occur in the context of estrogen (E) withdrawal, and the effects of E on brain structure and function in humans remain controversial. Hot flashes often begin as the sudden sensation of heat centered on the upper chest and face. In some instances, this will become generalized, lasting for several minutes, and can be associated with profuse perspiration, palpitations, or anxiety which may be very distressing and limit activities of daily living, particularly when they occur repeatedly during the day and at night. At night, hot flushes and night sweats will often cause insomnia that leads to fatigue.

Treatment for VMS may include hormone replacement therapy (HRT), since symptoms occur at a time when estrogen levels are dropping and "replacement" leads to relief. HRT comprises synthetic hormones that may be identical to those produced from the ovaries during the reproductive years (estradiol and progesterone) although other similar compounds (such as conjugated equine estrogens, estradiol valerate, and several synthetic progestogens) are widely used. Although there are alternative therapies for vasomotor symptoms, none are as effective as estrogen which is the most effective treatment for vasomotor symptoms and improving QOL in symptomatic women. In a dose-dependent manner, MHT reduces hot flash frequency by approximately 75% and severity by 87%, compared with 50% with placebo [4].

13.2.2 Anxiety and Depressive Symptoms

Depression and mood change is common at times of hormonal change, such as during the menstrual cycle, after pregnancy, and in the perimenopausal period. There is a robust relationship between gonadal hormones such as estrogens and mood disorders in women. There are several known female-specific depressive disorders that are linked to changes in hormonal status. Premenstrual disorders, postpartum depression, and perimenopausal depression are all characterized by a sharp decrease in estradiol associated with symptom onset. This association reinforces the role for estrogens in the maintenance of mood. Studying these disorders both in humans and in animal models will provide opportunities for development of more successful treatment options and will clarify the relationship between estrogens and depression.

Anxiety symptoms increase during the menopause transition and are associated with an increased likelihood of a major depressive disorder. MHT, alone or in combination with an antidepressant such as a selective serotonin reuptake inhibitor (SSRI), is effective for women who experience mood lability or depression during the menopausal transition. ET may improve mild-to-moderate depressive symptoms during or shortly after the menopause transition, whereas antidepressant therapy remains appropriate treatment for major depression [5].

Mood disorders are common during the menopausal transition, often coexisting with vasomotor symptoms. Two small, short duration clinical trials assessed MHT in women with depression or depressive symptoms during the menopausal transition. After 3 weeks, depression scores improved significantly in depressed women treated with transdermal estradiol (0.05 mg/day) compared to placebo [6]. After 12 weeks, depressive disorders were significantly more likely to remit with transdermal estradiol (0.1 mg/day) compared to placebo [7].

The present approach is to choose initial therapy based upon the woman's predominant symptom. If her main concern is depression and hot flashes are not severe, we start with an SSRI. On the other hand, if vasomotor symptoms are the major symptom and depression or mood symptoms are mild, MHT should be recommended. For women in whom depression and vasomotor symptoms are both severe, both estrogen and an SSRI may be an option, but it is mandatory to refer them to a psychiatric unit for further consultation and monitoring [8].

13.2.3 Skin, Cartilage, Connective Tissues

Estrogen receptors have been detected in many skin elements including keratinocytes, melanocytes, fibroblasts, hair follicles, and sebaceous glands, so it is likely that the withdrawal of estrogen at menopause will have measurable effects on skin health. Skin surface texture, water-holding capacity, collagen content of the dermis, and viscoelasticity have shown improvement with the use of estrogen [9].

A spectrum of musculoskeletal symptoms follows estrogen deficiency in a large number of women, from arthralgia to osteoarthritis (OA). The effects of estrogen in bone are well characterized, but data on the impact of estrogen on cartilage, skin, and connective tissues have been slower to emerge. Estrogen is synthesized by aromatases in most connective tissues. Critically, estrogen receptors are present in all joint tissues including articular cartilage, subchondral bone, and synovium.

Although no clear association has been found between lifetime estrogen exposure and the risk of osteoarthritis, generalized muscle and joint aches are among the commonest symptoms experienced by women at menopause. Furthermore, arthritis in women is more likely to be progressive and symptomatic [9]. Estrogen receptors ERa and ERb have both been identified in chondrocytes, and recent studies have also demonstrated estrogen receptors in synoviocytes [10].

It is unclear if arthralgia is related to estrogen deficiency or is a rheumatologic disorder, but in the WHI, women with joint pain or stiffness at baseline were more likely to get relief with either combined EPT or unopposed ET than with placebo in 45% [9, 11]. Joint pain increased slightly after discontinuation of treatment [12]. In the absence of specific studies, three related mechanisms are proposed for possible effects of estrogen, or of MHT in the disease:

13.2.3.1 Inflammation

There is a large amount of data to suggest that estrogen is anti-inflammatory and mildly immunosuppressive.

13.2.3.2 Bone

The effects of MHT on bone are well known. Targeting bone turnover may be one mechanism by which MHT could interfere with osteoarthritis.

13.2.3.3 Pain

Estrogen receptors and aromatase are present in hypothalamus, limbic system, neurons, and joint. Estrogen therapy has been shown to decrease synovial nerve fiber substance P in a rat model of osteoarthritis. Estrogen is antinociceptive, activating inhibitory pain pathways in the spinal cord, while progestins are pronociceptive.

13.2.4 Genitourinary Symptoms of Menopause

The female genital and lower urinary tracts share a common embryological origin, arising from the urogenital sinus and both are sensitive to the effects of female sex steroid hormones throughout life. The epithelial linings of the vagina and urethra are very sensitive to estrogen, and estrogen deficiency leads to thinning of the vaginal epithelium. Estrogen is known to have an important role in the function of the lower urinary tract, and estrogen and progesterone receptors have been demonstrated in the vagina, urethra, bladder, and pelvic floor musculature [13].

Estrogen deficiency results in Genitourinary Syndrome of Menopause (also called vaginal atrophy or atrophic vaginitis), causing symptoms of vaginal dryness, itching, dyspareunia, and sometimes urinary symptoms. Both systemic and vaginal estrogen are effective for genitourinary atrophy symptoms, but we suggest vaginal rather than systemic estrogen for women who have only Genitourinary Syndrome of Menopause without other menopausal symptoms such as hot flashes [14].

Low-dose vaginal estrogen therapy is effective for the treatment of vaginal symptoms with some evidence of additive benefit against recurrent urinary tract infections and dysuria. Several vaginal preparations are available, including vaginal creams, tablets, and a silastic ring that releases E2 locally over a 3-month period. Of these, the 10 mg E2 tablet and the 7.5 mg vaginal ring result in the least amount of systemic estrogen absorption. When low-dose vaginal estrogen therapies are used according to labeling, it is unlikely that endometrial stimulation will occur, and progestogen therapy is therefore not routinely recommended for women using only vaginal estrogen therapy.

Systemic SERM therapy is also available for treating dyspareunia due to menopause. Oral ospemifene, 60 mg daily, improves dyspareunia, vaginal dryness, and female sexual function. Ospemifene seems well suited for women who prefer oral therapy rather than vaginal estrogens and who are without contraindications. Cost, accessibility, and individual preferences should dictate the choice of treatment formulation for managing GSM.

13.2.5 Urinary Incontinence

The role of systemic estrogens in the management of postmenopausal women with lower urinary tract symptoms has been investigated in three large epidemiological studies examining the use of combined estrogen/progestogen and estrogen-only systemic hormone replacement therapy [10–12]. In all of these trials, systemic estrogen replacement therapy was found to increase the risk of developing both stress and urgency urinary incontinence, and, in those women who complained of urinary incontinence at baseline, the symptoms were found to deteriorate. This was also reflected in deterioration in quality of life.

13.2.6 Cardiovascular Disease

Cardiovascular disease (CVD) is the major cause of death in women in all European countries; below 75 years, 42% of women die from CVD compared with 38% of men. The lower rates of CHD in women—but not of stroke—may be interpreted as a protective effect of endogenous estrogens. However, exploration of trends over time and between countries shows that the relationship varies, making this an implausible explanation. Sex differences in dietary fat intake (rather than excess smoking in men) may be responsible [15].

Major primary prevention measures are smoking cessation, weight loss, blood pressure reduction, regular aerobic exercise, and diabetes and lipid control [9]. There is strong and consistent evidence that estrogen therapy may be cardioprotective if started around the time of menopause (often referred to as the "window of opportunity" or "timing" hypothesis) and may be harmful if started more than 10 years after menopause.

The American Heart Association (AHA) [16] published an update of its guidelines for the prevention of CVD in women, which emphasizes that recommendations are the same for both men and women, with a few exceptions. Use of the Framingham score is recommended but now includes a category of "ideal cardiovascular health" comprising absence of raised risk factors, BMI <25 kg/m^2, regular moderate-to-vigorous physical activity, and a healthy diet.

The Endocrine Society guideline suggests calculating cardiovascular and breast cancer risks before initiating MHT [17]. They suggest nonhormonal therapies for symptomatic women who are at high risk (>10% 10-year risk) for CVD or moderate (1.67–5% 5-year risk) to high risk (>5%) for breast cancer. For women at moderate risk of CVD (5–10% 10-year risk), they suggest transdermal rather than oral estrogen, with micronized progesterone for those with a uterus. They note that a population-based CVD risk calculator should be used to estimate CVD risk.

Although this represents the ideal approach, a formal CVD calculation may not be necessary in a thin, healthy, nonhypertensive patient who is well known to the clinician. For women at increased risk of venous thromboembolism (VTE), they also suggest transdermal estrogen with a progestin that has a neutral effect on coagulation parameters (e.g., micronized progesterone) [17].

We suggest not using MHT for the prevention of cardiovascular disease, even in young postmenopausal women. Although the risk profile appears to be more favorable in young women taking unopposed estrogen, use for prevention is still not warranted [18]. The hormone regimen studied in the WHI was conjugated estrogens and medroxyprogesterone acetate (MPA). While it is possible that other estrogen or progestin formulations or doses might not have the same negative cardiovascular effects as conjugated estrogen and MPA, data to support their use for prevention are not available.

13.2.7 Osteoporosis

Osteoporosis is a systemic skeletal disease characterized by diminished bone strength with the risk of sustaining a fracture when falling from own body height (fragility fracture) [19]. Bone strength is determined by a combination of bone density and microarchitectural integrity. Postmenopausal osteoporosis results from a failure to attain peak bone density, accelerated bone loss after menopause, age-related bone loss, or a combination of factors. Accelerated postmenopausal bone loss is induced by estrogen deprivation [9].

Assessment of bone mineral density is not a cost-effective population screening tool but is best applied on a selective basis, based on age and other risk factors such as a personal or family history of fractures, history of amenorrhea, primary ovarian insufficiency, low body mass, diet, smoking, alcohol abuse, the use of bone toxic medication, and rheumatoid arthritis [9].

MHT is the only therapy available with proven efficacy of fracture reduction in patients with osteopenia. Although MHT prevents fractures at any age after menopause, age at the initiation of MHT is important [16]. In the age group 50–60 years or within 10 years after menopause, the benefits of MHT are most likely to outweigh any risk and can be considered as first-line therapy [18]. Initiation of MHT in the age group 60–70 years requires individually calculated benefit/risk, consideration of other available drugs, and the lowest effective dose [18]. MHT should not be initiated after age 70 years.

Non-estrogen-based treatments for osteoporosis include bisphosphonates, denosumab, selective estrogen receptor modulators (SERMs), parathyroid hormone (PTH), and strontium ranelate. Bisphosphonates (such as alendronate, risedronate, ibandronate, and zoledronic acid) inhibit bone resorption by inducing apoptosis of osteoclasts, thus preventing age-related bone loss and deterioration of bone microarchitecture. They are the most widely prescribed drugs, mainly due to their low cost and the generally favorable safety profile. Denosumab is a human monoclonal antibody to the receptor activator of nuclear factor-kappaB ligand (RANKL), a bone-resorbing cytokine. It is administered as a subcutaneous injection every 6 months. All antiresorptive agents are associated with an increased risk of osteonecrosis of the jaw and atypical femoral fracture. But both conditions are rare [20].

The two SERMS approved for the treatment of postmenopausal osteoporosis are raloxifene and bazedoxifene. Both reduce the risk of vertebral but not hip fracture

and increase the risk of venous thromboembolism and hot flushes. They are both associated with a decreased risk of breast cancer in postmenopausal women with osteoporosis. Future treatments for osteoporosis include cathepsin K inhibitors which appear to have mixed antiresorptive and anabolic actions as they inhibit one of the major osteoclast digestive enzymes without suppressing bone formation, thereby leading to anabolic effects on bone [21].

13.2.8 Cognitive Function and Dementia

Numerous studies have reported an effect of estradiol on memory ability. Central and peripheral administration of estradiol levels mimicking proestrus improves spatial memory in ovariectomized rats. It appears that estradiol improves hippocampal dependent memory performance through activation of Erβ. Despite current knowledge of the memory impairments associated with depression, little effort has been placed on exploring cognitive deficits and hippocampal changes related to postpartum depression and perimenopausal depression. Human research on memory impairments has produced conflicting results [22].

We currently do not suggest the routine use of MHT for peri- and postmenopausal women who are experiencing cognitive symptoms (memory loss and difficulty concentrating). Although substantial biologic evidence supports the importance of estrogen to cognitive function, clinical trial evidence has generally ruled out any global (but not domain-specific) cognitive benefits.

In addition, we suggest not using MHT to prevent dementia. Although some epidemiologic data suggest that estrogen may be beneficial, clinical trials of MHT administered to women over age 65 years showed harm. Strong evidence of cognitive benefits for women taking MHT at younger ages (e.g., near menopause) is also lacking, and thus MHT should not be prescribed for preservation of cognitive function in younger women [23].

13.2.9 Sexual Disorders

Sexuality in women is a relatively new field of biomedical research. Psychological, relational, and environmental factors are regarded as being of paramount importance in influencing sexual function and behavior. Indeed, a comprehensive approach to women's sexuality requires more than the mere understanding of a physiological process. The most relevant variables are age, general and mental health, achievement of reproductive goals, education, body image, self-esteem, norms, and experiences. Even duration and quality of partnership, and general and sexual health of the partner, are important.

The known decrease in ovarian androgen production rates and serum androgen concentrations has caused concern that menopause might be associated with a decline in libido. An age-associated decline in sexual desire has been observed in both men and women. However, it is unclear whether the decline in libido in women

is age or menopause related, since studies in women have not shown a significant correlation between libido and the serum estradiol or testosterone levels.

Clinical trials of exogenous testosterone replacement suggest modest benefits of testosterone therapy in some postmenopausal women. However, there are potential risks associated with androgen replacement, and the use of testosterone is limited by the lack of approved and commercially available products for women. Until the beneficial effects of androgen replacement are better established, it cannot be routinely recommended to postmenopausal women.

13.2.10 Extended Use of MHT

Both the North American Menopause Society [2] and the International Menopause Society [9] agree that the use of MHT should be individualized and not discontinued solely based upon patient age. They suggest that extended use of MHT (beyond age 60 or even 65 years) may be reasonable when the clinician and patient agree that the benefits of symptom relief outweigh the risks. As noted, over 40% of women ages 60–65 years have persistent hot flashes that can impair sleep and quality of life.

For women who choose extended use of MHT (more than 5 years or beyond age 60 years), we restart estrogen at the lowest dose possible and make plans for a future attempt to stop the estrogen.

13.3 Summary and Recommendations

- The goal of menopausal hormone therapy (MHT) is to relieve menopausal symptoms, most importantly hot flashes (vasomotor symptoms). Other symptoms associated with perimenopause and menopause that respond to estrogen therapy (ET) include mood lability/depression, genitourinary syndrome of menopause (GSM; vaginal atrophy), and sleep disturbances (when related to hot flashes).
- Healthy symptomatic women in their 50s should be reassured that the absolute risk of complications for healthy, postmenopausal women taking MHT for 5 years is very low.
- For healthy, peri/postmenopausal women within 10 years of menopause (or < age 60 years) with moderate-to-severe vasomotor symptoms, we suggest MHT as the treatment of choice (Grade 2B). Exceptions include women with a history of breast cancer, coronary heart disease (CHD), a previous venous thromboembolic event or stroke, active liver disease, or those at high risk for these complications.
- We suggest transdermal 17-beta estradiol for many women starting MHT (Grade 2C). The transdermal route is particularly important in women with hypertriglyceridemia or risk factors for thromboembolism. However, the baseline risk of both venous thromboembolism (VTE) and stroke is very low in otherwise healthy, young postmenopausal women. Therefore, if a patient prefers an oral preparation

over a transdermal one (cost or personal preference), we consider oral estrogen to be safe. All types and routes of estrogen are equally effective for hot flashes.
- For women who experience recurrent, bothersome hot flashes after stopping estrogen, we initially suggest nonhormonal options. However, if this approach is unsuccessful and symptoms persist, we resume MHT at the lowest dose possible in carefully selected women.
- For women with an intact uterus who choose ET, progestin therapy must be added to prevent endometrial hyperplasia and carcinoma.
- We suggest micronized progesterone as our first-line progestin because it is effective for endometrial hyperplasia, is metabolically neutral, and does not appear to increase the risk of either breast cancer or CHD, although data are limited (Grade 2C).
- Recommendations for women who choose not to take systemic estrogen, have contraindications to estrogen, or have stopped their MHT and are having recurrent symptoms are found elsewhere.
- We currently suggest not using MHT for the prevention of chronic disease (osteoporosis, CHD, or dementia) (Grade 2B). However, women who cannot tolerate other options for osteoporosis may be reasonable candidates.

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The Impact of Hormone Therapy on Health

14

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14.1 The Impact of Hormone Therapy on Cognition and Mood

14.1.1 Introduction

The impact of the reduction of circulating estrogens on cognitive deterioration after menopause is being an area widely investigated. There is a considerable amount of experimental data favoring an interaction of estrogens with cognitive functions [1]. The issue, however, remains controversial at clinical level. For example, some investigators have found that users of HT performed better on specific tasks such as psychomotor speed, visual memory, nonverbal memory and attention, and digit span-forward and recall [2–5]. In contrast, other studies could not find a significant

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association with global function or with specific domains (verbal memory, verbal fluency, working memory, attention, or executive functions) [6, 7].

Memory has been the most studied domain within the cognitive universe, perhaps because it is more clearly affected and because it has a potential to predict the development of Alzheimer's disease (AD) [8, 9].

14.1.2 Psychobiological Feasibility

The background supporting the estrogen action arises from molecular evidence and from observations obtained in different experimental models. There is, for example, abundance of estrogen receptors (ER) at different areas related to cognition in the central nervous system (CNS). This is the case of the hippocampus and the frontal lobes, which subserve verbal memory, working memory, and retrieval [10]. Also, outside the hypothalamus, ER have been described in cortical and limbic areas that are involved in the processes of learning and memory [1].

In parallel, experimental work has shown that estrogens alter synaptic circuitry in the hypothalamus, hippocampus, and, more recently, neocortex (reviewed in [11]).

14.1.2.1 Studies in Animal Models

The availability of different types of animal models has facilitated the intensive study of the impact of estrogens on different cognitive functions.

Work in mice has shown that treatment with estrogens is followed by dramatic increases in hippocampal spine synapse density within minutes and that this is accompanied by improved general discrimination learning, probably through increasing formation of silent or immature synapses within hippocampus via ERα activation [12]. Other studies in rodents have focused on learning and working memory performance and have shown that ovarian hormones affect both cognitive processes and neural substrates that underlie those tasks [13–15]. Deficiencies in spatial learning capabilities and increases in the myelin sheath volume of the white matter were demonstrated by treatment with estrogens in OVX rats [16].

So, exogenous estradiol seems to behave as a crucial regulator of hippocampal morphology and plasticity and also of memory in rodents. Of interest, some groups have obtained similar findings in nonhuman primates [17–19].

However, data from animal studies are not unanimous. The positive effects described above were also accompanied by detrimental actions in some cases. Pompili et al. [15] described that estrogens selectively improved working memory but had a negative effect in spatial reference memory. As for any work with experimental models, it is possible that methodological differences may explain the discrepant findings.

The impact of progestogens has received some attention as well. The association of progesterone to estradiol was neutral when assessed on visual and spatial recognition memory in older monkeys [20]. However, a study in OVX rats obtained different outcomes depending on the type of progestogen; so, whereas levonorgestrel enhanced learning, two other synthetic progestogens, medroxyprogesterone acetate (MPA) and norethisterone acetate, impaired learning and memory [21].

14.1.3 Clinical Studies

14.1.3.1 Effects of HT on Cognition

The current clinical knowledge has been obtained from observational studies and, more recently, randomized controlled trials. Some attention has been paid to the specific form of HT, including hormone preparations, either estrogen alone or combined with progestogens, and route, either oral or transdermal.

The Study of Women Across the Nation (SWAN) constitutes a landmark despite its cross-sectional design, because a substantial number of participants were analyzed and also because information about circulating hormones was obtained. A total of 1657 community-based midlife women were stratified according to menopause stage, and their cognitive function was evaluated. When adjusting for covariates, no association was found between the measured cognitive performance tests and menopause stage or hormonal level, estradiol, and follicle-stimulating hormone (FSH) [22].

One main intervention study has been the Women's Health Initiative Memory Study (WHIMS). Conceived as an ancillary study of the WHI randomized controlled trial, WHIMS aimed at evaluating the effect of estrogen plus progestogen on the incidence of dementia or mild cognitive impairment compared with placebo [23]. At the early termination of the study after an average follow-up of 4.05 years, 40 women were diagnosed with probable dementia in the treatment group versus 21 in the placebo. The hazard ratio was 2.05. The incidence of mild cognitive impairment did not differ between groups. Of interest, a subset of 1403 women were measured for regional brain volumes, including hippocampal and frontal regions by magnetic resonance at an average of 3.0 years posttrial (WHIMS-MRI study). The use of hormones, either conjugated equine estrogens (CEE) alone or associated with MPA, was associated with greater brain atrophy, the effects being

more evident in women who already suffered cognitive deficits before initiating hormones [24].

As for other outcomes of the WHI study, there has been a debate on whether the unfavorable impact might be due to the relatively advanced age, 65 years or older, of participants in the WHIMS. A decrease in the responsiveness of neurons to estrogen with increasing age or the inability of the hormone to reverse neural loss and/or dysfunction, which may have occurred during the interim between menopause and the initiation of treatment, cannot be discarded. This caveat was one reason to design the Kronos Early Estrogen Prevention Study (KEEPS), another randomized controlled trial that had an ancillary study, the KEEPS-Cog. Women were now younger, 52.6 years average age, and 1.4 years since menopause. A total of 693 women were randomized to daily oral CEE or transdermal estradiol, in both cases associated with micronized progesterone (12 days per month), or placebo. The primary outcome was the effect on the Modified Mini-Mental State examination. Again, HT was not associated with clear benefit, although against the results in the WHIMS, no harm was found this time [25].

The WHIMSY (Women's Health Initiative Memory Study of Younger Women) study had a similar purpose. Cognition was assessed in women who had enrolled in the WHI study when they were 50–55 years of age. When 7.2 years had elapsed since the end of the trial, women were assessed by telephone, their mean age being 67.2 at that moment. As for the KEEPS-Cog, no substantial difference was found between women receiving hormones and the placebo-treated controls [6].

Some investigators have claimed that, despite the consistent evidence obtained in randomized studies, the duration of therapy might have been missed as a variable, since none of them followed participants for longer than few years. In response to this uncertainty, a cohort of women in France was assessed for cognitive function and the reported duration of HT was used as a variable. HT was associated with better performance in certain cognitive domains, and the associations were dependent on the duration of treatment [26]. This conclusion is further supported in another recent study in Finland [27].

To summarize, and consistent with the conclusion from experienced groups [7], the most solid evidence seems to favor the notion that HT does not have a clear impact on cognition, including episodic memory or executive functions. The neutral effect extends for a reasonable number of years. There is not enough evidence to support the existence of a window of opportunity in the immediate postmenopause. However, studies are still insufficient and late-life cognitive consequences are still poorly addressed.

14.1.3.2 Effects of HT on Mood

Mood disorders are prevalent during the menopausal transition, with figures that attain a 16.5% for depressed mood in midlife women [28]. The SWAN study found that women were two to four times more likely to suffer a depressive episode during the menopausal transition [29]. Other investigators have reported similar findings [30]. The known interaction of estrogens with serotonin and other monoamines

provides biochemical rationality to the clinical findings [31]. Mood problems have been found to increase in those with a history of mood continuum disorders but can also occur de novo as a consequence of the hormonal changes. In most cases, the period of vulnerability to mood problems [32] subsides when the hormonal levels stabilize and women enter full menopause. It is understood that it is hormonal fluctuations that more directly determine the mood changes [33].

The clear hormonal influence has prompted the postulation of HT as an efficacious remedy. One recent central study has been the previously mentioned KEEPS-Cog, a multicenter randomized trial that, in addition to cognitive effects, assessed the impact on mood, including depression and anxiety. Oral CEE, but not transdermal estradiol, effectively reduced scores of depression and anxiety over the 48 months of treatment [25]. The reasons for the difference remain elusive, although it is against the well-known stable levels provided by the estradiol patches. This effect of estrogens in KEEPS-Cog further confirms previous studies of different sizes and relevance, as shown in several reviews [32–34].

14.2 Cardiovascular Disease

Cardiovascular disease (CVD) remains the most common cause of death among women in Western countries. After menopause with decline of the ovarian function, the incidence of CVD in women increases rapidly to equal that in men. Postmenopausal HT has been used for more than 80 years mainly to alleviate hot flushes and other menopausal symptoms. However, during the past couple decades the health benefits and risks of HT have been under vigorous debate, particularly focusing on the impact of HT on the cardiovascular health.

Estrogen has various well-established direct effects on the vascular wall resulting in vasodilation and prevention of occlusive events [35, 36]. Furthermore, estrogen mediates a number of secondary changes in the vasculature that slow down the initiation and progression of atherosclerosis (Table 14.1). However, these beneficial vascular effects of estrogen are lost at later stages of more complicated atherosclerosis and may lead to propensity of plaque rupture and thrombosis [37]. This is in line with the recent clinical data indicating that HT is beneficial to the cardiovascular health if initiated soon after the onset of menopause but not anymore if started in elderly women with advanced atherosclerosis [38, 39].

Table 14.1 Mechanisms by which estrogen may exert beneficial cardiovascular effects

Direct effects	Indirect effects
Nitric oxide production and release ↑	Total cholesterol ↓, LDL ↓, HDL ↑
Prostacyclin production and release ↑	Antioxidant effects: Oxidation of LDL ↓
Endothelin-1 production and release ↓	Blood pressure ↓
Cytokine release ↓	Insulin sensitivity ↑
Inflammation ↓	Homocysteine ↓
Smooth-muscle cell growth ↓	Ischemia/reperfusion injury ↓
Atherosclerotic plaque progression ↓	Cardiac hypertrophy ↓

The majority of observational studies assessing the effect of HT on CVD come from women who have chosen to initiate HT close to menopause to alleviate various menopausal symptoms [40]. In general, these data suggest 30-50% reduction of CVD in HT users compared to nonusers. This dogma was challenged by the randomized Women's Health Initiative (WHI) study, where in women HT initiation at average of 63 years of age failed in primary prevention of CVD events [41]. This led to rapid decline in HT use and change in guidelines worldwide and, most importantly, ended the use of HT for primary prevention of CVD.

14.2.1 New Evidence to Support the Benefit of HT in Cardiovascular Health

There is a strong evidence that the discrepancy between the results of the large body of epidemiological studies and the primary results of the WHI study can mainly be explained by the "timing hypothesis"; i.e., HT initiation is beneficial for the cardiovascular health in healthy recently menopausal women but not in elderly women with various CVD risk factors [37–39]. This has been confirmed by several subanalyses of the WHI study [42]. Also the most recent clinical trials and epidemiological studies suggest that HT reduces the incidence of CVD in recently menopausal women [43]. In a Danish trial (DOPS study), women randomized to HT at a mean of 7 months after the onset of menopause experienced half the rates of myocardial infarctions, heart failure, and death than women randomized to no treatment [44]. In the Early versus Late Intervention Trial (ELITE-study), estradiol-based HT resulted in a significantly slower progression of carotid artery intima media thickness compared to placebo, but only among women who initiated HT less than 6 years after menopause [39]. These data suggest that HT suppresses the development of atherosclerosis and CVD when initiated early after menopause.

In a recent study, myocardial infarction attack-related death risk was 38% smaller in estradiol-based HT users compared to nonusers, and this may indicate HT-induced cardiac benefits before and/or during the myocardial infarction [45]. Furthermore, HT has been shown to reduce cardiac death risk the earlier the HT is initiated [38]. These data suggest that 60 years of age at the initiation of HT is not necessarily a threshold age, but the earlier the HT had been started, the smaller was the cardiac mortality risk. This is supported by the fact that atherosclerotic changes start to develop already in premenopausal age, and thus, the findings are in line with the "timing hypothesis."

Many women choose to discontinue HT due to recommendations that HT should be used for the shortest possible time, and furthermore, annual or biannual HT pause has become a routine practice to evaluate if a woman could manage without HT. In a recent large-scale population study, women who stopped estradiol-based HT relative to women who continued it had a 2.3-fold greater risk of CVD mortality within the first post-HT year [46]. Furthermore, these risk elevations were markedly higher in women who had been younger than 60 years at the initiation of HT use. Although the mechanisms behind these findings are not established, it is possible

that acute withdrawal of vasodilatory estrogen, as in discontinuation of HT, may result in constriction of coronary arteries and even fatal thrombogenic events. Thus, these findings strongly question the safety of the annual discontinuation practice, particularly in recently menopausal women.

14.2.2 Effect of Type and Route of HT in Cardiovascular Health

In the USA, most studies have been conducted with CEE, whereas estradiol has been used almost exclusively in Europe. More recent studies indicate that CEE could be more prothrombotic than estradiol [47]. Thus, more studies comparing head to head CEE and estradiol are needed, and for now comparisons between clinical CVD outcomes obtained with CEE or estradiol should be done with caution.

The progestogen component of HT, and particularly MPA, has often been associated with the failure of HT in primary prevention of CVD [48]. In a recent large study MPA, norethisterone acetate and a number of other progestogens used with estradiol were accompanied with overall comparable reductions in CVD mortality risk [38]. However, dydrogesterone being less androgenic progestogen than, e.g., MPA, showed a tendency of being more beneficial than other progestogens when HT was initiated before 60 years of age [38]. Thus, although there might be some differences in the cardiovascular effects of the different progestogens used in HT, they do not appear to fully antagonize the beneficial cardiovascular effects of estrogen.

Oral and transdermal administration results in different estrogenic milieus; oral route causes higher circulating levels of estrone than transdermal use of estradiol. By avoiding the hepatic first-pass metabolism, the transdermal route results in fewer adverse effects on coagulation markers compared to oral estrogens, and thus, the transdermal route is devoid of increased risk of deep vein thromboembolism [49]. However, comparisons between oral and transdermal estradiol with other CVD events as primary endpoints are needed. Interestingly, the use of local estradiol to alleviate vaginal atrophy leads to slight increases in circulating estradiol levels [50], and this estradiol rise appears to benefit heart; the risk of CVD mortality was significantly decreased in a study with 330,000 women using local estradiol [51]. Thus, even the very low levels of non-oral estradiol appear to provide cardiac benefits, and perhaps particularly in elderly women.

14.2.3 Conclusions

After the primary WHI publications, new research data have accumulated that uniformly support the beneficial effects of estradiol-based HT in cardiovascular health primary prevention of CVD. The control of hot flushes should remain the primary indication for prescribing HT; however, to get a concomitant cardiac benefit the use of HT should be started soon after the onset of menopause.

14.3 Osteoarthritis

14.3.1 Introduction

The increase in the incidence of osteoarthritis (OA) after menopause [52], together with the identification of ER in diverse joint tissues [53, 54], supports the hypothesis that estrogens have a role in the development of the disease. This fact has posed the possibility of including estrogen therapy (ET) as an option in the treatment of OA. Despite the wealth of studies postulating the chondroprotective effect of estrogens (Table 14.2), the mechanisms by which estrogens do so remain to be fully understood. Yet, experimental observations point to both direct and indirect effects on the articular cartilage; indirect effects seem to occur via inhibition of subchondral bone turnover [55], while direct effects include cell-autonomous actions on the articular chondrocyte. Herein, we will only focus on the latter ones.

The experimental observations have been paralleled by clinical studies examining the effect of the treatment with estrogens on OA [56]. More recently, selective estrogen receptor modulators (SERMs) have received some interest too.

14.3.2 Experimental Evidence

14.3.2.1 Beneficial Effect of Estrogens on the Cartilage

There are several actions of estrogens that have been considered beneficial for cartilage health. Previous studies established that estrogen deprivation decreases glycosaminoglycan (GAG) synthesis. Further, cartilage compression increased significantly GAG release and induced chondrocyte apoptosis. Against those observations, physiological concentrations of estradiol prevented the injury-related cell death and reduced the GAG release significantly in a receptor-mediated manner, suggesting that hormone therapy could be an option for OA [57].

Also, chondrocytes display a metabolism adapted to anaerobic conditions. Indeed, oxygen tension in synovial fluid can change and lead to ischemia-reperfusion phenomena. These changes can abnormally accelerate tissue metabolism and produce anomalous levels of reactive oxygen species (ROS) that have been described to increase the risk for OA development [58]. Estradiol has been postulated to affect oxidative stress. Claassen et al. [59] showed how the addition of estrogen to articular chondrocytes in vitro provided an antioxidant effect, which protects chondrocytes from ROS-induced damage.

Estrogens can also decrease the production of some pro-inflammatory cytokines [60]. The expression of MMP-13 and IL-1β in the chondrocyte was downregulated by

Table 14.2 Possible mechanisms of the chondroprotective effect of estrogens

Increases glycosaminoglycan synthesis
Prevents chondrocytes apoptosis
Decreases NF-KB, iNOS, COX 2, and ROS
Reduces prostaglandins
Decreases metalloproteinases 3 and 13
Prevents type II collagen degradation
Decreases subchondral bone turnover

the interaction of 17beta-estradiol with its receptor through the induction of miR-140 [61]. Moreover, the effects of IL-1alpha and TNF-alpha on the production of prostaglandin E2 are mainly due to an increase in COX-2 activity. Morisset et al. [62] found that 17beta-estradiol reduced prostaglandins through a decrease in the mRNA steady-state levels of cyclooxygenase-2 (COX-2) in bovine articular chondrocytes. This effect has been claimed to provide protection against ROS-induced chondrocyte damage. Figure 14.1 shows morphological features of cultured chondrocytes when attacked by the artificially generated oxygen radicals and the protective effect of estrogen.

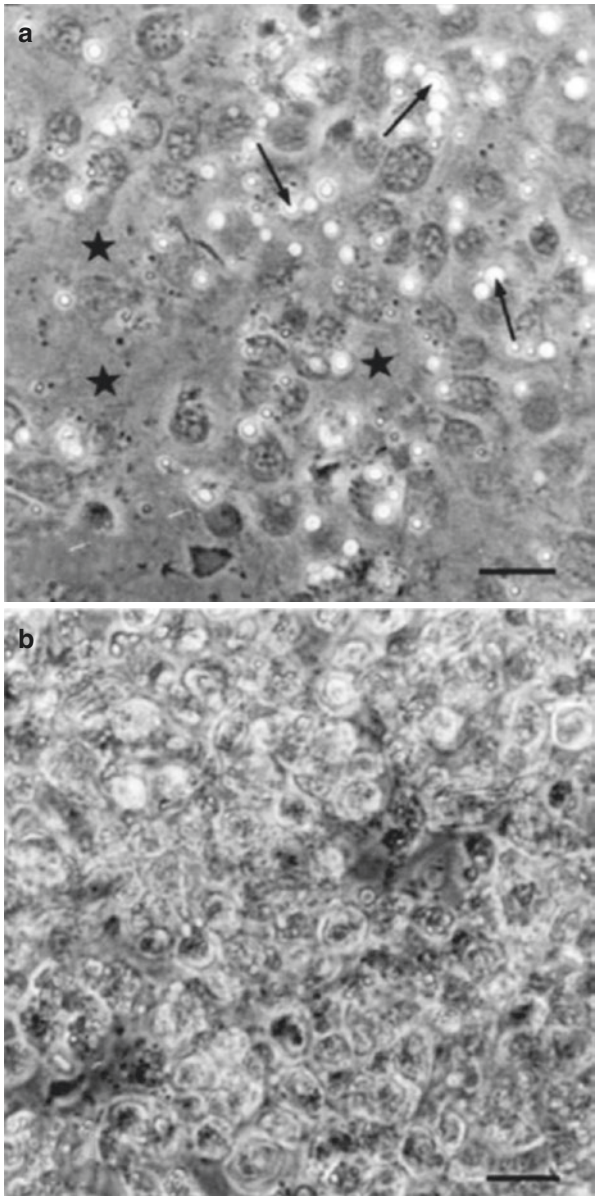

Fig. 14.1 Morphological features of chondrocytes in culture without (**a**) and with (**b**) estradiol and attacked by the artificial generation of oxygen radicals. Unprotected chondrocytes were characterized by the production of vesicles (*arrows*) representing damaged plasma membranes and cell organelles. In some areas (*stars*), chondrocytes were disintegrated. Chondrocytes exposed to estradiol (**b**) had a healthy morphology, without vesicles, indicating that estradiol protects them against ROS-induced membrane damage. Bars, 20 μm. With permission of Springer Verlag from Claassen H, et al. Cell Tissue Res. 2005;319:439–45. Permission obtained through Copyright Clearance Center, Inc

Other in vitro experiments performed in chondrocytes suggested that not only estrogens but also raloxifene, one well-known SERM, might have a potential chondroprotective role in OA. Decrease in proteoglycan levels and increase in both metalloproteinase-3 (MMP-3) and nitric oxide (NO) have been observed when cultured human chondrocytes are treated with interleukin-1 beta (IL-1β). Raloxifene, in a way not too different from estrogens, blunts the decrease in proteoglycan levels and the increase of both MMP-3 and NO, a deleterious effect induced by interleukin-1β (IL-1β) on cultured human chondrocytes. In addition, raloxifene decreased the gene expression of the inducible nitric oxide synthase (iNOS), which was noticeably expressed in IL-1β-stimulated chondrocytes [63].

14.3.2.2 Deleterious Effects of Estrogen Therapy on the Cartilage

In contrast to the beneficial effects reported by some studies, a deleterious effect on cartilage by estrogen therapy has been documented as well. The data were obtained in an experimental model of young ovariectomized (OVX) rabbits receiving either systemic [64] or intra-articular estrogen [65]. Surprisingly, both models developed the typical OA changes. At the cellular level, some authors found that high doses of estrogens induced proteoglycan degradation and MMP production, suggesting that estrogen might exert a dual effect on the joints, either positive or negative, depending on the final concentration achieved within the cartilage microenvironment [66].

14.3.2.3 A Possible Timing Process

Estrogen deficiency increases the erosion of the articular surface and accelerates the renewal of matrix molecules. Oestergaard et al. [67] showed how estrogen supplementation in OVX rats blunts the enzymatic degradation of type II collagen induced by sex hormone loss and decreases the cartilage damage induced by acute loss of estrogens. However, delayed initiation of estrogen therapy after OVX resulted in diminished efficacy in terms of preventing cartilage damage, as compared with early hormone intervention. It seemed that the beneficial effects of hormone therapy required a therapeutic window opportunity.

Taking all these data together, it can be concluded that, although more research is needed to understand how estrogens influence chondrocyte homeostasis, both optimal dose concentration and timing of administration after sexual hormone deficiency are two important factors to promote the beneficial effects of estrogens.

14.3.3 Clinical Evidence

The effect of estrogens on OA has been investigated in studies including both radiological imaging and clinical end points. As for the experimental studies, the impact seems mixed, with both protective and deleterious results on the disease.

14.3.3.1 Hormone Therapy and OA in Large Joints

Two classical cross-sectional studies gave favorable results for postmenopausal women using estrogens. The Chingford study in UK general population showed that women using estrogens for longer than 12 months were significantly less affected by

knee and distal interphalangeal OA [68]. Also, the Framingham Osteoarthritis Study in the USA found an inverse relationship between the use of estrogens and radiographic knee OA, although the effect was weak and nonsignificant [69]. Another cross-sectional study examined the possible association between drugs with a bone antiresorptive effect (estrogens, raloxifene and alendronate) with structural features of OA, as assessed by magnetic resonance. Both alendronate and estrogen were associated with significantly less OA-related subchondral lesions [70].

The relationship between estrogen therapy and OA in large joints has been also examined in some case–control studies performed some years ago. Denninson et al. [71] found a protective effect of long-term estrogens on hip OA. However, another study of similar design could not find any effect of life estrogen exposure, as assessed by age at menarche or menopause, contraceptive use, or postmenopausal hormone therapy and the diagnosis of OA [72].

Similarly, both the long-term follow-up of the Chingford and the Framingham Osteoarthritis Study found a protective effect of treatment with estrogens on radiographic knee OA, but the effect was weak and, importantly, nonsignificant [73, 74]. Furthermore, a nested case–control study examining the association of estrogen therapy and incident symptomatic OA (hand, hip, and knee) found that the new use of estrogen was associated with a higher incidence of OA [75].

14.3.3.2 Hormone Therapy and Risk for Joint Replacement in Large Joints

Some investigators have looked at the issue from a different angle and examined the possible association between hormone therapy and joint replacement because of OA. One important piece of evidence came from the WHI study, in which women receiving only CEE had a lower rate of hip arthroplasty, although the finding could not be reproduced in the group of women receiving estrogens plus progestogen [76]. On the same lines, the Nurse's Health Study, a cohort observational study, found that hormone therapy was a neutral factor for risk of total hip replacement [77]. A more recent study concluded that, possibly because of the bone antiresorptive effect of hormone therapy, the revision rates of hip and knee arthroplasty were reduced in hormone users [78].

However, some discrepant studies have been published as well. A case–control study in Sweden found that the use of estrogens after the age of 50 increased the risk for OA prosthetic surgery [79]. Another observational study including 1.3 million women found that the use of hormone therapy was associated with increased risk for hip and knee replacement [80].

14.3.3.3 Hormone Therapy and Hand OA

The effect of HT on hand OA has received insufficient attention. The initial cross-sectional Chingford study, previously mentioned because of the beneficial effect detected for knee OA in hormone users, could not find a similar protective effect on the hand [73]. Similar neutral effects were found in other cross-sectional studies [81].

Again, there is also some data suggesting that hormones might be deleterious for hand OA. For example, ever or current use of HT was associated with increased prevalence and severity of Heberden's nodes and distal interphalangeal OA in 348 Tasmanian women [82].

14.3.3.4 Studies on Biological Markers

Some investigators have looked at the impact of hormone use on biological indicators of cartilage health. The cartilage volume, as measured by magnetic resonance, and the changes in the serum or urinary levels of some biomarkers have been selected.

A study involving 81 women treated with hormones for longer than 5 years found that hormone users had more cartilage at the knee joint than untreated controls [83]. The same group could not reproduce the findings when examining the cartilage at the patella [84] or at the tibia when women were followed longitudinally for approximately 2.5 years [85].

Concerning circulating biomarkers, the cartilage oligomeric matrix protein (COMP) is considered an indicator of joint destruction that can be measured in serum. A case–control study found that estrogen therapy significantly decreased the levels of COMP after 6 months. This observation led investigators to suggest a role for estrogens in the prevention of joint damage [86]. In a different approach, the changes in the urinary levels of C-telopeptides of type II collagen (uCTX-II), a marker of cartilage degradation, were found to be decreased by oral or transdermal estrogen when using samples from two randomized, double-blind, placebo-controlled trials in Denmark [87].

14.3.4 New Agents: SERMs

A new approach to the involvement of the estrogen pathways in OA is provided by the modern SERMs, a class of compounds different from estrogens but with ability to interact with the ER. There is high-quality evidence showing the protective effect of SERMs in osteoporosis and the hypothesis has been raised that a similar effect might be extended to the joint and the cartilage. Some data support this contention. For example, levormeloxifene, a SERM from the triphenylethylene family, reduced by approximately 50% the urinary excretion of CTX-II [88]. There is additional information from animal models that suggest a protective role for SERMs [89], but clinical studies are still insufficient.

14.3.5 Conclusion

There is some evidence in favor of a protective effect of estrogens on the joints, but there are also neutral studies at both experimental and clinical level. Because there is also some evidence, though sparse, showing deleterious effects, the best judgment should be that the issue is controversial at present. Further, the favorable studies are not unanimous in what refers to the dose of estrogens, the length of treatment, or the optimal therapeutic window. More evidence is, therefore, required. This insufficiency also includes the needed clarification of the potential impact of SERMs.

14.4 Hormone Therapy and Cancer Risk

14.4.1 Introduction

The impact of menopause on the risk of cancer is tightly related to the role of ovarian steroids in the risk for malignancies of genital tract and breast. Indeed, cancerophobia has been one of the most frequently argued reasons for rejecting or abandoning HT [90]. While no particular oncogenic risk has been detected with the decline in estrogens during menopause, HT has been associated with increased risk of breast and endometrial cancer and perhaps also with ovarian cancer.

14.4.2 Biological Plausibility

The physiological changes of breast and endometrium in response to the oscillations of the circulating levels of estrogens are clearly perceived by women as a proof of the hormonal sensitivity of both tissues. Symptoms like cyclical breast tenderness and the own development of the gland during puberty strengthen the notion. The endometrial cycle, with menstruation as the final phase, is an obvious correlate at the level of the uterus. Estrogens have been considered mainly responsible of the observed clinical changes, and only after more careful work, the role of progesterone has become apparent. This all, in any case, has resulted from work performed several years ago.

The differential roles of estrogens and progesterone on the endometrium were unveiled by work on endometrial specimens [91] that was performed in the UK by Roger King and collaborators. According to the information provided by biopsies obtained during the menstrual cycle, it became clear that estradiol promotes endometrial proliferation, while progesterone stops the process and induces differentiation in glands and stroma. The preparation of the endometrium for an eventual embryo implantation was the biological result of this finely tuned coordination between estradiol and progesterone during the human menstrual cycle, as described in classical papers [92]. The mechanisms underlying these changes, and the corresponding fluctuations in the population of estrogen and progesterone receptors, have been exquisitely well described by investigators using basic biochemistry or immunohistochemistry.

The breast follows a different pattern. The role of progesterone, which was assumed to be antiproliferative like in the endometrium, turned to be opposite. The finding that breast biopsies during the luteal phase of the cycle [93] showed increased proliferation and mitoses puzzled clinicians and investigators. It is now evident, as confirmed in rodents, that progestogens increase proliferative activity in the breast. Moreover, recent work has shown that progestogens might act through interaction with the pathway of the receptor activator of nuclear factor κ (RANK), a receptor that binds RANK ligand (RANKL), a cytokine. This proliferative action of progestogens may convey the increased risk for breast cancer associated with hormones [94].

14.4.3 Hormones and Risk for Cancer

14.4.3.1 Endometrial Cancer

The early observation that the use of estrogens for HT in women with a uterus was associated with an increased risk for endometrial cancer [95] led to the use of combined estrogen plus progestogen regimes. Abundant literature has reproduced the association until recently [96], and more refined studies have detected an association with the lifetime exposure to estrogens, even in premenopausal women [97]. This is the interpretation given to the increased risk for women with early menarche or late menopause or high body mass index [98]. The promotion of proliferation and reduction of apoptosis by estrogens are taken as factors influencing the association.

The well-established antiproliferative action of progesterone was the argument to include the generalized use of combined treatments in women with a uterus. Two combinations have been in use since then, the cyclic and the continuous combined. The difference between them relies in the mode of progestogen administration, which accumulated for only some days of the cycle, usually 12–14 days, in the case of the cyclic formulations, or daily, together with the estrogen, in the continuous combined option. While the cyclic protocols leave a few hormone-free days to allow for withdrawal bleeding, the continuous combined regimes are prolonged uninterrupted to achieve amenorrhea. The daily progestogen dose is lower in continuous regimes, although the more prolonged use makes that the total dose per month does not differ significantly between them. The continuous combined formulations are not free of unscheduled bleeding episodes, particularly during the first year of use.

It is worth mentioning that the regular use of progestogens with estrogens in HT actually reduces the risk of endometrial cancer [99]. Because of this clear reduction in the risk for endometrial cancer, together with the unwanted bleeding episodes, the hypothesis was raised of whether using less progestogen might diminish side effects while maintaining a good endometrial control. One alternative protocol has consisted of the use of vaginal progesterone, which is less potent than synthetic molecules as a progestogen. The vaginal dose allows for a selective accumulation of progesterone in the uterus and a reduced systemic concentration [100]. In a further step, the use of interrupted formulations, in which the progestogen is given twice a week, has shown very competitive effectiveness [100]. Moreover, this formulation may be used with success with the use of micronized vaginal progesterone [101].

14.4.3.2 Breast Cancer

Whereas the risk of endometrial cancer has been apparently abrogated by the inclusion of a progestogen in the hormonal formulation, breast cancer has consistently arisen as an adverse effect of HT. In an almost unanimous form, the early evidence emerged in observational studies. Together with the biological plausibility and the social impact of breast cancer, the issue has arisen as a deterrent against the use of hormones by postmenopausal women [90, 102]. The association was detected for both estrogen and estrogen plus progestogen regimes, although the responsible role of estrogens was considered as granted. More solid conclusion was obtained when stronger evidence, as provided by randomized controlled trials, was available. A landmark in this sequence was provided by the WHI study, which confirmed an approximately 30% increase in risk in hormone users after approximately 5 years of

treatment. Of interest in the WHI, the division of the trial in two arms, estrogens only and estrogen plus progestogen depending on whether women were, or were not, hysterectomized, disclosed that while increased risk was found in women with combined treatments, women receiving only estrogen did not show increased risk [103]. The findings were consistent with the earlier and somewhat unexpected observations of a mitogenic role of progesterone on the breast, as described in breast biopsies taken during the luteal phase of the cycle [93].

A more refined perspective has arisen since then. The oncogenic role of estrogens remains supported by experimental studies and also by the consistent epidemiological association with features shared with endometrial cancer. Good examples are early menarche, late menopause, or high body mass index. Also, there is a relationship of breast cancer risk with the circulating levels of endogenous estrogens and estrogen metabolites [50]. And there are indirect data, yet inconclusive, suggesting association of the levels of circulating estrogens with breast density, a notable risk factor for breast cancer incidence and, perhaps, also progression [104]. And finally, the decreased risks provided by drugs reducing the estrogen exposure, like aromatase inhibitors and SERMs, are additional arguments. And to further reinforce this evidence, epidemiological data published subsequently to the WHI study keep confirming an increased risk associated with the use of estrogens in HT.

Having said so, the principal responsibility of progestogens seems warranted. It is not only the data of the WHI but also the confirmation provided by subsequent studies [105] showing increased risk with combination therapies, the risk being consistently higher than that of estrogens. To further support the role of progestogens, there is biological evidence showing that the RANK/RANKL pathway may convey the action of progestogens [94] (Fig.14.2). Consequently, the present view

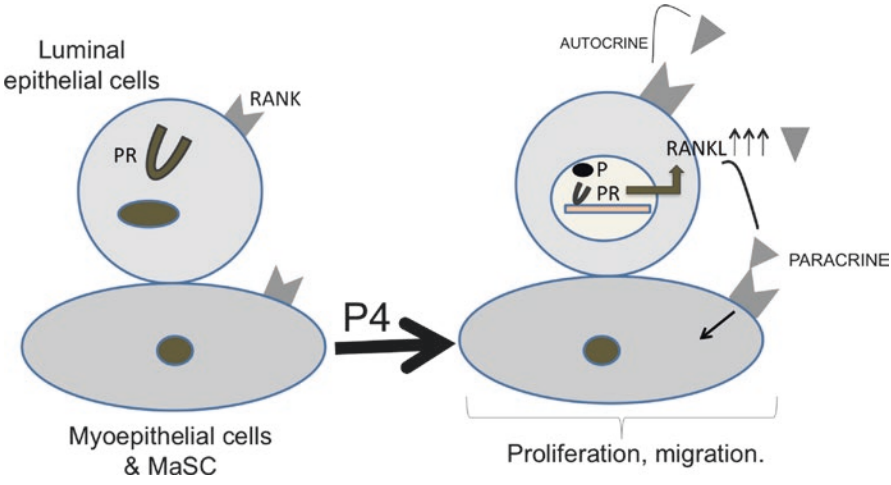

Fig. 14.2 Role of RANK/RANKL in progestogen-mediated proliferation of breast epithelium. Mammary stem cells (MaSC) and luminal cells express RANK at their membranes. Progesterone receptors (PR), however, are expressed only in luminal cells. The activation of PR by progesterone (P4) increases the expression of RANKL in luminal cells. Then, the cytokine acts through two possible ways, either autocrine, which further increases the production of RANKL, or paracrine, which increases proliferation, migration, and differentiation of MaSC

is that it is progestogen that mostly increases the risk of breast cancer, albeit a lower estrogen-mediated risk seems warranted as well.

There is also some debate on whether there is a class effect in the risk mediated by estrogens and progestogens. The topic is of high interest, because it raises the point of whether some variants of estrogens may be used with minor or undetectable risk. The debate has included estriol and the new estetrol.

Estriol is considered a weak estrogen because of the poor potential for inducing proliferation in target tissues. The main source of natural estriol is the placenta. No definitive conclusion can be offered at present, mainly because the data have been originated mainly in experimental models and results are controversial [106, 107]. The case of estetrol is not much different. Estetrol is originated also during pregnancy. Considered initially as a weak estrogen due to its low affinity for the receptor, recent research has evidenced that it is a potent estrogen with agonistic actions in most target tissues, with the exception of the breast [108]. This attractive profile makes estetrol a potentially valid agent for HT [109] and contraception [110], but the clinical experience is still sparse.

There is also some debate in what regards progestogens. Micronized progesterone, for example, and also some synthetic progestogens like dydrogesterone have been ascribed a more neutral role than other progestogens as inducers of breast cancer. The weakness of this claim is that the information is still sparse and comes from observational studies [111, 112].

Finally, there are also some data about tibolone, one synthetic compound vastly used in some European countries as an efficacious form of HT. A recent Cochrane systematic review could not detect an increased risk in women with no history of breast cancer, but the quality of the evidence was described as very low [113]. A study in Norway followed a cohort of 178,383 women who were prescribed HT for an average of 4.8 years. A total of 7910 invasive breast cancers were detected, tibolone being associated with a relative risk of 1.91, which was slightly lower than that of combined estradiol and norethisterone acetate, a synthetic progestogen [105].

There is a debate on whether HT only promotes the growth of cancers that were already in the breast, in a quiescent state, and that, perhaps because of so, the mortality of cases associated with the use of hormones would be lower. Investigators from the WHI trial found that survival after breast cancer was similar in users and nonusers of hormones. This finding made them to conclude that, because the prognosis was not different, increased diagnosis should translate into higher mortality [114].

However, the analysis of the nationwide reimbursement register in Finland, which followed HT users till death because of breast cancer (n = 1578 women), found that the cancer-associated mortality was approximately 50% of that in breast cancer nonusers of hormones [115]. Also of interest in this regard, and most probably because of other reasons too, global mortality seems reduced in users of HT from early postmenopause [116].

14.4.3.3 Ovarian Cancer

Ovarian cancer is first among the gynecological malignancies in terms of mortality. The possible association with HT has been highlighted relatively late, as compared with breast or endometrial cancer.

The link between HT and increased risk for ovarian cancer was first detected in observational studies, but the potential recall or selective participation bias blurred the consistency of the results [117–119]. The WHI study, a randomized controlled study, detected an increase in risk, but did not reach statistical significance [120]. Two subsequent meta-analyses agreed in an increased risk [121, 122], and similarly the Million Women Study, which found an increase in both incident and fatal cancer in women using HT in the UK. Investigators advanced that since 1991, roughly 1300 cases of ovarian cancer and 1000 additional deaths from the disease could be attributed to the use of HT in the UK [123]. Additional arguments provided the observed reduction in incidence in the USA after the drastic decline in the use of hormones in the years following the publication of the WHI study [124]. Information, however, is not unanimous, since a study based on the data from the Finnish Cancer Registry could only find an association with estrogen plus progestogen combinations [125].

Two more recent meta-analyses agree in that the evidence, albeit obtained in observational studies, unanimously suggests the association. Specifically, the increased risk in current users, even if for less than 5 years, attained a 43% (RR 1.43, 95% CI 1.31–1.56; $p < 0.0001$). The risk did not seem to be different for estrogen-only or estrogen–progestogen formulations and, when considering the tumor type, was clearly increased in the most common forms, serous (RR 1.53, 95% CI 1.40–1.66) and endometrioid (1.42, 1.20–1.67). Translating the risk to absolute figures, authors indicate that women who use HT for 5 years have about one extra ovarian cancer per 1000 users and about one extra ovarian cancer death per 1700 users [126]. Risk of similar size was found in another meta-analysis, which reproduced the increased risk for serous but not for endometrioid tumors [127].

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Non-Hormonal Management of the Menopause

15

Jenifer Sassarini and Mary Ann Lumsden

Menopause is defined by the World Health Organization (WHO) and STRAW Working Groups as the permanent cessation of menstrual periods that occurs naturally or is induced by surgery, chemotherapy or radiation [1].

With improved health care and increased life expectancy, women spend a considerable proportion of their lives (30 years on average) after the menopause, and it is estimated that within the next 25 years, more than one billion women worldwide will be older than 50 years, and approximately two million women in the US will reach menopause annually.

There are a number of symptoms associated with menopausal transition, and it is estimated that approximately 75% of women will experience some symptoms related to oestrogen deficiency during this time, although some women will experience none of these.

Symptoms include hot flushes and night sweats (vasomotor symptoms), vaginal symptoms, depression, anxiety, irritability and mood swings (psychological effects), joint pains, migraines or headaches, sleeping problems and urinary incontinence.

Vasomotor symptoms (VMS) are the most commonly reported and often the most difficult to manage effectively with non-hormonal therapies; we have attempted to cover the most commonly used alternatives in this chapter. We will also briefly touch on vulvovaginal symptoms, but it is simply not possible, within the remit of this chapter, to cover all possible treatments for mood disturbance.

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15.1 Vasomotor Symptoms

The most commonly reported symptoms are vasomotor symptoms, characterised by a feeling of intense warmth, often accompanied by profuse sweating, anxiety, skin reddening, palpitations and sometimes followed by chills. It was previously thought that they resolve spontaneously in most women after 2 years, but may persist for up to 15 years; however, recent research suggests that median duration is in fact 7.4 years [2]. The sleep disturbance, fatigue and decreased cognitive function associated with hot flushes and night sweats have been shown to lead to a significant reduction in HRQoL and an increased use of medical resources.

The exact pathophysiology of flushing is not well characterised, although it is generally accepted that falling oestrogens play a main role; flushes generally occur at times of relative oestrogen withdrawal and replacing it will result in improvement in most women. However, whilst oestrogen concentrations remain low after the menopause, most vasomotor symptoms will diminish with time, and therefore a fall in oestrogen concentration does not seem to provide the complete answer. It has also been found that circulating levels of oestrogen do not differ significantly between symptomatic and asymptomatic postmenopausal women.

Furthermore, it is thought that withdrawal of oestrogen, rather than low circulating oestrogen levels, is the central change that leads to hot flushes, and there are several observations to support this theory. The abrupt oestrogen withdrawal due to bilateral oophorectomy in premenopausal women is associated with a higher prevalence of flushes than in those women who experience a gradual physiological menopause, and young women with gonadal dysgenesis, who have low levels of endogenous oestrogen, do not experience hot flushes unless they receive several months of oestrogen therapy and then abruptly discontinue its use.

A hot flush closely resembles a heat dissipation response (sweating and peripheral vasodilation), and as such, dysfunction in the central control of thermoregulation remains our best understanding of the mechanism of flushing [3].

Changes in core temperature may also be associated with alterations in neuroendocrine pathways involving steroid hormones, noradrenaline (NA), the endorphins and serotonin. Noradrenaline and serotonin, particularly, are thought to play a key role.

The recently published NICE guideline (NG23) [4] has recommended that women should be offered HRT for vasomotor symptoms after a discussion of the short-term (up to 5 years) and longer-term benefits and risks. However, there are of course a group of women for whom hormonal therapy is not suitable. Fifty percent of the more than half million women living with breast cancer in the UK will not adhere to the recommended 10 years of tamoxifen, often as a result of the severity of the hot flushes that are associated with taking this drug. It is essential that we are able to safely and accurately advise women on treatment alternatives for symptoms of the menopause, particularly for these women to help them continue a potentially life-saving treatment.

15.1.1 Cooling Techniques and Avoiding Triggers

Hot flushes can be triggered by small increases in core body temperature, and therefore, it seems logical to suggest practices that lower body temperature or prevent it from rising. These might include loose clothing, made from natural fibres, fans and cool packs. There is no clinical evidence for either these interventions or the avoidance of triggers, which might be reported by some; spicy or hot food and drinks; and alcohol.

15.1.2 Lifestyle Modifications

There is evidence that body mass index (BMI), smoking, alcohol consumption and sedentary lifestyle are associated with reports of vasomotor symptoms; however, there are few papers reporting the direct effect modifications have on flushes.

It may be safe to assume, though, that there will be an improvement in symptoms if a risk factor for exacerbation of those symptoms is removed. Smoking cessation and weight loss have numerous other health benefits, not exclusively alterations in endothelial function, which may be involved in the hot flush mechanism.

15.1.3 Exercise

As well as having significant physiological benefits (e.g. cardiovascular and bone health), exercise may be one of the promising alternatives to HRT and, if demonstrated to be effective in the treatment of vasomotor symptoms, is an inexpensive intervention that typically has few known side effects.

The Cochrane Collaboration carried out a systematic review [5] to examine the effectiveness of any type of exercise intervention in the management of vasomotor symptoms in symptomatic perimenopausal and postmenopausal women. Only one very small trial was considered suitable for inclusion, which found, not unexpectedly, that HRT was more effective than exercise. There is no available evidence examining whether exercise is an effective treatment relative to other interventions or no intervention. Weight loss, however, has been shown to have a beneficial effect on vasomotor symptoms [6].

15.1.4 Pharmacological Preparations

15.1.4.1 Clonidine

Monoamines have been shown to play an important role in the control of thermoregulation, and animal studies have shown that noradrenaline (NA) acts to narrow the thermoregulatory zone. Noradrenergic stimulation of the medial preoptic area of the hypothalamus in monkeys and baboons causes peripheral vasodilation, heat loss

and a drop in core temperature, similar to changes which occur in women during hot flushes.

It has also been shown that plasma levels of a noradrenaline metabolite are significantly increased both before and during hot flush episodes in postmenopausal women.

Clonidine is an alpha$_2$-adrenergic agonist licensed for the treatment of hypertension, migraines and postmenopausal vasomotor symptoms. It is also used for postoperative shivering because it is thought that, like general anaesthetic agents and sedatives, it decreases shivering thresholds by a generalised impairment of central thermoregulatory control. It has also been demonstrated to increase the sweating threshold.

When used for the treatment of flushing, it has been shown to be more effective than placebo but less effective than SSRIs, SNRIs and gabapentin [7, 8]. However, it may not be well tolerated, because of adverse effects, including dry mouth, insomnia and drowsiness.

15.1.4.2 Selective Serotonin (and Noradrenaline) Reuptake Inhibitors

Serotonin is involved in many bodily functions including mood, anxiety, sleep, sexual behaviour and thermoregulation. Oestrogen withdrawal is associated with decreased blood serotonin levels, and short-term oestrogen therapy has been shown to increase these levels.

Selective serotonin reuptake inhibitors (SSRIs) are a group of drugs typically used as antidepressants, which are thought to function by blocking the reuptake of serotonin to the presynaptic cell. This increases the amount of serotonin in the synaptic cleft available to bind to the postsynaptic cell. SSRIs were commonly prescribed for the treatment of depression in women undergoing treatment for breast cancer. Anecdotally, these same women were noted to have an improvement in their vasomotor symptoms, which occurred as a side effect of treatment. Studies were then carried out to determine the efficacy of these as an effective treatment for flushing.

Meta-analyses [7, 9, 10] and a Cochrane review [7, 8] have demonstrated mild to moderate improvements in flush frequency and severity in symptomatic postmenopausal (surgical and natural) women. Statistically significant reductions in flushing were seen with paroxetine, escitalopram, citalopram, venlafaxine and desvenlafaxine. Sertraline and fluoxetine appear to be less consistent, although there was still a trend towards improvement.

SNRIs may produce significant nausea, but this typically improves in 2–3 days, and can be reduced by titrating the dose slowly.

Use of these drugs in women with breast cancer using tamoxifen is common; therefore, consideration must be given to potential interactions. Tamoxifen must be metabolised by the cytochrome P450 enzyme system, predominantly cytochrome P450 isoenzyme 2D6 (CYP2D6), to become active, and CYP2D6 is inhibited to varying degrees by SSRIs. Paroxetine is an exceptionally potent inhibitor, whereas sertraline inhibits to a lesser degree and citalopram and escitalopram are only weak

inhibitors. Evidence is conflicting on the success rates of tamoxifen in preventing recurrence of breast cancer when using a concurrent SSRI. For those women who need to begin treatment with an SSRI for depression, citalopram or escitalopram may be the safest choice; however, improvements in flushing are better with venlafaxine and desvenlafaxine, and these appear to be safe choices.

15.1.4.3 Gabapentin

The mechanism of action of gabapentin in the amelioration of vasomotor symptoms is unknown, but it is thought to involve a direct effect on the hypothalamic thermoregulatory centre.

Two double-blind randomised placebo-controlled trials, examined in a meta-analysis [7], both conducted in women with breast cancer, showed a significant reduction in the frequency and severity of hot flushes when taking 900 mg/day but not when taking 300 mg/day. Titration to 2400 mg/day continued to be superior to placebo but was not significantly different to oestrogen 0.625 mg/day. However, dizziness, unsteadiness and fatigue were reported in the gabapentin-treated group and resulted in a higher dropout rate than in the control group.

15.1.5 Non-Pharmacological Therapies

15.1.5.1 Phytoestrogens

Phytoestrogens are chemicals that resemble oestrogen and are present in most plants, vegetables and fruits. There are three main types of phytoestrogens: soy isoflavones (the most potent), coumestans and lignans. Soybean and red clover are also rich in phytoestrogens. These compounds are converted into weak oestrogenic substances in the gastrointestinal tract.

Isoflavones are the most researched, and Nelson's meta-analysis included 17 RCTs. From six trials comparing Promensil (red clover isoflavone) with placebo, only one fair-quality trial found a reduction in flush frequency with Promensil, although there was no overall reduction in the meta-analysis, and no improvement in flush severity was demonstrated in any of the included trials.

Soy isoflavones were compared with placebo in the remaining 11 trials. The meta-analysis revealed an improvement in hot flushes after 12–16 weeks (4 trials) and after 6 months (2 trials) but not significant decrease in studies examining 4–6 weeks use.

A systematic review [11] was also carried out by the Cochrane Collaboration. They included five trials in a meta-analysis, which demonstrated no significant decrease in the frequency of hot flushes with phytoestrogens.

Thirty trials were also studied comparing phytoestrogens with control. Some of the trials found that phytoestrogens alleviated the frequency and severity of hot flushes and night sweats when compared with placebo, but many of the trials were of low quality or were underpowered. The great variability in the results of these trials may result in part from the difference in efficacy of the various types of phytoestrogens used, the exact treatment protocol and the fraction of equol producers in

the cohort. It is claimed that only 30–40% of the US population possess the gut microflora responsible for converting isoflavones to the active oestrogenic equol. It should also be noted that there was also a strong placebo response in most trials, ranging from 1 to 59%.

15.1.5.2 Black Cohosh

Black cohosh (*Actaea racemosa*) is a species of flowering plant of the family Ranunculaceae. It is native to eastern North America, and it is thought to behave as a selective oestrogen receptor modulator (SERM) with mild central oestrogenic effects, although the active ingredients are unknown.

A 2012 Cochrane review [12] analysed 16 RCTS of 2027 perimenopausal and postmenopausal women. All studies used oral monopreparations of black cohosh at a median daily dose of 40 mg, for a mean duration of 23 weeks. There was no significant difference between black cohosh and placebo in the frequency of hot flushes. Evidence on the safety of black cohosh was inconclusive, owing to poor reporting, and there were insufficient data to pool results for health-related quality of life, sexuality, bone health, vulvovaginal atrophic symptoms and night sweats.

A meta-analysis of several short-term and relatively small RCTs comparing black cohosh use with placebo 'revealed a trend towards reducing vasomotor symptoms' but only in cases of mild to moderate symptoms [13]. This was particularly notable when hot flushes were associated with sleep and mood disturbances. This was confirmed in another 12-week study of 304 women in addition to improvements in mood, sleep disorders, sexual disorders and sweating. In contrast, however, the recent Herbal Alternatives for Menopause Trial (HALT) [14] which compared black cohosh to both placebo and oestrogen replacement over 12 months suggested that black cohosh was ineffective in relieving vasomotor symptoms.

Whilst there has been no confirmation of its efficacy, many women, both cancer-free and breast cancer patients and survivors, will use black cohosh to relieve vasomotor symptoms since describing a drug as no more effective **t**han placebo may mean that it may bring relief to over 30% of women. However, it is important to exercise caution as there is limited information on its potential to influence breast cancer development or progression. No effect has been seen on mammary tumour development, which would suggest that black cohosh would not influence breast cancer risk if given to women before tumour formation, but there has been an increase in the incidence of lung metastases in tumour-bearing animals when compared with mice fed with an isoflavone-free control diet. Additional studies will be needed to correlate these findings to women taking different black cohosh products at various times during breast cancer development; however, these results suggest caution for women using black cohosh, especially for extended periods of time.

Reports of possible hepatotoxicity associated with black cohosh began to appear after 2000; however, a recent critical analysis and structured causality assessment has shown no causal relationship between treatment by black cohosh and liver disease.

15.1.5.3 Dong Quai

Also known as *Angelica sinensis*, dang gui and tang kuei, dong quai is the root of the Angelica polymorpha Maxim var. sinensis Oliv. *Angelica sinensis* grows in high altitude mountains in China, Japan and Korea, and the yellowish brown root of the plant had been used in traditional Chinese medicine for thousands of years. It is reputed to be oestrogenic based on reports of uterine bleeding with use and uterotrophic effects in ovariectomised rats, but there is no evidence of oestrogenic activity in human studies [15].

Dong quai does not appear to be effective for hot flushes, and there may be some safety concerns, including possible photosensitisation, anticoagulation and possible carcinogenicity [16].

15.1.5.4 Vitamin E

Three trials show varying evidence for vitamin E for treatment of vasomotor symptoms. A randomised placebo-controlled trial, in which 105 women with a history of breast cancer received placebo and vitamin E 800 IU daily for 4 weeks in a crossover design [17], demonstrated no improvement in the frequency or severity of hot flushes. One-hundred and fifteen women were randomised to vitamin E or gabapentin in a further trial, with significant improvements in symptoms with gabapentin and a 35% dropout rate in the vitamin E group [18]. However, in another crossover trial of 50 postmenopausal women, 4 weeks of vitamin E (400 IU) followed by placebo, or vice versa, demonstrated a small reduction in hot flushes of two flushes per day and a reduction in severity with vitamin E [19]. Care must always be taken when a toxic vitamin is ingested in excessive amounts.

15.1.5.5 Evening Primrose Oil (*Oenothera biennis*)

Oenothera biennis is a flowering plant rich in linolenic acid and ý-linolenic acid. It is a widely used product for the treatment of menopausal symptoms, although the exact mechanism of action is not fully understood. Its effectiveness has been analysed in a double-blind randomised placebo-controlled trial of 56 postmenopausal women [20]. This trial used a combination of evening primrose oil (2000 mg/day) with vitamin E (10 mg/day) versus placebo and showed a significantly greater reduction in daytime flushes in the placebo group than in the treatment group. Unsurprisingly, there was a high dropout rate; only 18 women given in the EPO group and 17 in the placebo group completed the trial, due to unrelieved symptoms, and precluded reliable conclusions.

There are a number of other over-the-counter and herbal therapies that are reported to be effective in reducing vasomotor symptoms, and a comprehensive review of these can be found in the 2015 North American Menopause Society Position statement on non-hormonal management of menopause-associated vasomotor symptoms [16]. It is important to remember that herbal supplements are not as closely regulated as prescription drugs, and the amount of herbal product, quality, safety and purity may vary between brands or even between batches of the same brand. We must make it clear to women that these therapies may also interact with prescription drugs, and as such these must be declared health-care providers and may need to be stopped before any planned surgery.

15.1.6 Alternative Treatments

15.1.6.1 CBT

Cognitive behavioural therapy (CBT), group and self-help, has been developed to help women self-manage VMS. It has been shown to be effective in reducing the impact, but not frequency, of flushing in two randomised, double-blind controlled trials: MENOS 1 [21] and MENOS 2 [22]. Improvements were maintained 26 weeks after randomisation, and there were additional benefits to quality of life, with no adverse effects.

A follow-up study [23] has revealed that beliefs about coping and control over VMS, and belief about sleep and night sweats, mediated the effect of CBT on VMS problem ratings.

NAMS has recommended CBT as an effective non-hormonal management option for vasomotor symptoms for both breast cancer survivors and menopausal women, and NICE (NG23) has recommended CBT to alleviate low mood or anxiety due to menopause.

15.1.6.2 Acupuncture

Acupuncture is a traditional component of Chinese medicine in which thin needles are inserted into the skin at key points in the body to balance the flow of energy or *chi*. Western medical acupuncture is the use of acupuncture following a medical diagnosis, and it involves stimulating sensory nerves under the skin and in the muscles of the body. This causes the production of endorphins, which may be responsible for the beneficial effects experienced.

Sham acupuncture is a placebo treatment involving needles inserted into unrelated points on the body or of special needles that do not pierce the skin.

A Cochrane review [24], and other systematic reviews [25, 26], concludes that although acupuncture is superior to no treatment, or a wait-list control, acupuncture is not superior to sham acupuncture. NAMS concluded, in their recently published position statement, that needling at acupuncture points does not appear to reduce VMS frequency or intensity independently of the superficial touch of a sham needle [16].

15.1.6.3 Stellate Ganglion Blockade

Stellate ganglion blocks (SGB) have been carried out safely for more than 60 years, for pain syndromes and vascular insufficiency. 0.5% bupivacaine is injected on the right side of the anterolateral aspect of the C6 vertebra under fluoroscopy and an effective block confirmed by the presence of Horner's syndrome. Adverse events, such as transient seizures, or a bleeding complication, occur rarely.

A case report published in 1985 of a 77-year-old gentleman with flushing after orchiectomy for infarction in his remaining testis was treated with SGB based on the belief that the flushing centre has a sympathetic outflow to the stellate ganglion. This abolished his attacks of flushing.

Four uncontrolled, open-label studies [27–30] have shown that SGB reduced vasomotor symptoms, with effects ranging from a 45 to 90% reduction 6 weeks to several months after blockade. A pilot study of 13 women (age range 38–71 years), with a history of breast cancer, who suffered with severe hot flushes, demonstrated reductions in flush episodes and an improvement in sleep quality following stellate ganglion blockade [28]. A more recent study [27] revealed a benefit in only half of the 20 women in the study. The exact mechanism of action of SGB is unknown, but findings suggest that it may be an effective non-hormonal treatment for flushing. Larger trials are needed.

15.1.7 New Research

It is well accepted that reduced secretion of oestrogen at the time of menopause is associated with increased GnRH secretion from the hypothalamus, resulting in high luteinising hormone (LH) and follicle-stimulating hormone (FSH) concentrations.

The kisspeptin/neurokinin B/dynorphin (KNDy) signalling system in the hypothalamus is the proximate and obligate stimulus to GnRH secretion [31]. These KNDy neurons also project to the medial preoptic area (MPOA) [32], the hypothalamic site of thermoregulatory neuronal pathways.

Recent data demonstrate induction of hot flushes in healthy premenopausal women with administration of NKB [33]; therefore, it is possible that the mechanism of flushes may be tied to the hypothalamic control of pulsatile GnRH secretion by NKB and that an NKB antagonist may be an effective new therapy for hot flushes. There is a clinical trial currently recruiting to investigate this.

15.2 Vaginal Symptoms and Sexual Dysfunction

Vaginal symptoms become apparent 4–5 years after the menopause and objective changes as well as subjective complaints are present in 25–50% of all postmenopausal women [34]. Symptoms may include vaginal dryness (75%), dyspareunia (38%), vaginal itching, burning and pain (15%). Dyspareunia can adversely affect a postmenopausal woman's sexual quality of life or intensify pre-existing sexual disorders [35].

Vaginal oestrogens are effective in the treatment of menopause-related vulval and vaginal symptoms and a Cochrane review reported equal efficacy across all products tested: creams, pessaries, tablets and vaginal rings [36]. Local oestrogen therapy will lower vaginal pH, thicken the epithelium, increase blood flow and improve vaginal lubrication.

Vaginal oestrogen is controversial in women with a history of breast cancer, in whom vulval and vaginal symptoms are common, particularly those on endocrine therapy. In a case–control study, there was no documented increase in recurrence in those women receiving endocrine therapy and use of local oestrogen compared to

non-use [37]. However, in another study of breast cancer survivors, there was an initial, albeit unsustained, increase in circulating oestrogen levels [38].

Non-hormonal treatment options include lubricants and moisturisers. Lubricants are non-physiological, but may reduce friction-related irritation of vaginal tissues, whilst moisturisers are hydrophilic, insoluble, cross-linked polymers which reduce vaginal pH [34]. In a trial of vaginal moisturiser compared to low-dose vaginal oestrogen, both preparations were found to be effective, but the moisturiser provided only temporary benefit [39].

Ospemifene is a non-oestrogen, tissue-selective oestrogen receptor agonist/antagonist or selective oestrogen receptor modulator (SERM). It has recently been approved in the USA for dyspareunia secondary to menopause-related vulvovaginal atrophy. Studies have shown improvements in vaginal pH and dryness [40, 41]; however, it should not be used in women with, or at high risk of, breast cancer.

Conclusion

Clonidine, SSRIs and gabapentin have all shown a significant improvement in flushing, whilst vitamin E and evening primrose oil have been shown to be of no benefit. Adverse effects may limit the use of clonidine and gabapentin, but SSRIs and SNRIs have a well-established safety profile and appear to have only minor adverse effects.

The evidence surrounding the efficacy of phytoestrogens and black cohosh is contradictory. Soy isoflavones may be more effective with longer term use than other phytoestrogens, but black cohosh, or any compound with oestrogenic properties, should be used with extreme caution in women with a history of breast cancer or any other oestrogen-dependent disease.

The effectiveness of stellate ganglion blockade for vasomotor symptoms is unconfirmed; therefore, further studies are required. It is also worth considering that the uptake of this treatment may be limited as it is costly and invasive, and the short-term side effects of Horner's syndrome may be unacceptable to some.

NKB antagonist, as a potential novel treatment, is an exciting new development which may offer relief to many women with severe flushing who cannot use hormonal therapy.

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Complementary and Alternative Therapies for Menopausal Vasomotor Symptoms

16

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16.1 Introduction

Vasomotor symptoms, such as hot flushes and night sweats, are very common during the menopausal transition, affecting approximately 65–76% of women traversing the menopausal transition [1]. Although hormone therapy (HT) has traditionally been used as the most effective treatment to ameliorate these symptoms, since the publication of the Women's Health Initiative (WHI) Study in 2002 that generated concerns about the safety of this treatment, the prescription has dropped by 40–80% [2].

Nowadays, complementary and alternative medicine (CAM) has become very popular among women to treat their menopausal symptoms (up to 76% declare using any alternative therapy in a population-based survey) [3], either for personal beliefs or because they have any contraindication for HT, as a high cardiovascular risk or personal history of hormone-dependent cancers, among others.

The US National Center for Complementary and Alternative Medicine has defined CAM as "a group of diverse medical and health care systems, practices, and products that are not generally considered to be part of conventional medicine." When describing these approaches, people often use "alternative" and "complementary" interchangeably, but the two terms refer to different concepts. If a non-mainstream practice is used together with conventional medicine, it is considered complementary, and if a non-mainstream practice is used in place of conventional medicine, it is considered alternative [4].

Most complementary health approaches fall into one of two subgroups: natural products such as herbs, vitamins, minerals, and probiotics that often are sold as dietary supplements; or mind and body practices included yoga, chiropractic and

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osteopathic manipulation, meditation, massage therapy, acupuncture, relaxation techniques, hypnotherapy, among a variety of other therapies [4].

The CAM treatments for vasomotor symptoms includes a broad range of plant-based therapies such as phytoestrogens, black cohosh, Chinese herbs, and other herbs; and cognitive behavioral therapies (CBT) such as hypnosis, mindfulness training, paced respiration, and acupuncture.

This chapter reviews the characteristics, action mechanism, efficacy, and safety of these CAM therapies to treat the vasomotor symptoms in menopausal women.

16.2 Natural Products: Planted-Based Therapies

16.2.1 Phytoestrogens

Phytoestrogens are nonsteroidal plant compounds of diverse structure that are found in many fruits, vegetables and grains. They are categorized as isoflavones, coumestans, or lignans.

These compounds structurally resemble estradiol (E2), and in humans it has been suggested that they act as selective estrogen receptor modulators (SERMs), exerting antiestrogenic effects in the high estrogen environment of premenopause and estrogenic effects in the low estrogen environment of postmenopause. They act as weak agonists by stimulating estrogen receptors (ER) [5] with greater affinity for the ER beta (ERβ) than for the classical ER alpha (ERα). As a result, they preferentially express estrogenic effects in the central nervous system, blood vessels, bone, and skin without causing stimulation of the breast or uterus, mechanism by which phytoestrogens could protect against breast and endometrial cancer [6]. Thus, phytoestrogens may reduce vasomotor symptoms through their action on the vascular system without causing unwanted estrogenic effects on other body system [7].

Nonetheless, the mode of action has other complexities such as the binding affinity of isoflavones to progesterone and androgen receptors, they capacity for induce hepatic sex hormone binding hormone (SHBG) synthesis, within other effects by which phytoestrogens today are considered endocrine disruptors [8].

16.2.1.1 Isoflavones

Isoflavones are among the most estrogenically potent phytoestrogens, although they are much weaker than human estrogens. The most frequent sources of isoflavones are soy beans (*Glycine max*) and red clover (*Trifolium pratense*). Two types of isoflavones, genistein and daidzein are contained in the protein fraction of the soy bean, whereas that formononetin and biochanin A contained in red clover are precursors of genistein and daidzein [9].

After intake, phytoestrogen preparations are extensively metabolized in the gut to more or less potent metabolites by intestinal bacteria, one of them equol, the end product of the biotransformation of the daidzein that possesses estrogenic activity for both ERs. However, equol is not produced in all healthy adults in response to dietary challenge with soy or daidzein, it is estimated that only 30–50% of

individuals are able to produce equol [10], most of them vegetarian or of Asian origin. Host genetics contribute to interindividual differences in metabolism by determining gut microbial activity and genetic biotransformation enzyme expression. The ability to make equol is apparently the clue to the effectiveness of soy protein diets [8].

A Cochrane review in 2013 have evaluated the efficacy and safety of food products, extracts and dietary supplements containing high levels of phytoestrogens (>30 mg/day of isoflavones), to treat vasomotor menopausal symptoms in perimenopausal or postmenopausal women without personal history of breast cancer compared with placebo and HT [7].

The Cochrane review included four trials to assess the efficacy of treatment with genistein, in doses ranged from 30 to 60 mg/day and a treatment duration of 12 weeks to 2 years, for menopausal hot flushes. The studies found consistent benefit with reduction in frequency and duration of hot flushes when compared to placebo, but in a lesser extent than HT. No severe adverse events were reported, only gastrointestinal complaints in one study. Also, no significant differences in endometrial thickness were found [7, 11–14].

Asian women have a high level of soy consumption, estimated in 50–100 mg/dL of isoflavones compared to <1 mg/dL in Western women. Although there is contradictory evidence, many studies have found a significant inverse association between frequency of hot flushes and higher levels of soy consumption, which could explain the differences in incidence of hot flushes estimated in 14–18% in Asian woman versus 80–85% in European and American women [15, 16].

The efficacy of dietary soy was evaluated in 13 studies, with isoflavone content ranging from 42 to 134 mg/day. Of the 13 included studies, seven indicated that no significant differences were noted between the soy intervention and control groups. The remaining six studies found a significant difference in the frequency and severity of hot flushes [17–22]. The heterogeneity of the results was not explained by the level of isoflavones in the food products, and could have been caused by the ability to convert soy isoflavone to equol. Overall, no evidence suggested that a diet with high levels of soy phytoestrogens had a positive effect on hot flush frequency or severity. The most frequent side effects reported included bloating, nausea and weight gain [23]. No evidence indicates an estrogenic stimulation of the endometrium [7].

Nine of 12 trials included in the Cochrane review that assessed the efficacy of soy extracts in capsule or tablet form, with isoflavones levels ranging from 33 to 200 mg/day, reported a positive effect on hot flush frequency or severity when compared to placebo [24–31]. An increased rate of constipation was reported in women taking soy versus placebo, no adverse event were found regarding endometrial thickness [7].

It is important to highlight the strong placebo effect noted in most trials involving soy bean, with a reduction in frequency of hot flushes ranging from 1 to 59% [7].

The most studied red clover product is Promensil (brand name), a standardised product that contain a red clover extract. The data of five randomized trial that assessed the effects of Promensil (40 and 80 mg/day) were combined in a metanalysis [32–36],

and another four trials that assessed the effects of other red clover extracts were included in the review mentioned above. Neither reported significant differences in hot flush frequency or severity compared with placebo [7]. Neither showed an adverse effect on the endometrial thickness and even one reported a decrease of 15% of endometrial thickness after 12 weeks of treatment with Promensil versus placebo [37].

Given the known importance of producing equol in the metabolism of diadzein to obtain the benefits from soy isoflavones and taking into account that more than one third of women are non-equol producers [38], the Cochrane review includes one trial that assessed the effect of a standardised natural S-(–) equol in the form of SE5-OH (10 mg/day) for 12 weeks in postmenopausal women with low rates of equol excretion. The study reported a significant improvement in hot flush frequency and severity when compared to placebo [39]. This results are consistent with other studies that also have shown a benefit in mood-related symptoms in perimenopausal and postmenopausal women non-equol producers [40]. No serious adverse effects were reported, and no endometrial abnormalities were found, only a systemic rush in one woman [39, 40].

A recent meta-analysis included 21 randomised controlled trials (RCTs) showed that composite phytoestrogen supplementation and individual phytoestrogen interventions, such as dietary and supplemental soy isoflavones, were associated with improvement in some menopausal symptoms, including modest reductions in hot flashes and vaginal dryness but no significant reduction in night sweats. The association between overall phytoestrogen use and menopausal symptoms by type of phytoestrogen intervention (e.g., whole foods, soy protein, and isoflavone extract supplementation groups) yielded broadly similar results. On the other hand, the supplementation with red clover was associated with improvements in night sweats but not with the frequency of hot flashes [41].

Because of general suboptimal quality and the heterogeneous nature of the current evidence, further rigorous studies are needed to determine the association of plant-based and natural therapies with menopausal health [41].

16.2.1.2 Lignanos

Lignans such as enterolactone and enterodiol are found in flaxseed, lentils, grains, fruits, and vegetables.

In the Cochrane review mentioned above, three studies compared flaxseed dietary supplement or flaxseed extract versus placebo or control and found no evidence of benefit in frequency or intensity of hot flushes after flaxseed treatment. No serious adverse effects were reported [42–44].

16.2.1.3 Coumestans

Coumestans are another group of plant phenols that show estrogenic activity. The main coumestans with phytoestrogenic effects are coumestrol and 4′-methoxycoumestrol. Coumestans are less common in the human diet than isoflavones, yet similar to isoflavones, in that they are also found in legumes, particularly food plants such as sprouts of alfalfa and mung bean and they are especially high in clover and soy sprouts. Coumestrol as genistein have higher binding affinities to ER than the other phytoestrogen compounds [45].

The effectiveness of coumestans to treat menopausal symptoms has not been well studied.

16.2.2 Cimicifuga racemosa

The most popular and worldwide renowned herb for treatment of menopausal symptoms is *Actaea racemosa* or *Cimicifuga racemosa* (CR), commonly known as black cohosh. It was originally used by indigenous North American Indians to treat a variety of women's diseases. Later it proved to be efficient to alleviate climacteric complaints [46].

CR grew originally in North America but other Cimicifuga species grow in Far East-Asia. In many countries in which CR extracts are sold as food supplements the preparations contain Asian CR which chemical constituents are quite different from North American species and no clinical data of their effectiveness are available [46].

The therapeutic efficacy and safety of CR depend also of other factors such as pharmaceutical quality and extraction methods, indication, daily dose and the duration of intake, variables that make it difficult to determine its effectiveness in treating climacteric symptoms [47].

The CR contains triterpene glycosides and phenolic acids which are identified as the possible active compounds to relieve climacteric symptoms. Ligand binding assays and cell culture experiments indicated the presence of dopaminergic and serotoninergic compounds in CR extract (CR BNO 1055). Thus, it is possible that the proven effect of CR BNO 1055 on hot flushes is caused by dopaminergic, adrenergic and serotoninergic compounds [48]. Systematic examination of CR preparations has not find isoflavones or estrogenic systemic action. Although CR do not contain estrogenic compounds that bind to ERs, this does not exclude estrogenic effects which could be exerted via non-genomic mechanisms [8, 46].

In studies in experimental animal models, the extract of CR did not have estrogenic action in the mammary gland and endometrial thickness, and even shown a protective effect in the breast [46]. This is consistent with clinical studies that reported no effect of Klimadynon (brand name of CR extract) used for 6 months in the mammary gland density determined by digitized mammography [49]. Even a case control study involving breast cancer patients demonstrated that the use of CR had a significant breast cancer protective effect [50]. But on the other hand CR exhibits mild inhibition of CYP2D6 that might interfere with the efficacy of concomitant chemotherapy agents or enhance their toxicity [51]. Thus some groups suggest that women with breast cancer wait until more safety data are available before using it.

There have also been concerns about possible hepatotoxicity with CR, but a meta-analysis of five CR trials involving 1117 women found no evidence of this adverse effect [52].

A Cochrane review in 2012 included 16 RCTs to assess the efficacy of oral monopreparation of CR at a median daily dose of 40 mg for a mean duration of 23 weeks to treat perimenopausal or postmenopausal women. The review found no evidence of a benefit of the use of CR in the frequency of hot flushes when compared to placebo [53].

Further, a recent meta-analysis reported no difference in the hot flashes frequency and night sweats with the use of CR versus placebo [41].

Despite this results it appears that the dosage of the tested CR extracts may be of crucial importance. Most of the studies that demonstrated the effectiveness of CR used preparations containing 2.4–4 mg active ingredients from a standardized field-grown CR while the studies that could not show the effectiveness used lower or higher doses [54].

16.2.3 Chinese Herbs

Traditional Chinese medicine (TCM) is one of the most popular CAM therapies in Eastern countries, with a history of practice exceeding 2000 years. In the last few decades, it has significantly permeated a broad cross section of Western communities. Western medicine connects climacteric symptoms to a reduced function of the hypothalamic pituitary gonadal axis while TCM frequently attributes "renal deficiency" as the underlying mechanism [55].

Traditionally, drugs in Chinese herbal medicine (CHM) are not given as single substances. They are combined in complex prescriptions individually for each patient and his disease and then are modified at different stages of the patient's recovery or illness [56].

Traditionally prescriptions are prepared as decoction (raw materials are cooked over a longer period); but over the last decades, several additional forms of application have been proposed and investigated such as pills, liniments, plasters, and ointments to concentrated powder and liquid extracts prepared by modern pharmaceutical procedures. The routes of administration also differ, either oral, topical, intravenous, or injections into specific acupuncture points [55, 56].

More than 185 herbs and 73 classic formulae have been used to treat menopausal complaints. Some herbs such as Ren Shen (Radix Panax ginseng) and Dang Gui have been related to an estrogen-like effect, while in other formulae no estrogenic action has been detected, with the mechanisms of action still unknown [55].

A Cochrane review in 2016 included 22 RCTs to assess the effectiveness of CHM. The review found that CHM was no better than placebo for vasomotor symptoms in terms of frequency and severity. Also, it did not find a benefit in quality of life (QoL). No serious adverse events were reported, only mild to moderate symptoms such as diarrhea, tenderness of the breast, and gastric discomfort, among others, that resolved once the CHM was terminated [55].

16.3 Mind and Body Practices

16.3.1 Acupuncture

Acupuncture is among the most popular forms of complementary medicine with an estimated prevalence of acupuncture use by mid-life women ranges from 1 to 10.4% [57].

Acupuncture is defined as the practice of inserting a needle or needles into certain points in the body for therapeutic purposes. The most used types of acupuncture include traditional Chinese acupuncture (TCA) that involves the insertion of needles; electroacupuncture that involves passing small electric currents through the inserted acupuncture needles; acupressure, a technique that involves manual pressure on the acupoints; ear acupuncture that uses acupuncture needles, seeds, or magnetic pearls to stimulate the acupoints located on the ear and scalp acupuncture involves the use of acupuncture needles along the surface of the head. Sham acupuncture (SA), also called placebo, consists in light touches of the skin that are performed off the acupuncture points established by TCA [57, 58].

It has been suggested that acupuncture may have the potential to reduce hot flush frequency and severity, but the mechanism by which it might affect health or menopausal symptoms is not completely understood. It has been proposed that TCA may affect the release of serotonin and beta-endorphins in the central nervous system, therefore influencing and stabilizing the thermoregulatory center, normalizing body temperature, and reducing hot flushes and sweating [57, 58].

In the Eastern view of acupuncture which is based on Chinese medical philosophy, acupuncture tries to reestablish the energy balance in order to treat disease, through the stimulation of specific points. Acupuncture specific to menopausal symptoms is designed to correct a condition known as deficient heat [57, 58].

A Cochrane meta-analysis of 16 RCTs [58] was performed in 2013 to assess the effectiveness and safety of acupuncture to reduce hot flushes and improve the QoL of menopausal women. When compared acupuncture with SA, no differences were found in hot flushes frequency, but there is a benefit in terms of severity. No differences were found when compared with relaxation and electroacupucture in any outcome. More frequent hot flushes were reported in TCA group compared with HT group, but TCA proved to be significantly more effective than no intervention regarding hot flushes frequency, severity and in QoL. No serious adverse events were reported.

Another meta-analysis of 12 RCT in 2015 [59] was designed to investigate the effects of acupuncture on menopause-related symptoms and QoL in women experiencing natural menopause. Acupuncture compared with no intervention significantly reduced the frequency and severity of hot flushes with long-term effects remained up to 3 months. Regarding QoL, acupuncture improves QoL in the vasomotor domain of the Menopause-Specific Quality of Life questionnaire but not in the psychiatric, physical, or sexual domains. However, SA showed a comparable treatment effects with TCA. This could be explained by a limbic response induced by the touch of the skin of the SA, resulting in emotional and hormonal reactions such as release of endorphins, thus reducing the hot flushes.

This results are consistent with a recently published RCT [60] performed in multiples health centers in Australia. This study showed that an 8-week course of standardized TCA did not reduce menopausal hot flushes more than SA. Hot flushes decreased in both groups by approximately 40% with an effect sustained for 6 months. No effects were found over QoL for either acupuncture type.

Patients with cancer often show interest in complementary and integrative modalities because HT is contraindicated for these women. Several clinical trials have suggested a role for acupuncture in managing moderate to severe hot flashes in women with breast cancer. However, the superiority of acupuncture has not been demonstrated when using SA as a control or nonoptimal acupuncture intervention in women with mixed menopausal symptoms.

One RCT [61], involving 190 women with breast cancer, compared acupuncture (85 women received 10 TCA sessions involving needling of predefined acupoints) plus enhanced self-care, versus enhanced self-care alone (105 women received a booklet with information about climacteric syndrome and its management). The study shows that women with breast cancer treated with acupuncture plus enhanced self-care for 12 weeks experienced fewer vasomotor symptoms than women who received self-care alone. Acupuncture was associated with improvements in all health-related QoL outcomes except the sexual dimension, suggesting a specific effect of acupuncture. These effects persisted for at least 6 months after the end of treatment and were not associated with significant adverse effects during the study period.

A recent review [58] that included five RCT showed a slight superiority of TCA compared with SA for reducing the frequency and intensity of hot flashes in three studies, while other two studies suggested that both interventions, TCA and SA, are beneficial for the treatment of hot flashes because there was a reduction in symptoms, even though there were no significant differences between the two intervention methods.

The similarity between the results of TCA and SA may arise because the patient's expectations regarding the intervention influence its effects, or could be related to the different administration protocols used or by a limbic effect induced by SA as was mentioned above. This is a crucial aspect of clinical research that requires rigorous evaluation.

16.3.2 Mind–Body Therapies

Cognitive-behavioral, behavioral, and mindfulness-based therapies have been used to deal with menopausal symptoms, mainly depression though evidence is limited.

Mind–body techniques including yoga, meditation, hypnosis, and tai chi have been tested for pain and other chronic medical conditions in several clinical trials, but the paucity of data regarding menopausal symptoms does not permit any conclusion. Nevertheless, tai chi was associated with a positive effect on bone density and balance, as well as a reduction in the frequency of falls, in elderly women [62].

Paced respiration has been also tried as an intervention for hot flushes; however, its efficacy has not been demonstrated [63]. Telephone-guided self-help cognitive behavioral therapy seems to have a positive influence on menopausal symptoms [63].

A Cochrane review concluded that the evidence is insufficient to show the effectiveness of relaxation techniques as treatment for menopausal vasomotor symptoms,

or to determine whether this treatment is more effective than no treatment, placebo, acupuncture, superficial needle insertion, or paced respiration. No evidence indicates that relaxation reduces the number of hot flushes per 24 h or their severity [64].

16.3.3 Exercise and Lifestyle Modifications

There is evidence that body mass index, smoking, alcohol consumption, and sedentary lifestyle are associated with reports of vasomotor symptoms; however, there are few papers reporting the direct effect that modifications have on flushes [65].

A Cochrane review examined the effectiveness of any type of exercise intervention in the management of vasomotor symptoms in symptomatic perimenopausal and postmenopausal women. The evidence of five RCTs (733 women) was insufficient to show whether exercise is an effective treatment for vasomotor menopausal symptoms when compared with no active treatment, or with yoga [64].

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Lifestyle: Physical Activity

17

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17.1 Introduction

PA is related to protecting and promoting physical and mental health, increasing quality of life (QoL) and preventing premature death from any cause for people of any age, sex, or health status. In contrast, sedentary behaviour can triple the risk of disease, and exacerbate the risks associated with such health hazards as smoking, obesity, and hypertension [1].

Sedentary behaviour not only endangers postmenopausal women health but also increases the problems associated with this life stage. In this sense, there is abundant evidence linking PA practice improvements in many health indicators and QoL and with the prevention or treatment of various ailments that emerge during menopause. We can infer that PA is more than a lifestyle; rather, it constitutes a form of therapy in itself [2].

The increasing incorporation of women into social life has influenced the demand for therapies to improve signs and symptoms of ageing and allow them to reach old age with the best possible QoL. PA is a promoter of health in general. Its benefits include proper weight maintenance, stress relief, increased muscle strength, improved balance and coordination, increased bone strength, and increased mental focus [3]. In addition, PA improves the evolution of diseases such as hypertension, diabetes, osteoporosis, and dementia. The aim of this chapter is to analyse the impact of PA and to determine its benefits, requirements and the optimal types of PA for postmenopausal women.

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17.2 Risks of Sedentary Behaviour

Menopause is a transition period influenced by a multitude of physiological and psychological changes. It is not a disease, but it sometimes affects QoL and general health: it is accompanied by vasomotor symptoms and changes in body composition. These changes amplify those caused by a sedentary lifestyle; they can lead to real pathologies such as metabolic syndrome and cardiovascular diseases (CVD) and can increase the intensity and frequency of hot flashes.

Sedentary habits have been installed in modern societies, and new technologies continue to reduce the effort required to perform physical tasks jobs. Although it is not a disease, sedentary behaviour could be considered a risk factor (RF) or trigger for multiple diseases [3]:

- Overweight-obesity and excess abdominal fat are RFs for diabetes and CVD.
- Diabetes mellitus is a metabolic disease caused by insulin resistance caused mainly by high sugar intake but also by smoking, sedentary habits, and overweight.
- PA has been linked to increased HDL and LDL, while the sedentary lifestyle has an inverse effect on the lipid profile, increasing the risk of CVD.
- Fibromyalgia is a disease that causes marked functional and social limitations because of chronic pain in the joints and muscles. A sedentary lifestyle lowers the pain threshold and favours the development of this ailment.
- A sedentary lifestyle has been linked to many types of cancers, such as breast, colon, pancreas, and prostate cancer.

17.3 Cardio-Metabolic Benefits

It has been shown that PA alone reduces the risk of cardio-metabolic mortality regardless of age, sex, or weight. Consequently, PA reduces the risk of cardiovascular mortality in postmenopausal women, and it falls within the prevention recommendations for this disease. PA has a dose-dependent benefit; that is, the level of physical fitness is inversely related to mortality [4].

PA reduces the risk of cardiovascular mortality by reducing its main RFs (hypertension, dyslipidaemia, and diabetes). Improvements of hypertension have been observed with the practice of high intensive interval training (HIIT) [5].

In postmenopausal women, PA decreases hypertension by mitigating arterial ageing, causing functional and structural vascular adaptations that help to maintain or normalise arterial pressure levels. It has been observed that individuals who exercise more frequently exhibit less arterial stiffness than sedentary individuals and that when sedentary individuals engage in PA, arterial stiffness decreases. This seems to result from the release of a vasodilator (nitrous oxide), which improves the per-O_2 supply to the cells of the endothelium (the intima of the blood vessels), preventing deterioration and death [6]. PA also increases the sensitivity of the beta-adrenergic receptors and reduces the release of catecholamines [7].

Along with chronic systemic inflammation, oxidative stress, abdominal visceral adipose tissue, and dyslipidaemia, a sedentary lifestyle is an RF associated with metabolic syndrome in postmenopausal women. Aerobic PA (running, cycling) and muscle training with resistance (weightlifting) have be associated with general health improvements, including normalizing the lipid profile, anti-inflammatory responses, and antioxidant enzyme expression and reducing adipose tissue [8].

Aerobic PA has been shown to decrease weight and increase insulin sensitivity, which are important mechanisms for preventing diabetes and metabolic syndrome. Diabetes is also associated with overweight and increased visceral adipose tissue level. Additionally, postmenopausal hypoestrogenism results in fat redistribution (male-type obesity), which is not only undesirable aesthetically but is an important cardio-metabolic RF.

There is a direct relationship between PA and weight reduction: the more PA is performed, more fat mass is eliminated. However, after a PA session, the appetite increases and the individual tends to eat more; therefore, during the first few weeks of a PA programme, weight loss is not very evident and weight even tends to increase. Additionally, PA increases muscle mass. Therefore, PA should be a consistent part an individual's routine, along with a healthy diet. Although few studies have evaluated the effectiveness of PA in postmenopausal women, it appears that PA is more effective when it is more intense [9–11]. A systematic review found that in postmenopausal overweight/obese women, PA plus a hypocaloric diet for 54 weeks reduced BMI and abdominal fat [12].

17.4 Bone Benefits

In postmenopausal women, PA has been shown to have a beneficial effect on bone metabolism, both by preventing the loss of bone mass and by improving balance and reducing the risk of falls. A meta-analysis of 22 cohort studies with a total of 14,843 fractures showed a reduced risk of fractures in 29% of subjects [13]. Other meta-analyses found similar results and suggested that the fracture prevention benefits from PA result from the reduced risk of falls [14, 15].

Some studies have examined the most appropriate type of PA considering such factors as intensity, duration, and permanency. The most effective types of PA were those that combine resistance exercises (squats and push-ups), direct impact on the lower limbs (such as jumping and running), and light loads (weights) and possibly mechanical vibration. However, a recent meta-analysis found that only combined resistance exercise protocols had protective effects on bone mineral density (BMD) in postmenopausal women, whereas resistance-alone protocols produced a non-significant positive effect. Combined resistance training protocols were defined as the combination of resistance training and high-impact or weight-bearing exercise [16].

In comparison, PA such as swimming and cycling are performed under microgravity conditions. Studies have shown that the BMD of subjects who perform these types of PA is similar to that of a sedentary population and inferior to that achieved

with PA that includes impact [17, 18]. In addition, walking, which is likely the PA that most menopausal women prefer, has not shown a protective effect on BMD, even in the long term [19].

17.5 Sarcopenia

Sarcopenia is the progressive and generalised loss of muscle mass and strength. It is very common in older people, especially in postmenopausal women, and is related to the loss of oestrogen and testosterone. Recent studies have found that sarcopenia is closely related to osteoporosis and balance disturbances and that sarcopenia increases the risk of falls and bone fractures. Sarcopenia is also secondary to inadequate protein intake or physical inactivity after dieting. Although it is a sign of ageing, sarcopenia by itself increases the risk of physical disability, decreases physical function and results in a poor QoL.

PA is probably the best strategy for preventing and treating sarcopenia and balance disturbances. PA that combines strength and balance (e.g. Pilates) can improve postural muscle mass and tone. Other EFs, such as tai-chi, have also been shown to be effective for increasing muscle mass and improving strength.

It is estimated that the prevalence of sarcopenia in postmenopausal women is 10–40% [20], and although it can result from other causes, one of the principal factors in sarcopenia is hypoestrogenism [21]. During menopause, women experience a deterioration of balance that is related to android-type fat distribution, low BMD, and falls [22].

In addition to its effects on bone health, PA is a principal strategy for preventing and treating sarcopenia. Progressive resistance exercise (PRE) training programmes increase muscle mass and function; improve flexibility, balance, and physical function; and correct disability [23, 24]. Although it has not shown clear effects as the only strategy for improving balance and reducing the risk of falls, PA is successful when combined with *balance-training programmes* or aerobic exercise [25].

PE programmes based on virtual reality, which are alternatives to conventional PE, have been associated with improved postural control in older individuals [26].

Other recently popularised types of PA (e.g. Pilates) also show benefits for improving balance and preventing falls [27]. Step training and whole-body vibration training can improve function and restore balance, but not strength, in older individuals [28]. Recently, exercises that incorporate electrical muscle stimulation, increased muscle mass, and maximal isometric strength have also shown this benefit [29].

17.6 Quality of Life

QoL is defined as the perception of aspects of life that are most likely affected by changes in health status. It covers aspects such as health, physical and emotional functioning and limitations in performing different roles in everyday life and

social functioning. A variety of instruments and scales have been used to assess QoL, although not all of them are applicable to specific populations (female sex, menopause status), personal characteristics or clinics. Therefore, specific tools are needed for each condition, and in addition to being sensitive to physical changes, they must also evaluate psychological, social and sexual well-being. The Spanish Menopause Society recommends and prioritises the use of the Cervantes Scale [30].

The main complaints of postmenopausal women are vasomotor symptoms, especially hot flashes. Although there is disparity in results when only changes in hot flashes are rated, PA can affect hot flashes if other symptoms are reduced and the QoL is improved.

Insomnia is another symptom experienced by postmenopausal women. PA increases the production of melatonin, a hormone associated with wakefulness-sleep, thus allowing a better night's sleep. Menopause also affects mood because it is a new stage with many changes that are not always welcome; PA releases endorphins, which improve mood. Within the psychosocial sphere, PA improves anxiety, depression, and sleep quality [31, 32].

PA reduces weight and the consequences of obesity (aesthetic, medical, and mental) associated with menopausal symptoms. In addition, PA improves the pain of fibromyalgia, joint diseases and even some cancers, such as breast cancer. In breast cancer patients, PA improves pain, QoL and mood, allowing the patient to face the disease with greater hope, which results in improved adherence to treatment. In addition to being an RF for other diseases, weight gain worsens the QoL of postmenopausal women; however, it is unclear whether this is because of the weight gain alone or the existence of comorbidities (hot flashes, urinary incontinence, anxiety, and depressed mood) [33].

17.7 Cognitive and Mood Effects

PA is inversely related to the risk of dementia, and it improves cognitive functioning to a higher degree in middle-aged women than in men of the same age. A systematic review describes a 50% reduction in the risk of developing Alzheimer's disease when PA is continuous and intense [34]. In addition, beneficial effects have been recorded with respect to anxiety, depression, sleep quality, and the general perception of symptoms [35].

17.8 Pain During Menopause

There are many diseases that cause pain, and pain becomes more pronounced with age and is more common in women (e.g., osteoarticular pain and fibromyalgia). PA plus weight loss improves pain along with other health indicators and associated symptoms. In women with fibromyalgia, PA improves general health, the physical state, and the perception of pain [36].

PA can also have a positive effect on the pain produced by some cancers, such as breast cancer. In breast cancer patients, PA improves pain, QoL and mood, allowing the patient to face the disease with greater hope, which results in improved adherence to treatment.

PA also improves gynaecological and oncological pain. For example, the combination of pelvic floor exercises and local oestrogen was associated with a reduction in dyspareunia [37]. Nevertheless, PA was not sufficient for treating vaginismus, which required desensitization techniques and cognitive-behavioural therapy to achieve relief [38]. PA did not reduce pain in breast cancer patients who underwent surgery, but it did improve the welfare of these patients by reducing fatigue, depression, mobility, and postsurgical lymphoedema. Furthermore, PE alleviates joint pain derived from the use of aromatase inhibitors [39, 40].

17.9 Requirements

Generally, everyone should include PA in their daily activities. However, although it could be considered a form of therapy because of its multiple benefits, there are contraindications for its implementation. In any case, before starting PA, cardiovascular RFs should be evaluated, along with personal antecedents and relatives with cardiorespiratory and metabolic diseases. In postmenopausal women, the requirements for practicing PA do not differ from those for other healthy adults of the same age and either sex. The type of PA prescribed will depend on the patient's general state of health and level of physical fitness. Regardless, a medical history must be completed that indicates the presence of RFs (smoking, hypercholesterolemia, diabetes, sedentary lifestyle, and arterial hypertension) and existing symptoms (dizziness, syncope, chest pain, dyspnoea, and palpitations) [41].

The PA level in daily life can be used to classify women into distinct groups (sedentary, insufficiently active, active, and very active) and permits stratification by variables that predict performance and mortality; such classifications will determine the prescription and monitoring of PA to ensure that the patient can perform it safely.

Other tests may be necessary to determine the appropriate type of PA for a patient. We recommend following the indications of the Spanish Society of Cardiology and the American Heart Association (AHA) [42, 43]:

- For mild-moderate PA, no special proof is required, unless some of the above factors are present; if they are, a medical assessment will be necessary.
- For intense PA, more specific studies are needed (a baseline ECG for women over 50 years old and a stress test) to prevent serious complications, such as sudden death during exercise. In these cases, the medical history should emphasise the symptoms that occurred during previous PA (such as syncope or angina) [44]. The most frequently used test to assess the cardiovascular risks associated with PA in postmenopausal women is the ergometer or stress test. It is sensitive as a diagnostic test because of the higher prevalence of silent ischaemic cardiopathy in women than in men of the same age [45].

Table 17.1 Recommendations of the Spanish Menopause Society [3]

• PA produces cardiovascular and metabolic benefits in postmenopausal women. These benefits are manifested in the early months of practice. To maintain the benefits of PA, it must be continued and adapted to the individual's physical condition, medication use, and other lifestyle factors. PA should always be supervised and should be varied to improve adherence
• PA has proven to be beneficial for preventing and treating osteoporosis, sarcopenia, and balance disorders and reducing the risk of falls and their complications
• Although EF does not seem to lead to a significant reduction in vasomotor symptoms, the evidence does indicate that it improves quality of life, especially when associated with other psychosocial interventions
• PA has a moderate efficacy for reducing pain postmenopausal women, but its effectiveness increases if it is associated with education, nutrition, and physical therapy
• The recommendations regarding the practice of PA should be extended to all postmenopausal women in any condition. If moderate- or high-intensity PA is prescribed, cardiovascular, metabolic, and bone RFs should be determined using anthropometric, bone, ECG, and stress tests
• PA that combines HIIT and Pilates seems to be most appropriate type for postmenopausal women

Although any type of PA is welcome for postmenopausal women, the most highly recommended type of PA at this stage is probably a combination of HIIT with short recovery periods and exercises that promote the improvement of balance, such as Pilates. These activities yield fat loss and muscle gain in less time than conventional PA practiced alone (running, swimming, and cycling). They have the benefit of closely resembling daily activities and may have better adherence among users. Other types of PA, such as tai chi and yoga, have also been proven to be helpful, although not all of them provide all the benefits of HIIT [45–47].

Conclusions

A summary of Recommendations is given in Table 17.1. In general, PA is recommended for any woman, regardless of her age and condition, and has shown benefits at many levels (cardiovascular, bone, muscular, metabolic, QoL, etc.). Adherence to PA is an excellent way to treat some of the ailments that become more prevalent in postmenopausal women.

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Nutritional Management of Menopausal Women

18

Annamaria Colao

18.1 Introduction

The term "*menopause*" comes from the ancient Greek words "*meno*" (month) and "*pause*" (stop) and thus it indicates literally the date of last menstrual bleeding because of decreased estrogen and loss of ovulation. The absence of menses for 12 months is used as the definition of "natural" menopause that occurs from late 30s to late 50s, most women entering in the menopausal period between ages 48 and 55 years [1]. The most common symptoms of menopause are hot flashes or flushes, night sweats and trouble sleeping reported by 60%, 48%, and 41% of the women respectively [2]. Women undergoing hysterectomy and ovariectomy experience surgical menopause often associated with quick onset of vasomotor symptoms. Chemotherapy and radiation for cancer can also induce a rapid onset of menopausal symptoms: approximately 30% of women under 35 years of age experience ovarian failure after chemotherapy with increase in the proportion of ovarian failure related to the age of chemotherapy up to 75–90% for women over 40 years of age [3]. As age, the dosage of chemotherapy is a major predictor of premature menopause. Treatment of menopausal symptoms in this group is more difficult complex because of concomitant treatments for cancer and the associated risk related to cancer as well as the abrupt onset of symptoms.

Together with the specific symptoms of ovarian failure, there are relevant changes in body composition evolving naturally with aging. As reported by Munro [4] in a population of men only, in the 20 years of age muscle mass was >50% greater than fat mass; in the 40s muscle mass was virtually identical to fat mass while in the 60s and over data of muscle and fat mass was virtually the opposite of the values recorded in 20 years of age. In the woman population, aging causes similar changes in body composition particularly at the time of menopause: body weight and total body fat increase, with a concurrent decrease in fat-free mass [5].

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The reportedly changes in body composition have relevant clinical consequences. Among the most important effects, the progressive decrease in bone mass produces loss of height, changes in posture, and osteoporotic fractures [6]. Modifications of the spine cause alteration of the chest cage such as restriction and distortion so compromising pulmonary vital capacity and maximal breathing capacity [7]. Since overall skeletal mobility is impaired, all basic daily movements are limited so that daily energy expenditure is reduced. It should be also emphasized that a significant proportion of patients, as high as approximately 25% of all women having a hip fracture, never fully recover [8]. Moreover, the progressive loss of muscle and increase in fat tissue produce a progressive decrease of caloric requirements for weight maintenance with aging.

The decrease in metabolic rate with aging is largely attributable to these changes in body composition [9]. However some other alterations also contribute to a fall in energy expenditure. The thyroid function also falls with aging [10]: thyroid stimulating hormone and free triiodothyronine levels tend to reduce in elderly persons, even healthy elderly. This decline might contribute to the reduction in metabolic rate with aging, even if the magnitude hormonal decrement is probably too small to have a major effect on metabolic rate. The decrease in resting metabolic rate of aged subjects may be partly due also to a decrease in energy expenditure that occurs progressively throughout adult life from 20 to 100 years of age [11].

A body of evidence now clearly shows that reduced life expectancy in elderly individuals is associated with either major weight gain or major weight loss. In fact, many studies reported that mortality rates are function of BMI, exhibiting a U-shaped relation [12]: the mortality rate is the lowest in subjects with a BMI of ≈25 even if some investigators reported that relatively small overweight (BMI of 25–30) is not associated with increased mortality. Obesity instead has a striking effect on mortality and morbidity by inducing diabetes, hypertension, cardiovascular disease, and certain forms of cancer among adults with a mean age of 60 years [13].

On the other hand, it is increasingly appreciated that losing weight is not necessarily indicative of gaining good health [14]. Elderly individuals may be losing weight because of progressive or preexisting disease. In fact, before death, many elderly persons tend to lose weight and weight loss may be related tp frailty rather than of good health and so it greatly increases the risk of osteoporosis and fracture [15].

This chapter focuses on the nutritional management of menopause symptoms and on management of overweight/obesity that are considered the major problems of postmenopausal women. We do not consider the nutritional management of osteoporosis that is object of other chapter of this book.

18.2 Nutrition and Menopausal Symptoms

The most evident and complained symptom of menopause, the hot flashes are caused by dysfunction of the central thermoregulatory system when estrogens concentration is decreased. The central pathways of norepinephrine and serotonin likely lower the low the set point for the thermoregulatory nucleus, which allows heat loss

to be regulated by a subtle change in core temperature [1]. Endorphins and catecholestrogen, derivatives of estrogen and other sex hormones are considered to contraregulate the elevation in core temperature induced by norepinephrine and serotonin. Micronutrients, phytochemicals, and herbal supplements commonly used to treat menopausal symptoms include vitamin E, black cohosh (*Actaea Racemosa*), soy (and other phytoestrogens), which are used to treat the vasomotor symptoms, ginkgo biloba, ginseng, and St. Johns wort (*Hypericum perforatum*), which are used for mood related symptoms, and valerin has been used for sleep disturbances associated with menopause. Interpretation of study findings using these compounds is hampered by the small sample size, variability in the product tested (especially for the soy), and wide variability in the clinical characteristics of the study population. A list of herbs women-friendly is illustrated in Fig. 18.1. Research that focuses on micronutrient and related treatments is likely to increase to provide an evidence-based document to address questions posed by menopausal women and their care providers.

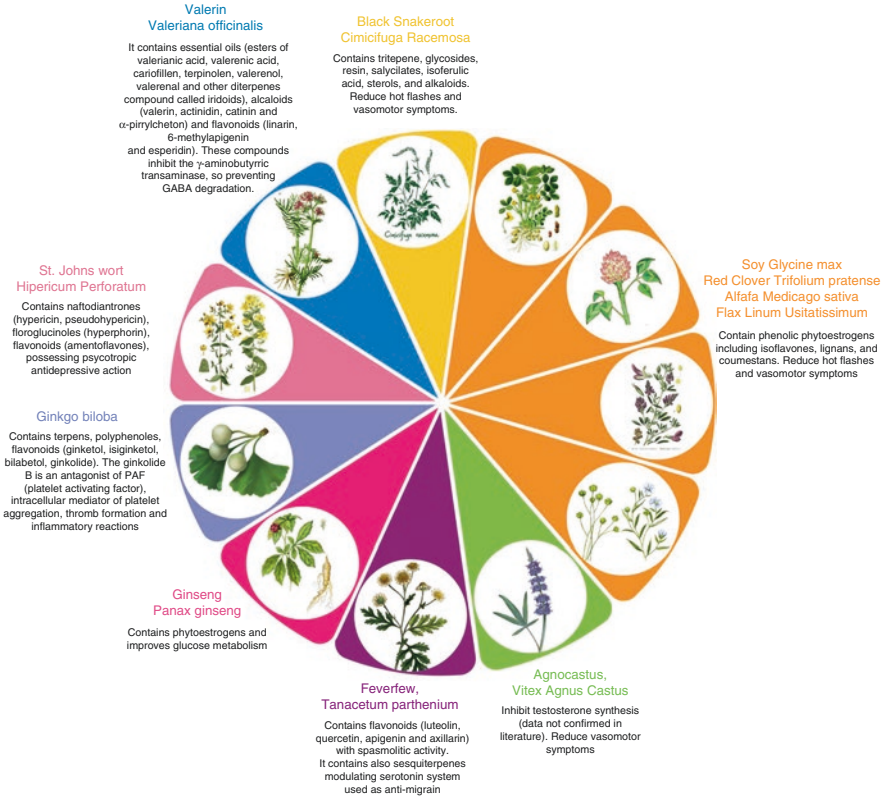


Fig. 18.1 This figure indicates a list of herbs women-friendly. To note that a few studies documented the detailed effects in postmenopausal women while many herbal integration comes from a old tradition in many different population

18.2.1 Vitamin E

Although vitamin E is widely used for treating hot flashes, the research database is extremely limited [16]. Barton et al. [17] in a randomized crossover trial (4 weeks per treatment condition) conducted in 120 women treated for breast cancer, found that Vitamin E (800 IU) resulted only in 1 fewer hot flash per day than the placebo. Whether these findings can be generalized to women undergoing naturally occurring or surgical menopause remains to be determined. Controlled studies are needed to assess the effects of vitamin E on symptoms using one of the standardized menopausal symptom questionnaires and on hormones affected by menopause. Research also needs to address how vitamin E affects the metabolic pathways involved in the hot flash reaction. Vitamin E concentration is high in fresh virgin olive oil.

18.2.2 Black Cohosh (*Cimicifuga racemosa*, Black Snakeroot)

Black cohosh, botanically a member of the buttercup family, has been widely used by Native Americans therapy for a variety of problems including dysmenorrhea, labor pains and menopausal symptoms [1]. It has been difficult to discern the effects of black cohosh despite the availability of a standardized formulation and reported findings from 3 of 4 randomized trials indicating a reduction in menopausal symptoms [18, 19]. Black cohosh contains a number of compounds with potential bioactivity including tritepene, glycosides, resin, salycilates, isoferulic acid, sterols, and alkaloids. Analysis of black cohosh from various woodlands in the Eastern USA and Remifemin did not find any formononectin inside, the phytoestrogen thought to account for the reported reduction in menopausal symptoms [18, 20] and thus the mechanism of action of black cohosh in reducing hot flashes is still not understood. Black cohosh does not modify the hormonal pattern associated with menopause, low estrogen accompanied by elevated luteinizing hormone and follicle-stimulating hormone. Additional rigorously controlled studies are needed to ascertain the true effects of black cohosh on menopausal symptoms and to make an evidenced-based decision regarding who may benefit and for whom its use the risks are likely to outweigh any potential benefits [19].

18.2.3 Phytoestrogens from Soy, Red Clover, and Flax

The phytoestrogens that have been isolated from a variety of plant food are phenolic (rather than steroidal) compounds; the major categories of phytoestrogens include isoflavones, lignans, and coumestans [21]. Phytoestrogens function as selective estrogen receptor modulators (SERMs) as they bind to receptors for estrogen metabolites. SERMs may function as estrogen metabolites in some tissues but not in others. SERMs developed in laboratory are widely used to treat women with estrogen receptor positive cancers, while SERM function of phytoestrogens is much less understood. Soy, other beans, red clover (*Trifolium Pratense*), and alfafa

(*Medicago Sativa*) contain isoflavone precursors, which are converted to genistein, daidzein, and equol by intestinal bacteria. Flax seeds (*Linum Usitatissimum*), other seeds, legumes, whole grains, and some fruits and vegetables (essential part of the Mediterranean diet) contain lignan precursors that can be converted to enterolactone and enteridiol by intestinal bacteria. The phytoestrogens can have estrogenic activity as potential dietary derived modulators with endocrine function.

Unfortunately to date the studies addressing the use of phytoestrogens to improve vasomotor symptoms of menopause are small and lack of statistical power, and aggregation is not possible due to differences in their methodologies. In the systematic review by Kronenberg and Fugh-Berman [18], only three of the 12 randomized controlled trials found that soy phytoestrogen supplements or soy products reduced the frequency or severity of hot flashes. In one of the studies the decrease in hot flashes was accompanied by increases in 17β-estradiol and decreases in total and LDL cholesterol [18]. Flax seeds have been reported to have estrogenic, antiestrogenic, and steroid-like activity [22].

Red clover contains the phytoestrogen formononectin, biochanin A, daidzein, and genistein but overall finding of research to date reports that red clover and its related supplements are not superior than placebo in controlling hot flashes.

The control of other symptoms of menopause from other micronutrients, phytochemicals and herbal compounds is not supported by sufficient data. In a recent systematic review, Izzo et al. [23] reported preliminary or satisfactory clinical evidence for agnocastus (*Vitex agnus castus*) for premenstrual complaints, flax seed for hypertension, feverfew (*Tanacetum parthenium*) for migraine prevention, ginseng (*Panax ginseng*) for improving fasting glucose levels as well as phytoestrogens and St John's wort for the relief of some symptoms in menopause but firm conclusions of efficacy cannot be generally drawn. In another cross-section of ethnically diverse women 40–55 years of age (35.5% African American, 60.2% Caucasian) study, Dailey et al. [24] documented that herbal product users reported more menopause symptoms than nonusers and 68% of the users said that the herbs improved their symptoms. Lastly, in a German revision of 22 studies by Aiselsburger et al. [25], high doses of isolated genistein were shown to reduce the frequency/intensity of hot flashes while low doses of genistein show no significant effect. Furthermore, intake of isoflavone extract such as genistein, daidzein, glycitein in various combinations did not have an effect on improvement of cognitive function or vaginal dryness [25]. The effect of black cohosh and hop extract for menopausal complaints cannot be determined since results are heterogenous [25]. The combination of isoflavone, black cohosh, agnocastus, valerian and vitamin E had a positive effect on menopause symptoms.

In summary, the 2003 position statement from North American Menopause Society [26] addressed alternatives to estrogen therapy. The specific recommendations were to indicate first lifestyle changes, either alone or combined with a nonprescription remedy, such as dietary isoflavones, black cohosh, or vitamin E. For moderate to severe menopause-related hot flashes some estrogen-containing treatments or progestogens, venlafaxine, paroxetine, fluoxetine, or gabapentin can be used [26].

18.3 Nutrition and Hair Loss

Hair loss during the period of pre menopause is physiological and is mainly due to estrogen reduction together with increase in androgen levels: hair loss appears as a spread thinning of hair mainly in central and forehead part, and sometimes also in parietal and occipital part [27]. Nutrition is essential in keeping hair strength and density in menopausal age [28].

18.3.1 Macronutrients: Proteins, Fat, Carbohydrates

Fundamental elements of any diet for hair building include proteins containing sulfur amino-acids such as cysteine and methionine which are precursors to keratin. Protein malnutrition impairs hair synthesis (hair fragility and brittleness), their strength (hair are in the form of lanugo) and causes hair loss [29]. Cysteine, as a keratin ingredient, occurs in hair in the highest amount (10–17%) and its synthesis depend on methionine presence. The hair growth rate, diameter, and keratin synthesis is related to cysteine concentration. The active form of pyridoxal phosphate (vitamin B6) increases L-cysteine incorporation to keratin, but other essential amino acids like L-lysine, mainly present in the inner part of hair root, are responsible for hair shape and volume. L-lysine has also a significant impact on zinc and iron absorption [30, 31].

Proteins should make 10–15% of energy value of the diet in the amount of 0.9 g/kg of body mass per day: the source of cysteine and L-lysine in diets is represented by cheese, yoghurt, fish, meat, poultry, legumes, seeds, nuts, grain products, and eggs.

Fats participate to steroid hormones synthesis (from cholesterol) thus have influence on keeping hair in skin integument but saturated fatty acids increase sebum secretion. The protective layer for skin integument and its products are ceramides, sterols, and phospholipids and also free fatty acids: thus, deficiency of these compounds in women's body causes decrease in hair hydration, even to their loss as a result of improper state of the hair bulbs. In a diet, reduced amount of linoleic and linolenic acids and long-chain polyunsaturated fatty acids causes hair loss. Fatty acids from the omega-3 polyunsaturated fatty acids (EPA and DHA) family are found mainly in fish, flax seeds, walnuts, wheat sprouts [28]. Omega-6 polyunsaturated fatty acids, present in plant oils, are also needed for a proper hair building but their excess might lead to inflammation states, which in turn might cause hair asthenia and their loss [32]. Fats should constitute 25–35% energy value of the diet and their source should be fish, poultry, eggs, olive oil, and rapeseed oil.

Carbohydrates also influence the state of hair: consumption of simple sugars stimulates sebum secretion by sebaceous glands and sebum excess becomes food for microorganisms found on skin, which cause decomposition of triacylglycerols inside contained [33]. Furthermore, excessive intake of simple sugars implies hyperglycemia and hyperinsulinemia, which directly contributes to increase synthesis of ovarian androgens and indirectly through suppression of sex hormone

binding globulin synthesis in liver, and insulin-like growth factor-1. In hair follicles insulin has a direct impact on hair growth, on increase of DHT concentration which leads to miniaturization [21], and also on local microcirculation nourishing the scalp, thus leading to local hypoxia which contributes to hair loss [34]. On this basis, a healthy diet should contain products rich in complex carbohydrates, with low glycemic index and load containing fiber regulating carbohydrate-lipid metabolism of the body, as beautifully indicated in the scheme of the Mediterranean diet [35]. Carbohydrates should form 50–70% energy value of the diet from full grain breads, grits, rice, whole meal pasta, vegetables, and fruit with low glycemic load.

18.3.2 Micronutrients: Vitamins and Minerals

Vitamins have relevant impact on the state of hair in particular, vitamins of group B, vitamin C, vitamin A, and vitamin D (Table 18.1).

The folates contribute to red blood cells and hemoglobin production, so in oxygen transport to all organs and also to tissues building hair. The dietary source of folates is constituted by green vegetables and some fishes like halibut and cod but also in small amounts consumed eggs and poultry liver. Pantothenic acid (vitamin B5) prevents early hair graying and can also restore their natural color, has anti-inflammatory properties, protects, has moisturizing abilities, regulates functioning of sebum glands, and accelerates melanin creating [28]. Products rich in B5 vitamin that is a mixture of pantothenic acid, pantein, pantenol, and coenzyme A are mushrooms, cauliflower, liver, soya, hen eggs, and baking yeast, whole grains, beans, milk and green leafy vegetables [28]. Biotin (vitamin B7, vitamin H) is a vitamin taking part in fat and protein metabolism and its deficiency might lead to hair loss; biotin deficiency induces increase in palmitic acid concentration in liver and hypercholesterolemia, leading to erythematous and seborrheic skin inflammation (conjunctivitis, greasy hair, hair loss, and nails brittleness) [44]. Biotin can be found in cereal germs, milk and vegetables (free form), in meat, liver, egg yolk, yeast and some nuts (bound form). Niacin (vitamin PP) detoxifies skin and its main source is meat, whole wheat grains, legume vegetables, seeds, milk, green leafy vegetables, fish, peanuts, shellfish, and yeast.

Insufficient supply of vitamin C in diet influences the creation of the hair shaft and might be an indirect cause of telogenic baldness. Vitamin C increases absorption of non-heme iron, originating from plant products, and it is present in vegetables (green parsley leaves, kale, horseradish, peppers, Brussels sprouts, broccoli, cauliflower, spinach, and savoy) and fruit (black currants, strawberries, wild strawberries, kiwi, red currants, and citrus fruit).

Vitamin A is responsible for moisturizing and protects hair giving them resistance from being fragile, and thus its deficiency may cause decrease in cycle speed of cell regeneration. However, vitamin A excess, coming from animal products cumulates in liver, can also be a cause of hair loss, so a good source is its form derived from carotenoids present in vegetables and fruit [28].

Table 18.1 The vitamins helpful for hair and skin health in menopause

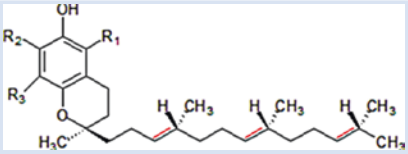
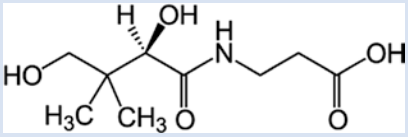
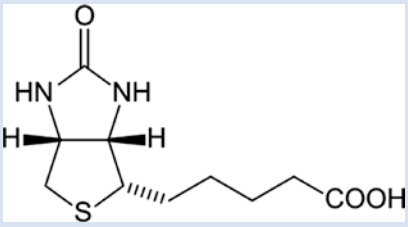
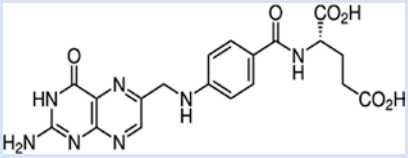
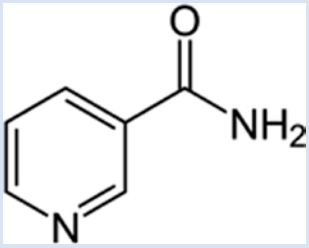
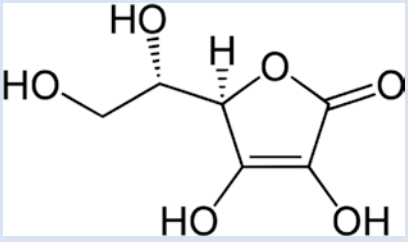
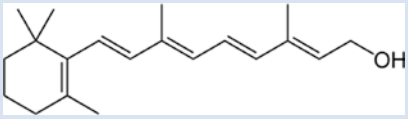
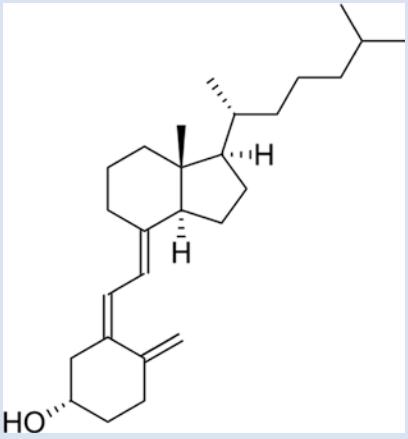
	*Tocopherol—Vitamin E* α-Tocopherol is the main source in the European diet (olive and sunflower oils) while γ-tocopherol is the main source in the American diet (soybean and corn oil). The recommended daily amount (RDA) is 15 mg/day. Low-fat diets can its levels. Vitamin E is widely used as an inexpensive [36, 37] antioxidant in cosmetics and foods. It reduces vasomotor symptoms
	*Pantothenic acid—Vitamin B5* Vitamin B5 is found in whole unprocessed foods, in meat such as turkey, tuna, liver, legumes (pulses or beans), whole grains, mushrooms, cauliflower, soya, and hen eggs. It is involved in the oxidation of fatty acids and carbohydrates. Coenzyme A, synthetized from pantothenic acid, is involved in the synthesis of amino acids, fatty acids, ketones, cholesterol, phospholipids, steroid hormones, neurotransmitters (such as acetylcholine), and antibodies [38]. It prevents early hair graying and can also restore their natural color, has anti-inflammatory properties, and regulates functioning of sebum glands and accelerates melanin creating. Its deficiency results in acne and paresthesia
	*Biotin—Vitamin B7* Biotin is found in cereal germs, milk and vegetables (free form), in meat, liver, egg yolk, yeast and some nuts (bound form). It plays a key role in lipids, proteins and carbohydrates metabolism. It is a critical coenzyme of four carboxylases: Acetyl CoA carboxylase, which is involved in the synthesis of fatty acids from acetate; pyruvate CoA carboxylase, involved in gluconeogenesis; β-methylcrotonyl CoA carboxylase, involved in the metabolism of leucine; and propionyl CoA carboxylase, which is involved in the metabolism of energy, amino acids and cholesterol [39]. Biotin deficiency induces increase in palmitic acid concentration in liver and hypercholesterolemia, leading to erythematous and seborrheic skin inflammation (conjunctivitis, greasy hair, hair loss, and nails brittleness)

Table 18.1 (continued)

	*Folic acid—Vitamin B9* The dietary source of folate is constituted by green vegetables and some fishes like halibut and cod but also in small amounts consumed eggs and poultry liver. Folic acid acts as a coenzyme in the form of tetrahydrofolate (THF), involved in pyrimidine nucleotide synthesis, so is needed for normal cell division, especially during pregnancy and infancy, which are times of rapid growth. Folate also contributes to production of red blood cells [40] and so in oxygen transport to all organs and also to tissues building hair
	*Nicotinamide–Niacin—Vitamin PP* Vitamin PP is found in meat, whole wheat grains, legume vegetables, seeds, milk, green leafy vegetables, fish, peanuts, shellfish, and yeast. Nicotinamide in the form of a cream is used as a treatment for acne: It has anti-inflammatory actions and thus may be beneficial to people with inflammatory skin conditions. Nicotinamide increases the biosynthesis of ceramides in human keratinocytes in vitro, and improves the epidermal permeability barrier in vivo. There is tentative evidence that it may reduce the risk of skin cancer and bullous pemphigoid [41]
	*Ascorbic acid—*L*-ascorbic acid—Vitamin C* Ascorbate and ascorbic acid are both naturally present in the body increase absorption of non-heme iron, originating from plant products and are found in vegetables (green parsley leaves, kale, horseradish, peppers, Brussels sprouts, broccoli, cauliflower, spinach, and savoy) and fruit (black currants, strawberries, wild strawberries, kiwi, red currants, and citrus fruit). Vitamin C is a cofactor of at least eight enzymatic reactions, including several collagen synthesis. Ascorbate also acts as an antioxidant, protecting against oxidative stress. Insufficient supply of vitamin C in diet influences the creation of the hair shaft and might be indirect cause of telogenic baldness

(continued)

Table 18.1 (continued)

	*Retinol–Retinal–Retinoic acid—Vitamin A* Retinol, the vitamin A form from animal food sources, is a yellow, fat-soluble substance. The carotenes alpha-carotene, beta-carotene, gamma-carotene; and the xanthophyll beta-cryptoxanthin serve as provitamin A in herbivores and omnivore animals, which possess the enzyme beta-carotene 15,15′-dioxygenase for cleaving beta-carotene in the intestinal mucosa and converting it into retinol. Vitamin A is found in many foods: high amount are present in cod liver oil, liver turkey, beef, pork, chicken and less in some vegetables such as red capsicum, sweet potatoes, carrots, broccoli, spinach, pumpkin, and cantaloupe melon. Vitamin A plays a role in a variety of functions throughout the body [42] such as vision, gene transcription, immune function, embryonic development and reproduction, hematopoiesis. For menopausal women vitamin A is relevant for bone metabolism, skin, and cellular health, and it is responsible for moisturizing and protecting hair, giving them resistance from being fragile, and thus its deficiency may cause decrease in cycle speed of cell regeneration
	*Calcitriol—Vitamin D* Vitamin D refers to a group of fat-soluble secosteroids involved in intestinal absorption of calcium, iron, magnesium, phosphate, and zinc. Very few foods contain vitamin D: fat fish (marcel, salmon, and sardines), whale or tuna liver oil, and lower amounts inmeat, poultry, eggs and full fat diary. Consumption of mushrooms and yeast will additionally supply body in D2 (ergocalciferol). Vitamin D synthesis (specifically cholecalciferol) is in the skin. Dermal synthesis of vitamin D from cholesterol is dependent on sun exposure (specifically UVB radiation). In humans, the most important compounds in this group are vitamin D3 (also known as cholecalciferol) and vitamin D2 (ergocalciferol). Cholecalciferol and ergocalciferol can be ingested from the diet and from supplements. In the liver, cholecalciferol (vitamin D3) is converted to calcifediol. Ergocalciferol (vitamin D2) is converted in the liver to 25-hydroxyergocalciferol (a.k.a. 25-hydroxyvitamin D2—abbreviated 25(OH)D2). Part of the calcifediol is converted by the kidneys to calcitriol, the biologically active form of vitamin D. Calcitriol circulates as a hormone in the blood [43], regulating the concentration of calcium and phosphate in the bloodstream and promoting the healthy growth and remodeling of bone. Calcitriol also affects neuromuscular and immune function. Vitamin D promotes hair follicle differentiation, without affecting proliferation

Finally, Vitamin D promotes hair follicle differentiation, without affecting proliferation. Endogenous vitamin D synthesis starts in the skin (mainly in the prickle layer of epidermis) with 7-dehydrocholesterol under the influence of UVB (290–315 nm), subsequently undergoing two hydroxilations in the liver and in the kidney. The best source of D3 vitamin in women's diet should be fat fish (marcel, salmon, and sardines), whale or tuna liver oil, and also products containing lower amounts such as meat, poultry, eggs and full fat diary. Consumption of mushrooms and yeast will additionally supply body in D2 (ergocalciferol). Overweight and obese women have low serum levels of calcitriol (the active form of vitamin D) and after the age of 70s it is reported a low synthesis of vitamin D from sun exposure [45]. In animals studies the activation of VDR receptor was shown to play a significant role in the hair follicle cycle, especially in anagen initiation and is independent of calcium and phosphorus content in diet [46].

Many minerals influence hair growth namely Zn, Fe, Cu, Se, Si, Mg, and Ca. Zinc takes part in carbohydrates, proteins and fats metabolism and at the same time influences hair follicles and hair growth. Zinc also influences vitamin A keratinizing hair. Its deficiency in diet suppresses hair growth, can lead to telogen effluvium, thin white and brittle hair and cause hair fall, especially in women using diuretic drugs [28]. Iron deficiency has been associated with hair loss as in alopecia areata, androgenetic alopecia, and telogen effluvium [47]. The best iron sources are animal products containing better assimilated heme iron (beef and pork, poultry, pork and lamb liver, and fish) but valuable diet variety are plant products such as: soya, white beans, pasticcio nuts, green parsley leaves, dried apricots and figs [28]. Copper is crucial for aminoxidases required for oxidation of thiol groups to dithio- cross-links, and is essential for keratin fiber strength, has a stimulating effect on the proliferation of keratinocytes and fibroblasts in monolayers, has a vital role in the activation of key enzyme systems specific to tissue formation and repair, and participates in the cross-linking and maturation of collagen in healing wounds [48]. Copper is present in the same products as iron. Selenium is an essential component for antioxidant defense, formation of thyroid hormones, DNA synthesis, fertility, and reproduction, and it is a component of at least 35 proteins many of which are enzymes and with its deficiency in the body hair loss with pseudo albinism occurs [28]. Although much less common than selenium deficiency, selenium toxicity can affect individuals as a result of oversupplementation, which results in hair loss. The main food groups providing selenium in the diet are bread and cereals, meat, liver, fish (cod, canned tuna), eggs, and milk/dairy products. Fruit and vegetables typically contain relatively small amounts of selenium [49]. Calcium is also an element playing significant role in keeping hair in proper state and in hair Calcium concentration exceeds by 200 times that in blood serum and erythrocytes. Women in particular in the perimenopause period are exposed to its deficiency and so they should be supplemented. Calcium in diet in present in all dairy products containing lactose facilitating its absorption and also soya, parsley green leaves, hazelnuts, white beans, kale, walnuts, fish, and cabbages. Magnesium, taking part in protein transformation, is responsible for division, growth, and maturation processes of cells, taking into consideration its role in immunological reactions, protecting and alleviating

inflammation states, and thus its deficiency directly or indirectly contributes to hair fall. The sources of magnesium in women's diet are cocoa, grits, whole grain breads, nuts, and legumes.

18.3.3 Liquids

Water influences the hydration degree and state of hydrolipid layer on its surface. Physiologically, the amount of water in skin represents 20% of the total [50]. That is why mineral and spring waters containing minerals are a very good source of water and minerals. Liquids should be consumed in the amount 30–35 mL/kg of body mass/day including 1.5 L in the form of water (boiled, mineral) best between meals.

In summary, to prevent hair loss diet should include large amount of fresh vegetable and grains, with a proper intake of proteins and fat, and the best scheme is represented by the Mediterranean diet [51]. External supplementation of micronutrients might be indicated after medical consultation.

18.4 Nutritional Management of Overweight and Obesity

In 2008, overweight was recorded in greater than 50% of individuals in the European region of OMS [52]. Of these 23% of women and 20% of men are obese. In 2013, the report of the 53 WHO European Region Member States (2013) shows overweight in men ranging from 31% in Tajikistan to 72% in Czech Republic while in women it ranged from 31% of Tajikistan to 64% of Turkey. In Italy, overweight is present in 35.6% of the adult population and 10.4% is frankly obese [53]. There is a gap between North and South in Italy, with the southern regions presenting the higher prevalence of obesity (Puglia 12.9% and Molise 13.5%) or overweight (Basilicata 39.9% and Campania 41.1%) than the northern (Liguria 6.9 and 32.3%, respectively). The prevalence of overweight and obesity increases with aging up to a maximum at the age of 75 years, then it lowers slightly. Similar data are reported in Canada where 58% of the women aged 40–59 years are considered overweight or obese [54].

Poor eating habits and physical inactivity contribute to the increasing prevalence of overweight and obese individuals.

As stated before in this chapter, during the menopause transition body composition changes by increasing in abdominal fat mass as well as associated alterations in cardio-metabolic risk due to hormone-related decreases in energy expenditure and fat oxidation [55, 56].

Lifestyle interventions to minimize gains in fat mass and changes in body composition and body fat distribution predominantly include exercise and healthy nutrition. Current guidelines recommend (a) assessing factors contributing to overweight (body mass index (BMI) 25–29.9 kg m^2) and obesity (BMI $\geq$ 30 kg m^2) in adults and (b) intervening with counseling and treatment of obesity [57].

Jull et al. [54] systematically reviewed the effectiveness of exercise and/or nutrition interventions on mitigating changes in body weight, body composition, and

body fat distribution in women specifically in menopause transition stage. They reported that only one study was appropriate for this aim [58], and this study included women exposed to a program of combined exercise and caloric restriction dietary interventions for 54 weeks. Using this combine program women had improved body weight and reduced abdominal adiposity and significant reductions in waist circumference and body fat were maintained beyond 4 years [58]. In other studies with less stringent study design, exercise or both exercise and caloric reduction interventions were able to limit the process and patterns of weight gain and change in body fat distribution during the menopause transition stage [59, 60].

These findings are consistent with guidelines on the prevention and management of obesity that recommend lifestyle intervention as the first approach for preventing or treating obesity.

Evidence points towards a role of the Mediterranean diet in preventing obesity [61–63]. It covers most nutritional recommendations, like low content of refined carbohydrates, high fiber content, moderate fat content—mostly unsaturated—and moderate-to-high content of vegetable proteins, and energy expenditure via a daily physical exercise (Fig. 18.2). The Mediterranean diet also appears as a safe strategy

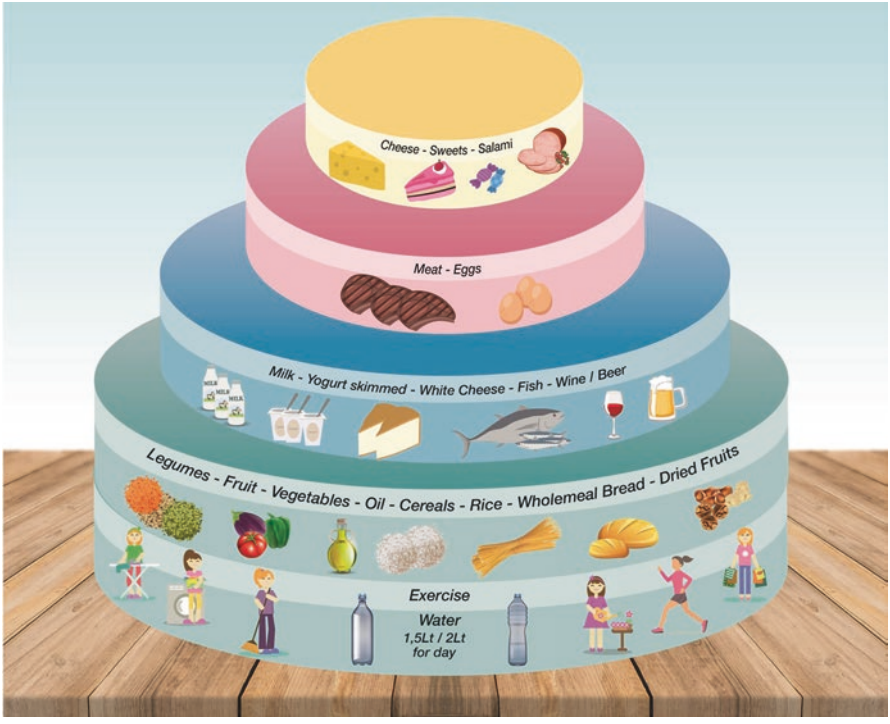


Fig. 18.2 The pyramid of mediterranean diet redrafted for women. The first step includes the required daily activities and food to be consumed. The second step includes food to be used only 3 times per week (wine and beer are alternatives). The third step includes food to be used only one time per week and the top step includes food to be seldom used in the month

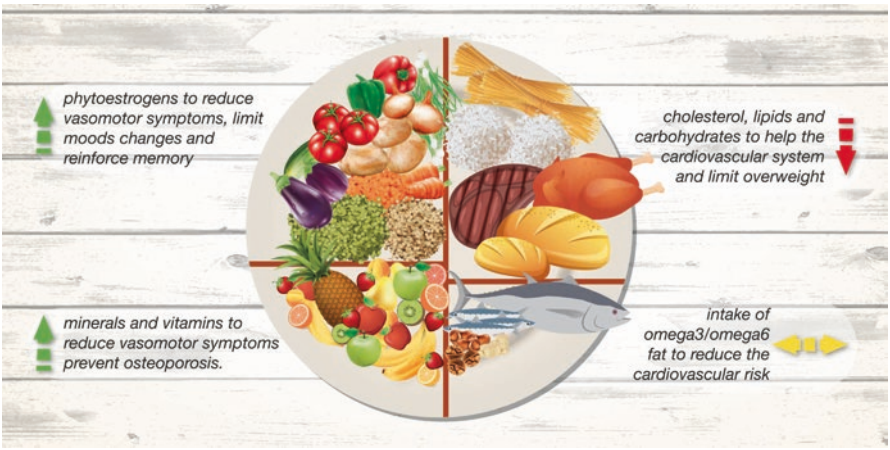


Fig. 18.3 This is the perfect plate to eat everyday. More fibers, vegetables and integral pasta or rice, little portion of fish, and some fruit ensure a perfect balance of minerals, vitamins, and good proteins, carbohydrates, and fat for limiting the appearance of chronic comorbidities

to treat metabolic syndrome and to reduce associated cardiovascular risk [61], to combat obesity, and to reduce low-grade inflammation, thus limiting the onset of many of the modern noncommunicable diseases.

Conclusion

Nutrition plays an essential role in menopausal women both in limiting clinical complaints, such as vasomotor symptoms and hair loss and in preventing more serious diseases such osteoporosis (discussed in other chapters of this book) and overweight/obesity. A good daily plate for menopausal women is reported in Fig. 18.3: this together with constant physical exercise will produce lifelong sustained benefits.

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Part V

Menopause in the Context of Healthy Ageing

Frailty and Comorbidities. Frailty in Women

19

Esperanza Navarro-Pardo, Patricia Villacampa-Fernández, Ruth E. Hubbard, and Emily Gordon

19.1 Introduction

"Frailty, thy name is woman!"
Hamlet, Act 1 Scene II.

In the past, "frailty" was associated with the female sex. Before reproductive biology was understood, women's recurring menstrual cycles were considered to render them unstable and imperfect. Aristotle argued that menstruation was a sign of women's inferiority, a direct cause of their physical weakness. Victorians expanded on this hypothesis, proposing the uterus as the weakest part of the female body (since it failed to hold its contents) through which emotional problems could both originate and manifest. Locating physical and psychological weakness in the womb excluded men from such faults.

It is now accepted that frailty may be seen in both sexes, but it is not identical. Men and women tend to age in different ways. Women experience more disability, dependency and chronic disease yet have a longer life expectancy. Compared to

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their age-matched male peers, women could be considered both *more* frail (because they have poorer health) and *less* frail (because they are less vulnerable to the adverse outcome of death).

In this chapter, we explore the frailty concept by reviewing its definition and different approaches to its measurement. The link between frailty and chronic disease is reviewed before considering how frailty in older women differs to that of older men.

19.2 Frailty

To a contemporary layperson, frailty is a derogatory term, identifying multiple losses: of strength, social engagement, levels of activity, and even moral stature [1]. In gerontological research, on the other hand, frailty represents a dynamic and multidimensional clinical condition characterized by depletion of the system's reserve that translates into a loss of redundancy and increased vulnerability when facing any stressor event. This loss of resilience implies not only a poorer and harder recovery of baseline homeostasis, but a disproportionate increment in deleterious health outcomes when facing even minor insults.

Regarding the factors involved in the triggering of frailty, it appears that the losses and cumulative damaged imposed by aging, the impact of acute or chronic disease, the psychosocial resources and coping strategies, and the individual's own genetic endowment may be at play [2, 3]. However, a holistic and definite knowledge of the aetiology of frailty remains yet to be accomplished. Clegg and colleagues [2] identified the nervous, endocrine, immune, and musculoskeletal as the main systems in which the development of frailty has been best investigated, and provided a very illustrative description of the role each systems plays in the so-called *spiral of physiological decline*.

The concept of frailty may be understood as what Schefer [4] calls a *foreseeing tipping point*, namely, as a broad and comprehensive indicator that determines whether the complex biopsychosocial system is on the brink of a dramatic shift or collapse due to the loss of its redundancy. In order to facilitate a better understanding of the frailty concept, a visual representation of the increased vulnerability to stressors due to the system's redundancy depletion linked to its loss of reserve is displayed in Fig. 19.1.

19.2.1 Frailty Paradigms

Consensus has not yet been achieved among the scientific and practitioner experts of the field for a definitive operational definition of frailty [5, 6]. There are, even so, two main paradigms that have received most of the attention within the community: the Frailty Phenotype [7] and the Frailty Index [8]. Both approaches consider frailty as an age-related, dynamic, stochastic, multidimensional, and nonlinear depletion of systems that leads to a loss of physiological reserve and redundancy where even

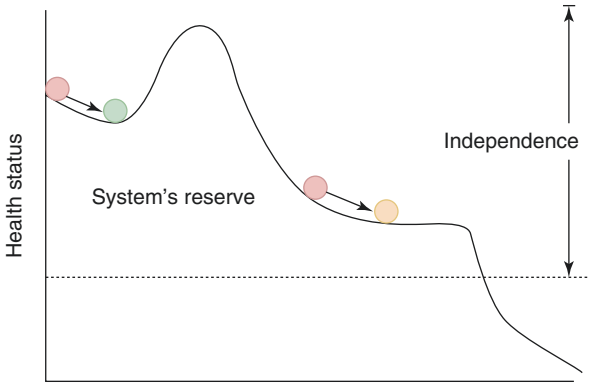

Fig. 19.1 Increased vulnerability to stressors of frail individuals due to the system's reserve depletion. The *green circle* represents a robust elder person, while the *orange circle* represents a frail one. *Red circles* represent a certain minor insult. The *horizontal dashed line* represents the cutoff between dependency and independency regarding functional capacity. Due to the depletion in the system's reserve and loss of redundancy, when facing the same minor stressor event, the frail individual presents a higher risk of adverse health outcomes, loss of functional capacity, and difficulty to recover baseline homeostasis. On the contrary, the preservation of the system's reserve and redundancy buffers the strain repercussions for the robust individual, making it more resilient by preventing a disproportionate impairment of health status and allowing a quick and easy recovery of homeostasis. *Note*: for the elaboration of this figure, inspiration was drawn from the visual representation of tipping points and leading indicators provided by Schefer [4] as well as from the diagram of vulnerability of frail elderly people provided by Clegg and colleagues [2]

minor stressors can lead to adverse health outcomes and complications due to the inability of the system to recover homeostasis [7–13]. Notwithstanding, they differ in their conceptual framework, naming them differently: a cycle of frailty versus a model of fitness and frailty. Based on the differences regarding their conceptualization of frailty, each operationalization has generated a distinct assessment tool (see Table 19.1).

- The *Frailty Phenotype* recognizes frailty as a clinical syndrome identified by the presence of three or more of the following components: sarcopenia (weight loss), weakness (grip strength), exhaustion (poor endurance and energy), slowness (gait speed), and sedentary lifestyle (low physical activity) [7]. This operationalization considers as intermediate, or prefrail, people with one or two of those characteristics present, and as robust all those free of any of those features. The most consistent critic to this conceptualization is the omission of important dimensions, like cognitive and other psychosocial components [6, 8, 14–16].
- The *Frailty Index*, also known as cumulative deficit model, is a mathematical model that identifies frailty as an accumulation of health deficits [8]. It can be based on Comprehensive Geriatric Assessment (CGA) and the principle is to count health deficits in a whole range of areas from purely physical to more psychosocial. These health deficits should be age-related yet not too early

Table 19.1 The dominant frailty paradigms

	Elements	Interpretation
Frailty phenotype [7]	*Sarcopenia*: Unintentional weight loss *Weakness*: Low grip strength *Exhaustion*: Poor endurance and energy *Slowness*: Low gait speed, *Sedentary lifestyle*: Low physical activity	None present: Robust 1–2 present: Pre-frail 3 or more present: Frail
Frailty index [17]	Accounts for the *accumulation of health deficits*: Symptoms, signs, diseases, disabilities Computes a *ratio* between the health deficits counted in the list and the ones present in the individual assessed. *Criteria* for the elaboration: – deficits must be associated to health status (e.g., grey hair cannot be considered) – deficits must be age-related – deficits must not saturate too early (e.g., impaired vision cannot be considered) – it must cover a wide range of systems from purely physical to psychosocial – for longitudinal assessments the deficits list must remain unaltered	Frail: (approximately) ≥ 0.20 The higher the ratio, the frailer the individual Upper limit: (approximately) 0.7

saturated, and would include symptoms, signs, diseases, disabilities or laboratory, radiographic or electrocardiographic abnormalities [17]. Frailty, then, is operationalized as the ratio between the number of deficits present in an individual and the total number of deficits counted [8, 10, 17–19]. It is important to note that, although the theoretical maximum of the frailty index by definition is 1, the 99% upper limit has consistently been proven to be less than 0.722 [9].

Existing evidence supports the ability of both operationalisations to predict health status impairment with its consequent decay in functional capacity and mortality [11]. Up to now, most of the interest within the community has been captured by the Frailty Phenotype. A great part of its success resides in the categorical nature of the approach [12]. The discretization of the individuals in categories (i.e., robust, pre-frail, or frail), rather than providing a certain ratio, increases the assessment outcome intuitiveness and ease of interpretation for general practitioners. Even so, the Frailty Index is the preferred operationalization for policy makers and the majority of the researchers, as its continuous character turns it more sensitive to changes plus a better and more sensitive predictor of deleterious health outcomes [6, 8, 15, 16].

19.3 Frailty and Comorbidities

The clinical conditions of frailty, comorbidity, and disability have traditionally been used interchangeably as they are highly interrelated and overlapping in a considerable amount of people [20]. However, they represent three distinct clinical concepts [7, 21]. The differentiation between disability and comorbidity and frailty is quite apparent due to the former representing a clear impairment in functional status. Nonetheless, to disentangle frailty and comorbidity is a more complex task [5].

19.3.1 Comorbidities

The term comorbidity designates the co-occurrence of different noncommunicable diseases (NCDs) in the same individual, that is, the presence of two or more chronic diseases in the same person [22–24]. Some authors have proposed a distinction between comorbidity and multimorbidity, but this conceptual differentiation goes beyond the scope of the present chapter, where both terms are used interchangeably (see Fig. 19.2). Chronic diseases are those diseases that are permanent, caused by nonreversible pathological alteration, and/or require rehabilitation or a long period of care. The traditional concept of chronic diseases has been integrated in the more recent and increasingly popular denomination of NCDs [25]. The cluster of cardiovascular diseases accounts for most of the deaths related to NCDs, followed by cancer, chronic obstructive pulmonary disease, and diabetes mellitus. These four clusters of diseases account for the majority of the NCDs related mortality. Other common NCDs are painful conditions, depression, anxiety, heart failure, stroke/transient ischemic attack, atrial fibrillation, and dementia [22].

It is worth noting, however, that comorbidity does not just represent the sum of different NCDs but a clinical condition itself [25]. Indeed, it is envisaged as a synergy of the different NCDs associated with worse health outcomes and a more complex clinical management than the simple addition of the single NCDs [26] (see Fig. 19.2). Low socioeconomic status and female gender have been confirmed as

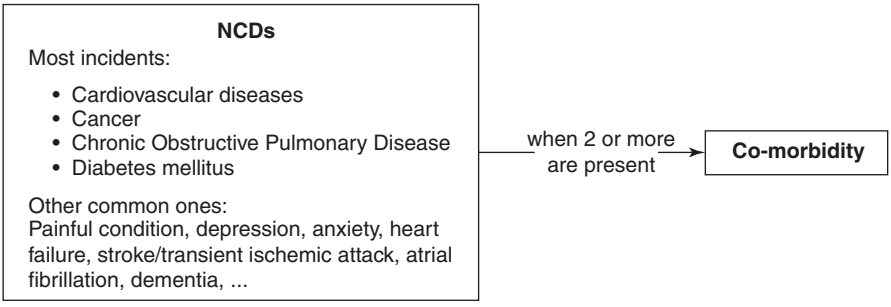

Fig. 19.2 Noncommunicable diseases and comorbidity

social risk factors for comorbidity [27, 28], while a large social network appears to be a protective factor [24]. Like frailty, comorbidity is age related, for its prevalence rates increase substantially with aging, ranging from 55 to 98% in people aged 65 years or older [22, 24, 26]. Comorbidity prevalence rates, however, are strongly affected by the operationalization of the condition, that is, the cutoff point taken for the number of diagnoses and the range of health conditions that is contemplated. Most researchers usually take a conservative approach establishing the presence of three (instead of two) or more NCDs as a cutoff point for the presence comorbidity in order to prevent the disproportionate prevalence rates associated to a lower cutoff point. The prevalence rates variations between studies, nonetheless, is possibly due also to methodological biases, or other reasons.

As a way to find consensus among the wide variety of operationalizations for comorbidity, the European General Practice Research Network [28] proposed a comprehensive definition of the concept as:

> Any combination of chronic disease with at least one other disease (acute or chronic) or biopsychosocial factor (associated or not) or somatic risk factor. Any biopsychosocial factor, any risk factor, the social network, the burden of diseases, the health care consumption, and the patient's coping strategies may function as modifiers (of the effects of multimorbidity).

19.3.2 Frailty–Comorbidity Connection

Existing evidence supports the role of frailty and comorbidity as risk factors for each other, as well as to be both predictors of diminished quality of life, of health and well-being, of disability, and of mortality [15, 17, 19, 22, 24, 27, 29].

As proposed by Villacampa-Fernández and colleagues [21], both comorbidity and frailty are crucial clinical conditions in the system failure process of an aging individual (see Fig. 19.3 for the graphical representation). Comorbidities, as already discussed above, are major predictors for an increase in health deficits. This

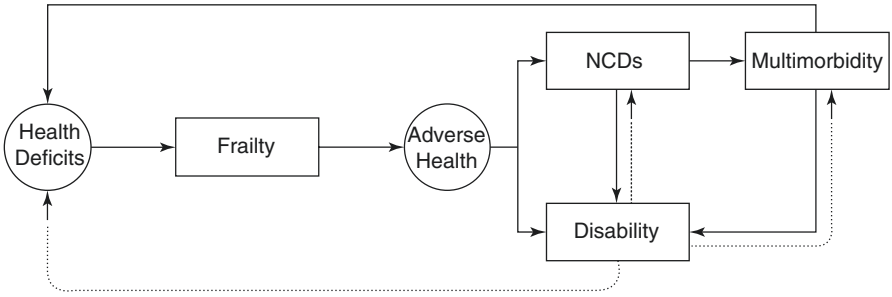

Fig. 19.3 Flowchart of the aging system failure process. *Notes*: *circles* represent inputs/outputs, *rectangles* represent clinical conditions, *continuous lines* represent direct effects, *dotted lines* represent indirect or secondary effects, *NCDs* noncommunicable diseases. *Source:* Villacampa-Fernández et al. [21]

accumulation of health deficits triggers a depletion of the system's reserve and redundancy, leading to a higher vulnerability to stressors known as frailty. Frailty, in turns, leads to a highly increased probability of adverse health outcomes when facing minor insults. By adverse health outcomes, a range of possible diseases and/or impairments is included, with institutionalization and mortality as the worst scenarios. Within the wide range of diseases and/or impairments that trigger the adverse health outcomes related to frailty status, the already discussed NCDs and their consequent comorbidities, in conjunction with disability, stand out for their deleterious effects on the individual. Disability is proposed to indirectly trigger NCDs and comorbidity, along with frailty through the increase in health deficits.

19.3.3 Sex Differences in Comorbidities

While older males and females acquire new comorbidities with age, females have been found to acquire slightly more overall [30]. In addition, the types of diseases commonly acquired by females, such as osteoarthritis, depression, and anxiety, appear to be more likely to impact negatively on function and quality of life [31–35]. While males and females differ in terms of their approach to defining and assessing well-being, the number and nature of chronic illnesses has been found to be a significant confounding factor for sex differences in self-rated health [31]. Women also report (and experience) more disability than men [30, 32, 34–36]. The high prevalence of functional limitation experienced by women may be due to a higher incidence (in the setting of low physical activity and "disabling" chronic conditions) and/or lower recovery rates [37, 38].

19.4 The Sex–Frailty Paradox

Women tend to live longer lives than men. The sex differential in longevity is seen in most countries across the developed and developing world [39]. At a global level, the gap between the sexes has remained stable (at approximately 4.5 years) over the last 25 years [40]. Historical data suggests that this is not a recent phenomenon [41, 42]. Yet, as we have discussed, older women experience more chronic disease and disability. So while increasing frailty is associated with worse mortality for both sexes, women seem to be able to tolerate a higher level of frailty. This so-called sex–frailty paradox [43, 44] is one of several fundamental paradoxes of aging that remain unexplained.

19.4.1 Why Do Women Have Poorer Health?

Psychosocial factors have been identified as potential mediators of the sex–morbidity gap. In studies using self-report data, conclusions regarding sex differences in comorbidity, disability, and self-rated health depend to some degree upon whether

males and females assess and report health in the same way. Even though it has been hypothesized (and sometimes assumed) that sex differences in disease incidence reflect a female tendency to overreport and a male tendency to underreport health problems, the literature is far from conclusive [36, 45, 46]. Females have been shown to access healthcare services more often than males (even after removing reproduction-related presentations) [46]. While this might contribute to higher female incidence of self-reported medical diagnoses, it is not clear whether this is due to real sex differences in morbidity prevalence or sex differences in health–illness perception or help-seeking behavior.

Sex differences in biological factors, such as inflammatory cytokines and sarcopenia, are emerging in the literature and likely underpin sex differences in comorbidity, functional decline, and, ultimately, frailty [47, 48]. Abdominal adiposity, which accumulates to a greater extent in older women than men, may play a particularly important role in the chronic inflammatory state thought to be at the crux of frailty [48].

While sex differences in pathophysiology may develop in middle to late age, it is also possible that differences stem from divergent physiological investment during reproductive years. The "disposable soma" theory proposes a trade-off between somatic maintenance and reproduction, which would manifest as an inverse dose–response relationship between parity and life expectancy [49, 50]. Arguably, a relationship between parity and frailty may be expected to emerge first, but this has not been examined in the literature to date. In keeping with this theory, there is some evidence that pregnancy and childbirth are associated with chronic medical conditions, poor functional performance and self-rated health, as well as late-life mortality, in older women [51–54]. However, the fact that nulliparous women have not demonstrated superior longevity and the life expectancies of fathers were not insensitive to increasing parity oppose this theory and emphasize that other (probably psychosocial) factors are relevant [50, 51]. The impact of reproduction on the late-life health of women remains a focus of contemporary research.

19.4.2 Why Do Women Live Longer Lives?

Multiple factors contribute to sex differences in longevity. Certainly, there are biological factors, such as sex differences in immunocompetence and hormonal modulation of inflammation, that may contribute to mortality rates [46]. In particular, the favorable impact of estrogen on lipid profiles with subsequent delays to the onset of cardiovascular disease after menopause has been frequently cited in the literature [55]. Longevity benefits associated with the presence of two X-chromosomes has also been speculated [44, 55]. Risk-related activities, such as smoking and alcohol intake, have also been identified as contributing to higher male mortality rates, possibly through their contribution to increased incidence of "lethal" comorbidities [31, 34, 44, 46]. Sex differences in health-care utilization, particularly in terms of access to early intervention and preventative medicine [44, 46], also probably contribute to the male–female mortality gap.

19.4.3 Why Do Women Tolerate a Greater Frailty Burden?

These health and longevity factors, however, do not explain the "male–female health–survival paradox"—why or how do females live longer despite greater frailty? It has been proposed that the paradox is an artefact of female longevity. That is, females have more time to acquire a greater number of health problems, which they then have for a longer period of time. But the frailty differential emerges in middle age and, as a result, cannot be solely attributed to longer life span [44].

Perhaps the sex paradox is underpinned by sex differences in the "nature" of chronic medical illnesses. There is some evidence to suggest that females experience chronic conditions that are typically "non-life-threatening" or "disabling," resulting in high morbidity and low mortality, whereas males experience more "life-threatening" chronic conditions, resulting in high mortality [30–32, 56, 57].

The sex paradox may also transpire because males have lower physiological reserve than females. Studies using the cumulative deficit model of frailty have determined sex differences in frailty limits (i.e., the frailty score at which survival approaches zero) [35, 58]. In particular, the frailty limit was found to be significantly lower for males than females and males reached the frailty limit at a younger age [35].

Hubbard and Rockwood [44] proposed that there are evolutionary drivers for sex differences in physiological reserve. In males, optimal physical function in youth may be achieved at the expense of longevity. In evolutionary terms, this fitness-frailty pleiotropy is advantageous to the species as it maximizes progeny. But the consequence is lower physiological reserve with early system failure (relatively to females). In females, on the other hand, pregnancy and childbirth may be key drivers. Reproduction is physiologically demanding and may lead to early decrements in system reserve. Thus, in order to maximize fecundity, there would need to be an evolutionary increase in female physiological reserve. This fertility–frailty pleiotropy would mean that even though females acquire damage during their reproductive lives and are more likely to enter middle and late age with frailty, the sexes would have a similar life expectancy. The mortality gap between the sexes, therefore, might be indicative of the contemporary trend towards limiting parity, whereby females enter their post-reproductive years with less system damage.

An alternative, or complementary, theory is that the benefits of the post-reproductive female life may drive an evolutionary increase in physiological reserve. The "mother effect" emphasizes the advantage of women living for some years after the birth of their last child to ensure that their children achieve sexual and economic maturity [59]. The presence of grandmothers may also convey a survival advantage by supporting offspring to successfully produce their own progeny [59]. However, it may be argued that the "grandmother effect" does not drive biological evolution of female systems; rather the advantage may lie in supporting daughters to cope with increased frailty during and after reproduction.

It has been hypothesized that females tolerate frailty better than males because they have increased social supports [60]. However, higher levels of social support

for females have not been consistently demonstrated, particularly when marital status and cultural background have been taken into account [34, 61–63]. Socioeconomic factors have been independently associated with frailty and mortality [63–67] and there is some evidence that the size and direction of the impact differs between the sexes [62, 64, 68]. Overall, it is unclear how social factors may impact the male–female health–survival paradox.

Conclusions

Frailty is a construct for examining health status and risk of adverse outcomes in the aging population. It is related to, but distinct from, comorbidity. Even though consensus regarding the best way to diagnose frailty has not been reached, it is generally agreed that at the crux of this condition is the increased vulnerability to stressors in the setting of reduced system's reserve and redundancy.

Frailty affects both sexes. But the relationship between sex and frailty is not straightforward. Consistent with the observation that women tend to have more health problems than men in old age, women are more frail. But women also appear to be more resilient to the deleterious effects of frailty. This paradox, well cited in the literature, remains controversial but highlights future directions for aging research.

The ultimate aim of frailty research is to identify targets for intervention in the hope that frailty can be delayed or slowed, thereby improving the health and quality of life of older adults. Although it is tempting to focus on untangling the weaknesses that contribute to frailty in women and mortality in men, it is equally important to explore resilience in older, frail women. Interventions targeting modifiable behavioral risk factors for frailty and comorbidity, such as physical activity, nutrition, responsible consumption of drugs and education, are likely to be highly beneficial and cost-effective. From a health policy point of view, greater understanding of the balance between vulnerability and resilience in aging may help to shift care of the elderly from a traditional disease-centered paradigm to a preventive, multidisciplinary approach that promotes functionality and independence.

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Dynapenia and Sarcopenia During Female Midlife

20

Faustino R. Pérez-López

20.1 Introduction

Primary sarcopenia is the loss of skeletal muscle mass associated with decreased functional muscle strength, while dynapenia is the loss of muscle strength without significant changes in muscle mass. However, the term sarcopenia is frequently used as a global denomination, with or without a real reduction of muscle mass. From the fifth decade of life there is a decrease of the functional capacity of skeletal muscle (dynapenia) and a gradual reduction of muscle mass (sarcopenia) [1]. In general, the process is more evident and prevalent in women than in men, suggesting some relationship with gonadal aging which is more abrupt among women. Using quality of life tools in perimenopausal and postmenopausal women, musculoskeletal symptoms are more prevalent than the typical vasomotor complaints, persisting long after hot flushes disappear or become mild [2–4]. Despite this, the majority of these instruments do not have the ability to establish the precise causes or pathophysiology of skeletal symptoms. On the other hand, the menopausal transition is also associated to critical biological, psychological and social changes and many co-morbid conditions unrelated to the menopause that may potentiate musculoskeletal symptoms [5]. Postmenopausal women are at higher risk of obesity, sarcopenia, and osteoporosis as compared to men of the same age [6, 7]. Dynapenia and sarcopenia may produce a greater risk of falling and bone fractures. In addition, individuals lose independence and are at risk of other health issues, disabilities, frailty, and early mortality.

Sarcopenia has recently been included in the International Classification of Diseases with a specific code (M62.84) due to its clinical relevance, increasing prevalence, and an evident growth of scientific interest [8]. A third of adults aged 60 or more suffer from sarcopenia. Many of them will have progressive physical limitations and finally some will develop frailty [9]. Two chronological steps may be considered in muscle

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alteration, first dynapenia and later sarcopenia. Hence, preventive interventions would be more effective by acting as early as possible to preserve muscle function.

20.2 Change in Female Muscle Composition and Function

Body composition is highly labile during the menopausal transition. Longitudinal studies report that there is a 3.4 kg increase of fat mass and a decrease in skeletal muscle mass of 0.23 kg during a 6 year menopausal transition, which are associated with a 5.7 cm gain in abdominal circumference [10]. However, body composition and distribution is explained by aging and lifestyle changes, rather than, per se, by menopausal hormonal changes [11, 12].

Age-related muscle changes are due to an "unbalance" between muscle protein synthesis and protein destruction. The situation may be aggravated by catabolic factors, physical inactivity, inflammation, and endocrine changes occurring during the menopausal transition. Contrary to this, physical activity may benefit body strength, cognitive performance, and cardiorespiratory fitness in mid-aged subjects [13]. In postmenopausal women with 8–30 years of menopause, higher lean body mass is associated with higher muscle strength, better physical performance and the fulfillment of daily lining activities. At the same time, higher fat mass is related to lower physical performance, less physical activity, and a higher risk of disability [14]. Other studies have confirmed that physical function is better predicted by appendicular muscle mass corrected by body fat mass [15]. Muscle function alterations are associated with an inflammatory status. Higher interleukin 6 (IL-6) levels are correlated with a decline in muscle strength. When results are adjusted for confounders (e.g., sociodemographic, health, and lifestyle factors) high IL-6 and C-reactive protein levels increase sarcopenia risk [16].

20.3 Pathophysiology of Dynapenia and Sarcopenia

During the first half of life, the musculoskeletal system synchronically gains both bone and muscle mass in response to genetic information, hormone factors and environmental stimulus. Aging has parallel and inverse effects on bone mass (osteopenia) and muscle mass (sarcopenia) along with negative changes on physical function, mobility, fall and fracture risk [17]. Starting at 35–40 years of age there is a reduction of muscle mass at an annual rate of 1–2%, and a 1.5% reduction of muscle strength which can reach a 3% by age of 60 [18, 19]. These changes may be masked by the increase of fat infiltrating within muscle fibers. At the same time, motor units are substituted by adipose and connective tissue and there is a deficit of muscle regeneration [20]. Thus, the combination is frequently called *sarcobesity*. Furthermore, these two conditions have negative influences on the bone metabolism, creating a biologic triangle referred to as *osteosarcopenic obesity* [6, 7].

Simultaneous studies regarding muscle quantity and quality show that dynapenia develops earlier and faster than muscle mass loss [1]. On the other hand, changes in body composition are mutually related to biochemical (hormones, cytokines, and

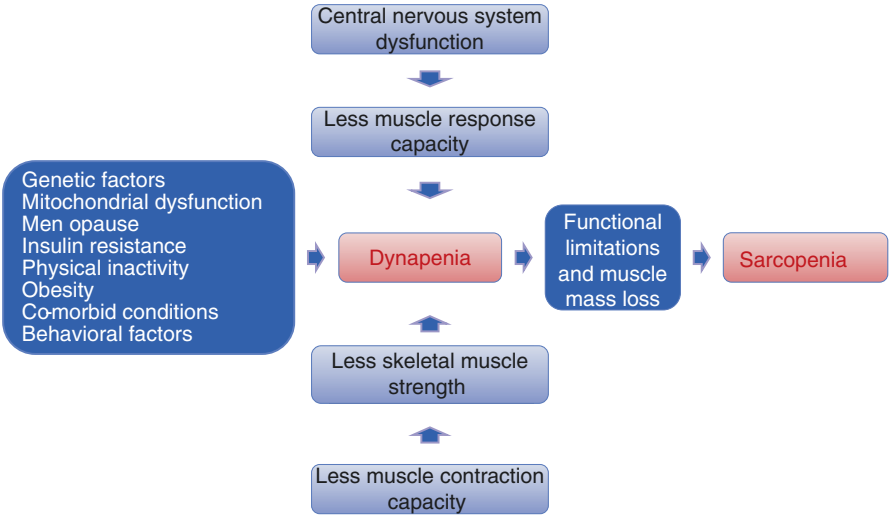

Fig. 20.1 Pathophysiology and factors involved in the genesis of dynapenia and sarcopenia

other molecules) changes, neurological mechanisms, and nutritional and physical activity factors (Fig. 20.1).

20.3.1 Growth Hormone, Insulin Growth Factors, and Fat Hormones

Low growth hormone (GH) levels are associated with low muscle strength. GH and insulin growth factors (IGFs) regulate lean and fat mass content. Indeed, GH secretion maintains a low fat mass and stimulates muscle metabolism and function, while IGF-1 stimulates muscle protein synthesis, inhibits proteolysis, and reduces inflammation and fibrosis [21]. Alterations of the GH/IGF-1 axis are associated with the risk of sarcopenic obesity and fat liver gain which are linked to insulin resistance and lower circulating GH levels [22]. Age-related reductions of IGF-1 levels are associated with lower muscle strength and less mobility which are aggravated by the age-related low muscle response to IGF-1. In addition, muscle condition would be worse if there is dietary protein deficiency [23].

On the other hand, there is an inverse relationship between appendicular muscle mass and circulating leptin levels (a marker of fat mass). Subjects with sarcopenic obesity have a blunted response to GH [24].

20.3.2 Androgens and Estrogens

Gonadal steroids regulate the growth and maintenance of skeletal muscle mass and function as well as fat distribution. Women spend the second half of their lives with

an unfavorable balance between estrogens and androgens while men have a smooth reduction of testosterone secretion. In both sexes, dehydroepiandrosterone has a more important role during physiological gonadal aging; despite the fact that this hormone displays an age-related mild reduction [25]. In perimenopausal and postmenopausal women, gluteofemoral fat deposit is changed to a dominant visceral or an abdominal dominant site.

Despite the high contractions of circulating testosterone in women, the role of androgens on muscle function is not completely known in detail. Testosterone blood concentration decreases with age and could be responsible or may contribute to muscle mass loss. Some studies indicate that it improves cognitive status and musculoskeletal health in postmenopausal women [26]. Androgens have an anti-inflammatory effect without the adverse effects of antiinflammatory glucocorticoids that reduce muscle mass [27].

20.3.3 Insulin Resistance

Perimenopausal and postmenopausal women have an increased risk of insulin resistance and the metabolic syndrome which are related with the endocrine adjustments of the menopausal transition, changes in body composition and excessive weight, sedentary lifestyle, aging, and other factors [28]. These factors reduce insulin sensitivity (increase of insulin resistance) which is associated with a subclinical inflammatory status that favours lack of muscle strength and sarcopenia. In addition, some subjects may have normal insulin sensitivity, yet display alterations in protein synthesis, being less effective for muscle protein synthesis, with a trend to increase muscle adiposity [29]. Over the years, adipose tissue infiltrates muscle (myoesteatosis) and eventually perpetuates insulin resistance without improving contractile ability. These changes are related to physical inactivity, estrogen deficiency, glucocorticoid exposure and intramyocellular lipid accumulation [30]. Another subcellular mechanism of insulin resistance includes skeletal mitochondrial functions which are altered in obesity and hyperinsulinism [31].

20.3.4 Ghrelin and Obestatin

Ghrelin is a peptide produced in the stomach that increases appetite, regulates glucose and energy metabolism, stimulates GH/IGF-1 secretion, and inhibits inflammation [32]. Aging is accompanied by decreased circulating ghrelin levels; and values are lower in subjects with sarcopenia [33]. Decreased ghrelin may play important roles in the age-related GH reduction, changes in body composition, and age-related anorexia [34]. Obestatin is a gastrointestinal hormone that originates from the same precursor of ghrelin. It is an anorectic hormone with anti-ghrelin effects that has a negative correlation with the hand grip test and increases muscle weakness in older women, but it is not related to fragility and low cognitive ability [35].

20.3.5 Vitamin D and PTH

Vitamin D acts on the skeletal muscle through specific receptors, and muscle performance has been related to endogenous vitamin D status [36]. Vitamin D fulfills numerous functions on bone and muscle metabolism [37–39]. Its deficiency increases protein degradation and increases parathormone (PTH) levels with negative effects on muscle [40, 41]. In addition, there is a correlation between serum vitamin D metabolites and muscle strength [37].

Vitamin D deficiency is very prevalent during the second half of life, associated over the years with low sun exposure, vitamin D decreased skin synthesis, decreased intestinal absorption and deterioration of liver and renal hydroxylation capacity [37, 42]. Moreover, aging seems to decrease muscle vitamin D receptors [43]. Vitamin D deficiency has been associated to sarcopenia in a gender (female) specific manner; affecting women aged 50 or more, independently of different variables such as body composition and PTH levels, diet and menopause hormonal therapy use [44]. In older subjects, low vitamin D and high PTH levels have been associated with an increased risk of sarcopenia as compared to subjects with low PTH levels, without gender differences observed [45].

Different studies have reported that women with serum 25-hydroxyvitamin D [25(OH)D] levels below 50 nmol/L have worse muscle function endpoints, whereas during exercise programs higher levels are associated with improvements in physical fitness. In some studies reduced vitamin D levels are associated with increased PTH levels [41].

20.4 Sarcopenia Diagnosis

Lean mass may be measured by anthropometric indices, bioelectrical impedance analysis (BIA), dual-energy X-ray absorptiometry (DXA), magnetic resonance imaging (MRI), and computed tomography (CT) scan. These tools are useful in a research setting, but not easily or routinely used in the daily clinical practice. Different anthropometric endpoints correlate with DXA muscle mass measurements; although sex and age-related skin changes and fat distribution may reduce the accuracy of clinical assessment. Despite the fact that DXA does not measure muscle fat, as compared to CT-scan and MRI, it is considered the most common procedure to assess muscle mass [46]. DXA studies may distinguish four muscle phenotypes: normal, sarcopenia, obesity, and sarcopenic obesity.

Sarcopenia has been defined with different criteria following the recommendations of scientific organizations. Muscle mass is considered normal if it is within one standard deviation (SD) of the mean for young adults of the same sex, while sarcopenia type I corresponds to values between one and two SDs, and sarcopenia type II when values are below two SDs of the mean [47]. This approach is very similar to bone mineral density cut-off values used to define osteopenia and osteoporosis.

Several scientific societies and organizations consider that measuring muscle in isolation is not enough; hence, muscle function assessment is also needed for the diagnosis of sarcopenia (Table 20.1). Furthermore, there are different proposals regarding on how to assess muscle function. Therefore, diagnosis of sarcopenia, its prevalence and predictive capacity to assess fracture risk may be different depending on how the subject is assessed. Definition of the International Working Group on Sarcopenia (IWGS) identified the most cases of the condition (8.3% of the cohort) and was linked with significantly higher number of falls and prevalent fractures in the prior year (Table 20.2). Contrary to this, using diagnostic criteria of the European Working Group for Sarcopenia in Older People (EWGSOP) or the Foundation for the National Institutes of Health Sarcopenia Project (FNIH), only a third of cases had sarcopenia (3.3% and 2.0%, respectively) [48]. Hence, it seems

Table 20.1 Methods used to assess muscle mass and function and sarcopenia endpoint cut-off values by gender

Method	Endpoint	Cut-off by gender
Dual-energy X-ray absorptiometry	Muscle mass index = appendicular muscle mass/height^2	Men <7.26 kg/m^2
		Women <5.5 kg/m^2
Bioelectrical impedance	Muscle mass index = skeletal muscle mass/height^2	Men <8.87 kg/m^2
		Women <6.42 kg/m^2
Muscle strength	Hand grip strength	Men <30 kg
		Women <20 kg

Table 20.2 Sarcopenia definitions according to several scientific societies

ESPENSING	Low muscle mass as compared to subjects aged 18–39 years	Low muscle strength assessed by walking speed of <0.8 m/s in a distance of 4 m, or low capacity of any functional muscle test
		Sarcopenia = low skeletal muscle mass and low muscle strength
EWGSOP	Low muscle mass (sarcopenia) if muscle mass is more than two standard deviations (SD) below the mean reference value of healthy young subjects of the same sex	Either low muscle strength (e.g., handgrip) or low muscle performance (e.g., walking speed or muscle power). Most common used is gait speed and a cut-off <0.8 m/s used to identify the risk of sarcopenia.
		Categories: Pre-sarcopenia, sarcopenia, and severe sarcopenia. Severe sarcopenia is diagnosed when all the three conditions are present.
IWGS	Objective muscle mass measurement: Muscle mass loss alone or in conjunction with increased fat mass. Sarcopenia is more than two SD below the mean reference value of healthy young subjects of the same sex	Functionality assessed by walking speed. Risk of sarcopenia if walking speed is <1 m/s

ESPENSING European Society of Parenteral and Enteral Nutrition Special Interest Groups, *EWGSOP* European Working Group on Sarcopenia in Older People, *IWGS* International Working Group on Sarcopenia

that the IWGS definition may be better at identifying sarcopenia cases and predict associated risks such as falls and fractures.

Assessment of appendicular muscle mass and physical function has been proposed in postmenopausal women [15]. Indeed in this population, the handgrip strength is a simple test that has a good correlation with dynapenia and functional muscle capacity [49]. Beaudart et al. [46] have also proposed some tools such as the Red Flag Method (based on physical manifestations, symptoms and nutritional habits), the Simple Questionnaire to Rapidly Diagnose Sarcopenia scored 0–10 (a result ≥4 could be a reason for a complete assessment of sarcopenia), the more complex Skeletal Muscle Index (SMI), or different predictive equations [50, 51].

20.5 Preventive Interventions for Sarcopenia in Mid-aged Women

The onset or aggravation of age-related changes in skeletal muscle occurs before the onset of the menopause. Muscle strength declines with age, and this drop is much more important among subjects who eat less healthfully, are sedentary and lose a significant amount weight. Indeed, body weight reduction affects not only fat mass, but also lean mass. Therefore, sarcopenia preventive interventions should be initiated in pre-sarcopenic stages, around 40–50 years of age; these include programmed exercise, appropriate nutrition, hormone treatment and new pharmacologic options. The main goal is to neutralize muscle weakness, fatigue, and decreased functional capacity which may provide physical independence and reduce negative outcomes.

20.5.1 Physical Activity and Exercise

Physical activity and exercise are essential for musculoskeletal health, and the maintenance of muscle contractile capacity, potency and mass. The benefits are manifested by the maintenance of neuromuscular function and a reduction in the risk of type 2 diabetes, the metabolic syndrome, insulin resistance, or the accumulation of visceral fat mass. Exercise increases glucose cell uptake by 50 times, transporting it through the muscle cell membrane, and establishing an intracellular flow that guarantees energy during maximal physical activity [52]. In addition, exercise is a promoter of mitochondrial function and insulin sensitivity which may be useful to prevent and treat type 2 diabetes mellitus [53]. Progressive resistance exercises, performed two or three times a week, improve physical condition and the function of the lower limbs, muscle mass (gain of more than a kilo after an average of 20 weeks), and walking speed [54]. Other types of exercise, such as aerobics, flexibility and swing, and functional training, also have positive effects at preventing or treating sarcopenia.

International agencies recommend that individuals perform muscular strengthening activities, preferably resistance, with moderate to vigorous intensity at least twice a week to prevent sarcopenia [55, 56]. However, training with less intensity during the second half of life produces the same effects on protein synthesis and muscle mass

gain [57]. This option is better accepted by the general population and individuals with comorbidity (e.g., osteoarthritis, excessive weight, and cardiovascular risk), and hence achieving greater adherence to exercise prescription [58]. The benefits of exercise have been demonstrated in a meta-analysis including more than one million adults without diabetes who performed moderate exercise (150 min of exercise/per week). This intervention group reduced the risk of type 2 diabetes as compared to sedentary subjects. This effect is independent of other factors such as diet, age and body mass index [59]. Greater physical activity than the reviewed may probably yield even greater benefits.

The Pilates method is a combination of exercises, concentration, breathing and fluid movements, recommended to increase strength, agility, coordination, and psychological well-being. The fundamental principle is to achieve lumbopelvic stabilization and motor control. In postmenopausal women, it can improve body balance, reduce fear of falls, and enhance personal autonomy [60]. Despite this, there is no evidence that it improves muscle mass or body composition [61].

Body vibratory platforms do not appear to have significant effects on muscle mass or bone tissue in postmenopausal women [62].

20.5.2 Diet and Nutrition

Proper nutrition in adults aged 40–50, is advisable to prevent muscle dysfunction. The quality and components of the diet have a great value for muscle function and the prevention of muscle mass loss. Intake of protein and amino acids, acceptable levels of vitamin D and polyunsaturated omega 6/omega 3 fatty acids are recommended. Customized diets have been proposed to maintain muscle mass including fish four times a week or the intake of polyunsaterated omega-3 fatty acids and vitamin D supplements [63].

The effects of different degrees of adherence to the Mediterranean diet in non-institutionalized individuals aged over 60 were analzyed after 3.5 years. Subjects with greater adherence to the diet had the lowest risk of slow motion and weight loss. In addition, higher risk of frailty was related to lower fish consumption [64]. The benefits of a Mediterranean-type nutritional pattern have also been studied in a United Kingdom cohort, demonstrating less muscle adipose tissue and greater muscle explosive capacity in the legs, with no change in grip strength and C-reactive protein blood levels [65].

Unless contraindicated (e.g., renal failure or other reasons) elder individuals should eat more protein than younger ones. Aging causes destruction of tissues throughout the body, and muscle is a source of amino acids required for the repair process. In postmenopausal women, the intake of 1.0–1.2 g of protein per kilo of weight in each meal is recommended along with the daily equivalent of 800 IU of vitamin D and 1 g of calcium and exercise or physical activity 3–5 times per week [56]. Proteins are important to maximize muscle biology. It is recommended that individuals have a balanced diet with increased protein content as well as to perform physical exercise. Eggs have the highest content of digestible proteins, and a significant amount of leucine which is appropriate for muscle synthesis, as well as other

recommended components required for healthy aging such as polyunsaturated omega-3 fatty acids and vitamin D [66]. Despite the general perception that increased egg intake per day increases cholesterol levels; some European countries have eliminated the restriction regarding on how many eggs should be eaten per day.

Dietary weight loss among postmenopausal women with excessive body weight is associated to muscle mass loss; whereas women who followed the same dietary pattern and perform aerobic exercise do not display significant reductions of lean mass and may be effective for the prevention and treatment of sarcopenia [67].

20.5.3 Hormone Therapy

In postmenopausal women, estrogen deficiency has negative effects on muscle mass and strength. Estrogen treatment has beneficial effects on muscle strength and reduces the inflammatory state; in addition, it activates satellite cells responsible for muscle fiber regeneration [68, 69]. Menopause hormone therapy delays muscle changes related to aging and prevents the deposition of adipose tissue in the muscle [70]. A meta-analysis of randomized controlled trials of women without diabetes reported that oral and transdermal estrogen was associated with reductions of abdominal fat, glucose levels, and the onset of new cases of type 2 diabetes mellitus [71].

High endogenous free testosterone levels have been reported in older women (67–94 years) with increased lean body mass [72]. In postmenopausal women, combined treatment with estrogen and testosterone produces greater increases of muscle mass and strength as compared to those receiving just estrogens [73].

In vivo animal experiments show that GH treatment results in increased lean body mass and plasma and hepatic IGF-1, and antioxidant enzyme levels; while decreasing aged-induced cell injury. These effects are accompanied by increased muscle protein synthesis and mitochondrial biogenesis [74].

Creatine supplements can increase muscle mass during resistance training. Creatine can increase cellular hydration and myogenic transcription factors, increasing the activation of specific muscle genes such as heavy chain myosin, and hence producing muscle hypertrophy [75]. In a 12-week randomised trial in elder sarcopenic individuals, the combination of exercise and nutritional supplementation [including whey protein (22 g), essential amino acids (10.9 g) and vitamin D (100 IU)]: (1) increased lean mass, strength, IGF-1 levels, and quality of life, (2) reduced malnutrition and inflammation, and (3) produced a well-being sensation [76].

The combination of cholecalciferol, leucine, and medium chain triglycerides for 3 months improved muscle strength in older subjects with sarcopenia [77].

20.5.4 Vitamin D

Vitamin D supplementation has reported controversial results regarding its effects on muscle mass and function, and whether or not it is beneficial at preventing falls and fractures. From the clinical point of view, vitamin D status is a marker of muscle function improvement in subjects with low physical activity. Vitamin D can

prevent muscle fatigue by regulating biosynthesis of creatine kinase, lactic acid dehydrogenase, troponin I and hydroxyproline through anti-free radical mechanisms [78]. A positive association between vitamin D deficiency and sarcopenia has been reported in Korean women over 50 years of age (but not in men), regardless of other covariates and factors such as body composition, serum PTH, dietary components and menopausal hormone therapy use [44].

A double-blind randomized study has reported the effects of supplementing with 800 IU/day of cholecalciferol or calcifediol in postmenopausal women with a mean age of 60 years and mean 25(OH)D blood levels of 13.2 ng/mL. Women treated with calcifediol achieved mean levels of 69.5 ng/mL while those treated with cholecalciferol had 31.0 ng/mL; however, most importantly was finding a much better improvement of lower limb function with calcifediol. Both treatments modified five immunological markers with no hypercalcemia observed [79].

A meta-analysis of 30 randomized studies reported the effects of vitamin D supplementation, with or without calcium, on muscle function in individuals with a mean age of 61.1 years [80]. The resulting evidence is that supplementation has a favorable effect on overall muscle strength, although it has no effect on muscle mass or muscle power. The results on muscle strength are most important when 25(OH)D levels are lower than 30 nmol/L, and appear more effective in subjects 65 or older as compared to younger ones.

A meta-analysis of randomized double-blind studies of individuals with a mean age of 65 years or older who were treated with active vitamin D supplements indicates that high-dose treatment reduces the risk of falls by 19%. Daily supplement dosages of less than 700 IU or achieving 25(OH)D levels lower than 60 nmol/L do not reduce the risk of falls [81]. In a recent meta-analysis, the risk of fractures is 29% lower in individuals with 25(OH)D levels between 50 and 70 nmol/L as compared to those with the lowest quintile (<30 nmol/L). Vitamin D status appears to be inversely related in mid-aged adults, whereas in older subjects the relationship between vitamin D and fracture risk has a J shape [82].

20.5.5 Pharmacologic Treatments in the Pipeline

Prevention and treatment of dynapenia include clinical strategies of global health in an individualized manner, and the search for new strategies for the management of aging considering future changes in demographics [83, 84]. Basic research is focused on a series of biological preparations and synthetic molecules that aim at maintaining muscle function these include: myostatin inhibitors, selective androgen modulators, and fast muscle activators [85, 86].

Drugs that may improve musculoskeletal health include selective androgen modulators (e.g., enobosam), ghrelin agonists (e.g., anamorelin), megestrol acetate, rapid muscle troponin inhibitors, and spindolol. These compounds and others (infliximab, bimagrumab, and MABp1) have shown effectiveness at improving sarcopenia with limited effect on physical activity [87–89].

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The Health Challenges at Menopause and Midlife: Sustainability, ICT Technology and Patient Empowerment

21

Antonio Cano and Vicente Traver

21.1 Introduction

The effective management of symptoms and the reduction of the risk of disease are two main needs of menopausal women, both deriving from the decline in estrogen production. The impact on the risk for disease, as that of ageing or genetic predisposition, may be attenuated by adherence to healthy lifestyle [1–4].

Lifestyle behaviour is a wide concept including the avoidance of toxics like tobacco or alcohol excess, the maintenance of normal weight, the adherence to a healthy diet, and the regular practice of physical activity (PA). One main problem with the long-term implementation of healthy lifestyle, however, is the requirement for the change of habits that are deeply embedded in daily routine. The purpose to change is not enough in the case of many individuals, who face how the renounce to the gratification provided by the unhealthy behaviour, like smoking, unlimited eating or inactivity, adds to the daily efforts to set aside habits that are profoundly implanted in their lives for years. Quitting smoking is a good example [5] in which the challenge is further complicated by the involvement of different neurobiological circuits creating dependence [6]. A real addition is therefore the problem, which makes the task a difficult one [7].

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21.2 Adherence to Physical Activity

21.2.1 Physical Activity and Risk for Disease in Menopausal Women

As for toxic avoidance, PA entails adherence difficulties, although with their own specificities. The health revenues of its regular practice in menopausal women have been well established [8].The cardiovascular tree, bone metabolism or cognition are only some of the systems favourably affected by PA in menopausal and older women [9]. Moreover, physical and mental wellbeing are also improved through the release of endorphins and other central nervous system modulators [10].

Despite those multiple benefits, sedentariness is a global phenomenon affecting both developed and underdeveloped countries [11]. Indeed, the World Health Organisation (WHO) has considered the health impact of physical inactivity similar to hyperglycemia or hyperlipemia in the loss of disability-adjusted life years (DALYs) [12].

The role of PA in menopausal women makes special sense, since the decline in estrogens may speed up the subclinical progression of some non-communicable diseases, osteoporosis or cardiovascular disease being main examples. The deterioration of bone or the vascular tree may be stopped by estrogen therapy if administered in the initial years of menopause, but the substantial reduction in the use of hormone therapy in the latter years, together with the elimination of disease prevention indication in most countries, has created a gap in the drug armamentarium against the biological mechanisms underlying disease progression. It is unlikely that other drugs may substitute estrogens, because the rapid implantation of absolute risk calculators, like the WHO-developed FRAX risk score for osteoporotic fracture [13] or the Framingham risk calculator for coronary [14], has made scientific societies to issue very restrictive guidelines in the use of drugs for primary prevention of disease. Consequently, in here there is another key role for PA, which may meet some of the menopausal deficits covered by HT.

21.2.2 Variables Affecting Adherence to Physical Activity

The high prevalence of physical inactivity calls for a world-scale strategy. Scientific societies, policy makers and global health agencies, like the WHO or others [15] have created guidelines and programmes to promote the long-term practice of PA. This is why much interest has arisen in relation with the variables affecting the long-term implementation of PA.

The experience gathered across the latter years has shown that one first determinant to achieve long-term adherence is the proper acceptance and enrolment in a programme, something that some authors define as the “uptake”, i.e. the initial participation. Adherence, in turn, is defined as the proportion of participants that complete the programme, in total or in a predefined number of the available sessions.

One important source of information concerning the determinants associated with adherence to PA has been the exercise referral scheme (ERS), a model of interventions to promote PA that was established in the UK in 1990. The programme has instituted that individuals with risk factors are referred from primary care settings to specific facilities, where customised exercise programmes have been tailored to the individual needs of the participant. A systematic review of observational and randomised studies has provided global data about uptake and adherence to ERS [16]. As important findings, the pooled level of uptake was 66% (95% CI 57–75%) across the observational studies and 81% (95% CI 68–94%) across the randomised controlled trials (RCT). The corresponding values for adherence were 49% (95% CI 40–59%) for observational studies and 43% (95% CI 32–54%) for RCT. Similar rates of adherence, with dropping out of 50% within the first 6 months, have been found for osteoporosis patients in another systematic review by other investigators [17]. The authors report that some variability exists, with higher rates of adherence in some studies. Alternative options are the community groups, which provide the benefits derived from the traditional support groups. Again, the literature is scattered, but a recent review on programmes of duration ≥6 months has found a mean adherence rate of 69.1% [18].

One useful message from the literature concerns the variables affecting uptake and adherence, which are the basis for improvement. In the case of the ERS programme, gender affected in that women were more likely to accept but had a poorer adherence, whereas age was a positive factor, elders being more likely to accept and adhere. Subsequent reviews of the ERS experience have described barriers reported by users, which included the inconvenient timing of sessions, their cost and location, an intimidating gym atmosphere, a dislike of the music and TV, and a lack of confidence in operating gym equipment [19]. In patients with osteoporosis, the lack of time and difficulties in transportation were the number one barriers in most populations [17]. Also in that regard, participants in community-based programmes have reported social connectedness, participant perceived benefits, or programme design as important barriers [18].

There is also some literature about this topic from the area of psychology. Concerning acceptance, frequently identified barriers are educational level, health literacy, mood status, or the subject beliefs and interpretations about the required behavioural change [20].

The analysis of barriers has prompted some strategies to improve. Psychologists have proposed "motivational interviewing" to improve uptake [21]. This measure consists of a conversational approach that in the healthcare setting includes the consideration of different magnitudes by the subject, like the readiness to implement the change, the importance given to the change, or the own confidence about the possibilities to make the change. Based on the ERS experience, the NICE-supported measures to improve adherence included the convenience to assist participants to maintain PA or to offer alternatives to gym-based activities that give a degree of personal choice [22]. Despite the different proposals, long-term adherence to PA continues being an unmet challenge.

21.3 Information and Communication Technology (ICT) as an Enabler

The use of ICT technology is increasing in the field of menopause. The options are varied and include (1) purely educative web sites from a variety of providers, including scientific societies, (2) web-based decision support systems, and (3) gaming features to improve knowledge, skills or functional performance at various levels [23]. Importantly, web-based resources offer some features that may be of interest as a tool to behavioural change and long-term adherence to healthy lifestyle.

On line education and decision-making support offer benefits like the absence of geographical and time restrictions [24]. This is an advantage in general, but particularly for population layers with difficulties to access to the health system because of geographical, socio-economical or other reasons. One important feature of technology is that different functions may be integrated. For example, both education and decision-making support may be added a possibility of in-person control, or even on-line coaching services. The initial experience shows that the health profile of the coacher favours the impact of the intervention [23]. Despite so, there is still little information on the width of the use of these tools in basic aspects as, for example, the number of log-ins by the participants or the real impact in health outcome indicators.

21.3.1 ICT to Promote Adherence to PA

The practice of exercise is a plastic activity with many possibilities to promote adherence. And for that, ICT technology has potential specific advantages. As mentioned above, some poor adherence factors reported by users, like difficulties for transportation, inconvenient timing of sessions, cost, lack of time, etc. may be overcome by ICT technology.

Indeed, ICT offers the possibility of non-face-to-face (NFTF) interventions, which is being proposed as a novel alternative to foster PA in older adults. NFTF interventions have benefits like cost-effectiveness, easy dissemination and wide coverage and, although still insufficiently developed, seem to reach success in promoting the practice of PA in elders [25]. One form of NFTF intervention is home based programmes, which have been shown to be as effective as centre-based programmes in older adults [26].

Together with the potential for home-based PA, the versatility of modern ICT technology also offers the possibility of preserving some of the advantages of the community-based programmes through virtual networks. For example, face-to-face group sessions have been shown to be most effective in promoting PA, particularly in women. Advantages of the group are interaction with peers, which generates mutual support, complicities, and healthy competition to maintain adherence in the long term [27]. The possibility that technical staff may supervise face-to-face groups has been shown to offer advantages, although the option is less cost-effective [28].

In this regard, there is much interest in disclosing whether the virtual groups created by the modern social networks may be a substitute of the face-to-face alternative.

The idea of virtual support groups is not new. The initiative has been proposed as a particularly useful tool for creating interpersonal dynamics, which may be accelerated by the powerful online disinhibition effect [29]. A systematic review addressed whether social networks were effective in achieving changes in health-related behaviours affecting different health domains, which included PA. The authors concluded that the interventions seemed effective, but that there was considerable heterogeneity [30]. In contrast, another systematic review examining the impact on healthy diet and PA concluded that no difference might be detected, although the authors again claimed that studies had a low level of participation [31].

21.4 Empowerment of Menopausal Women Using ICT Technologies

The insufficient attention to the symptoms and health effects of menopause has been a source of frustration in women since some years ago. This feeling was reflected in a survey performed before an initiative to empower women and make them to participate in decision making around issues that relate to their own health [32]. It was assumed that by empowering women a quicker acquisition of health literacy skills and a stronger awareness about duties, rights and commitments might be expected. Interestingly, this may have an impact on their close environment, since women occupy the centre of an ecosystem, where family and neighbourhood are integrated.

The influence of women in their setting is not a new issue as it was already collected by Yazdkhasti [33]. Matters like information, tools, content production, type of content, focus, relationship or roles can be managed by women, thus moving towards a new paradigm where they produce, share, review and comment through blogs, doctor wikis, podcasting and forums. Health-related video, audio, images and texts may be produced by women in a holistic patient-centred approach. Their participation may materialise in different ways according to Traver [34] (Fig. 21.1)

21.4.1 Exchange of Best Practices and Information

Women may build the community and facilitate the exchange of best practices and experiences. This atmosphere may help information exchange and shared decision-making in healthcare consultations, as reported by Edwards [35] in a systematic analysis where patient-dependent influences were motivations to seek and engage with information, the appraisal of information before a consultation, and ways of addressing the risk of poor information. A paradigmatic case is breast cancer and how thanks to this exchange of practices, patients benefit from participating in medical decision making [36, 37].

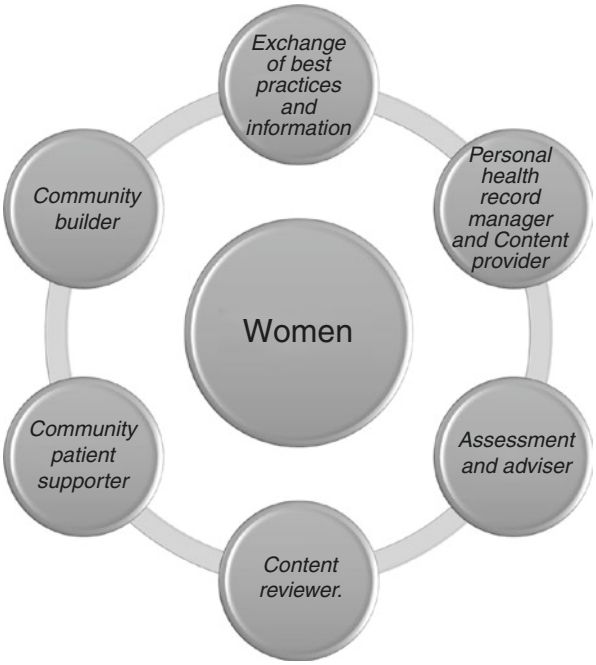

Fig. 21.1 Roles of women for ICT based heath support (original by the authors). There are different experiences showing how women may actively engage into the management of their own health through the use of ICT. Details are provided in the text

21.4.2 Personal Health Record Manager and Content Provider

Different initiatives as Apple Care Kit [38] can allow women to introduce data from sensors, medical (i.e. sphygnomanometer, pulseoxymeter) or non-medical (i.e. pedometer, activity). Therefore, each woman can manage her Personal Health Record for improving her own health and, at the same time, for supporting work carried out by health professionals through the Apple Research Kit. As content providers, women are enriching different platforms as YouTube or Twitter with text, audio, video, images, etc. Good examples are the content created about pelvic floor muscle exercises to promote continence on YouTube [39] or the case of breast cancer patients' Internet spaces [40], always with the goal to improve women's quality of life.

21.4.3 Assessment and Adviser

Citizens are using Internet to assess, advise and evaluate healthcare services, as Patient Opinion in the UK. Assessment and advice is based on data, including blogs posts and comments on health-related websites and social media platforms about

menopausal women facts. These data are providing an unprecedented opportunity to improve medical care from different perspectives [41, 42].

21.4.4 Content Reviewer

Menopausal women can rate and review content. For example, according to Reed [43], the information about menopause and hormone therapy on the web is often of dubious calibre, with incomplete information being commonly provided. The authors recommend healthcare professionals to direct women to reliable sites, such as those owned by the pharmaceutical industry, community pharmacies, governments, and charities. This can be the fastest solution but not the proper one as in doing so, it would be prudent to advise women that commercial sites may be biased towards particular products. Therefore, crowdsourcing can detect and alert about such bias.

21.4.5 Community Patient Supporter

Mamá ponte guapa (get pretty, mom) by Raquel Rebollo or other initiatives collected by Brown [44] are different examples where menopausal women with depression or other health problems provide support to any member through forums, posts, blogs, and data sharing.

21.4.6 Community Builder

Menopausal women are using Internet to strengthen relationships through community building. This is not new as in 1997, Kathleen I. MacPherson reported about how nurse educators could use computer technologies in order to build knowledge and communities on the Internet about menopause, integrated care and preventive actions [45].

So, in conclusion, ICT may support the paradigm-shift of a more active role of menopausal women in today's healthcare systems. Some of the most prominent new roles are: content provider, content reviewer, community builder, adviser, community patient support, exchange of best practices, and Personal Health Records manager. There are specific health areas where involvement and results are more promising as depression [32], hormone therapy [43], breast cancer [36, 40], urinary incontinence [39, 46], physical exercise and healthy lifestyle [2, 8].

Today, the role of women and their environment is changing rapidly due to the incidence and accessibility of Internet, social media platforms and the raise of the patient empowerment. Unfortunately, patient empowerment supported by ICT has yet to be understood better by public and private healthcare providers, medical staff, and policy makers in order to redefine healthcare processes and services towards a menopausal women-centred care.

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