Chapter

# Quality of Life and Menopause

*César Velasco-Téllez, Manuel Cortés-Bonilla, Guillermo Ortiz-Luna, Linda Sánchez-Zelayeta, Horacio Méndez-Serrano, Cinthya Salazar-Jiménez, Abraham Zavala-García and Alicia Sánchez-Cevallos*

## Abstract

Since the middle of twentieth century, the concept of Quality of Life (QoL) has been a point of interest for many investigators and clinicians for different health and physiological issues. Menopause has not been an exemption of this, due to the increase of the life expectation, the importance of Women's Health and the view of this period of life as important as the reproductive one. Many of us work, trying to offer these women with treatments, health solutions, and psychological tools to embrace and enjoy this new chapter in her life. In this chapter, we present a review of the QoL studies on this period and the new trends on treatments and help for these women on health problems, their mental and sexual well-being.

**Keywords:** menopause, quality of life, HRQoL, depression, sexuality, estrogen, ovarian, Climateric, GSM, vasomotor symptoms, MHT

## 1. Introduction

According to the World Health Organization, menopause is the permanent termination of menstruation as a result of the cessation of ovarian activity. The climacteric phase is characterized by a decrease in ovarian activity, a decay in probable fertility, and the manifestation of various symptoms along with irregular intervals of menstruation. The period covers a fragment of premenopause and the parts of peri- and post-menopause, up until ancient age [1]. The transition into menopause is related to different physical and mental changes that may affect women's health. Studies show that the physical, psychological, social, and sexual changes in menopause have an adverse effect on women's quality of life. It has been expressed that 96% of women have menopausal complaints and their quality of life is affected not only physically and psychologically but also socially. It is reported that the quality of life of women is especially adversely affected in the perimenopausal and early postmenopausal periods [1].

Health-related quality of life (HRQoL) states to the effects of an individual's physical condition on all phases of psychosocial functioning. For climacteric women, HRQoL is the particular universal standard that is critical for their daily well-being. Symptoms suffered throughout menopause and sociodemographic particularities have an influence in quality of life in postmenopausal women. In younger, symptomatic, postmenopausal women, HRQoL could be meaningfully reduced influenced by many supplementary, non-menopausal factors. However,

quality of life after menopause is influenced by many additional, non-menopausal factors [2]. Therapeutic methodologies that treat climacteric symptoms and all measures improving adverse non-hormonal factors could improve HRQoL among climacteric women. This includes marital and sexual therapy as well as psychosocial actions. Menopausal hormone therapy (MHT) may inverse this decline of HRQoL if it is due to postmenopausal estrogen deficiency [2].

## 2. Menopause

Menopause is a transitional period marked for many women by fluctuating physiological changes, which affect short-term quality of life such as vasomotor symptoms, sleep, and mood disorders; as well as for long-term changes such as genitourinary symptoms and decreased bone mineral density [3].

Four of five women experience physical and psychological symptoms around menopause with different degrees of severity and impact on quality of life [4]. Clinicians and women usually identify the transition to menopause by the onset of menstrual irregularities [5, 6]. This period called perimenopause is variable, but can range from 5 to 10 years before menopause.

Natural menopause is defined as the absence of menses for 12 months without a pathological cause. The average age of menopause is 51.4 years, but can vary according to race, socioeconomic status, smoking habit, etc. [3]. During the menopausal transition, women experience: irregular menses, vasomotor symptoms, fluctuating fertility, sleep disturbances, depression and anxiety, genitourinary symptoms (including vaginal dryness), and sexual dysfunction.

Some studies show that 87% of women who report hot flashes experience daily symptoms, and a third of them experience more than 10 days [7, 8]. Its prevalence is approximately 40% in the early menopausal transition and 60–80% in the first 2 years after menopause [9, 10]. African-American women have more vasomotor symptoms, while white women have more psychosomatic symptoms. Asian women have the least number of symptoms compared to the other races. In the Penn Ovarian Again Study (POAS), African-American women had more physiological symptoms (hot flashes, dizziness, urinary incontinence, and vaginal dryness) compared to white women [8, 9]. In the Study of Women's Health Across the Nation (SWAN) and PSOAS, obese women had greater vasomotor symptoms [6, 11] and highly active smokers had a more than 60% greater likelihood of reporting severe hot flashes [12, 13]. Changes in menstrual bleeding patterns often signal the beginning of the menopausal transition. The acronym PALM-COEIN is useful to recall the main causes in each category [14].

Cutoffs for the endometrial thickness measured by ultrasound vary by guidelines. The American College of Obstetricians and Gynecologists (ACOG) establishes normal endometrial thickness of 4 mm or less in postmenopausal women, while the American College of Radiology (ACR) suggests 5 mm or less; and in premenopausal women, it proposes a value of 16 mm or less as a cutoff [15]. Endometrial sampling using Pipelle has a sensitivity of 90% for endometrial cancer and 82% for atypical hyperplasia. Studies show regression of hyperplasia over 6 months when treated with levonorgestrel-releasing intrauterine device (LNG-IUD) or oral progesterone, 10 mg, 10–14 days per month [3].

Management of acute bleeding, which is appropriate for medical treatment, options include: LNG-IUD, combined hormonal contraceptives, progestin therapy, tranexamic acid, and non-steroidal anti-inflammatory drugs. The surgical options are also varied, being able to perform dilatation and curettage, endometrial

ablation, uterine artery embolization, polypectomy, myomectomy, or hysterectomy, depending on the cause [3]. The North American Menopause Society (NAMS) recommends contraception for 12 months after the last menstrual period [3]. For women above 50-years old utilizing progestin-only contraceptives, follicle-stimulating hormone (FSH) is able to measure to help identify menopause. The National Institute for Excellence in Health and Care (NICE) guidelines suggest measuring FSH 6 weeks apart, and if the amounts are greater than 30, then the contraceptive scheme might be discontinued after a year [16].

The Faculty of Sexual and Reproductive Healthcare (FSRH) recommends stopping most methods at age 55, except for combined hormonal contraceptives and depot medroxyprogesterone acetate, which should be suspended at the age of 50 to avoid the increased risk of cardiovascular disease. FSRH also recommends women with a copper IUD placed after age 40 can remain use until menopause, and women with a 52 mg levonorgestrel-releasing IUD located after 45, can continue use until 55. If the LNG-IUD is being used for endometrial protection instead of contraception, it should be replaced every 5 years [17].

Vulvovaginal symptoms affect up to 45% of postmenopausal women. Since 2014, the International Society for the Study of Sexual Health of Women (ISSWSH) and the American Menopause Society (NAMS) have approved a new terminology for menopausal genitourinary and sexual symptoms, previously called vulvovaginal atrophy or atrophic vaginitis. This condition now labeled as genitourinary syndrome of menopause (GSM) as a result of the deficiency of estrogen effect not only on the vaginal mucosa but also on the urethra and sexual functioning [3]. The GSM usually become apparent 2 or 3 years after menopause and continues to worsen as the years go by, having an intense influence on the postmenopausal women's quality of life, disturbing intimacy, satisfaction of sexual intercourse, sleep, and relationships. Physical examination findings include pale and thin vaginal epithelium, a pH greater than 5 (normal pH is 3.5–4.5), and augmented parabasal cells on the maturation index [3]. Prasterone, an intravaginal dehydroepiandrosterone preparation, was approved by the FDA in November 2016 and has also recognized efficacy in treatment of symptomatic GSM and dyspareunia [3]. Intravaginal estrogen therapy continues as the leader option for GSM. Local estrogen is marginally absorbed systemically and does not stimulate endometrial growth, so associated progesterone supplementation is not necessary. The recommended dosing using pills or cream normally starts with daily application until the symptoms improve and then weans down to anywhere between one and three times a week [3].

Women with an intact uterus on estrogen therapy should also receive adequate progesterone treatment to prevent endometrial hyperplasia and cancer. Micronized progesterone has a more favorable safety profile than synthetic progestins, but its twice daily dosing may be an obstacle in therapeutic compliance. Women who cannot tolerate the side effects of progesterone (fatigue, dysphoria, and fluid retention), an alternative agent for endometrial protection, is the selective estrogen receptor modulator, bazedoxifene. The LNG-IUD has also been used for this purpose and has been shown to be equal to or superior to other progesterone formulations in providing endometrial protection [3].

To minimize the risks of hormone therapy, the prescription should be with the lowest effective dose and the shortest duration necessary to improve the symptoms. There is no consensus on the recommended duration of hormone therapy or about its withdrawal, either with gradual dose reduction or abruptly. Approximately, half of the women will experience the return of vasomotor symptoms when they discontinue hormone therapy. The decision to discontinue hormone therapy should be individualized based on the patient's symptoms and medical history [3].

## 3. Quality of life and menopause

The common conception of QoL was originally believed a useful assistant to conventional conceptions of health and functional status. An ideal health evaluation, therefore, would take account of an assessment of the patient's physical health, a measure of physical, social, and psychological functioning, and a measure of QoL. Such an assessment would include main physical, psychological, social, and spiritual dominions of life. QoL is defined as individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns. It is a wide-ranging concept influenced in a multifaceted way by the persons' physical health, psychological status, degree of independence, social interactions, and their connexion to relevant features of their environment [18].

Transition into menopause is related to different physical and mental changes that may affect women's health. Studies show that the physical, psychological, social, and sexual changes in menopause have an adverse effect on women's quality of life. It has been expressed that 96% of women have menopausal complaints and their quality of life is affected not only physically and psychologically but also socially. It is reported that the QoL of women is especially unfavorably marked in the perimenopausal and early postmenopausal periods. Simultaneously with the growing extension of the expected life span, the time that is spent in the climacteric period is also growing. Warranting that women having an elevated QoL in this phase may be made likely by showing the complications they suffer, along with associated aspects and defining the status of their QoL [19].

Apparent QoL is difficult to determine and there is no global conformity on how it should be measured. Objective dimensions of health condition (HRQoL) may not obtain the patient's judgment of overall life satisfaction. QoL can be expressed as an indication of an individual's belief about functioning and achievement. HRQoL may be seen as the individual's perception about her physical, cognitive, and mental health as well as social status. Valuations of overall QoL for climacteric patients require taking in count physical symptoms (hot flushes, night sweats, and urogenital atrophy), psychological symptoms (depression, mood swings, irritability, and anxiety), and life conditions (functioning at work and other social scenarios). Thus, overall QoL may include four main factors: occupational, health-related, sexual, and emotional. Consideration of HRQOL is also influenced by women's augmented risk of multiple chronic diseases related to menopause, including osteopenia, osteoporosis and associated fractures, and cardiovascular disease [20].

Symptoms experienced during menopause and sociodemographic characteristics affect the quality of life in postmenopausal women. In younger, symptomatic, postmenopausal women, health-related quality of life (HRQoL) may be significantly diminished. However, quality of life after menopause is influenced by many additional, non-menopausal factors. Management alternatives to manage climacteric symptoms and all measures amending adverse non-hormonal aspects could increase HRQoL among climacteric women. This includes marital and sexual therapy as well as psychosocial actions. Menopausal hormone therapy (MHT) may reverse this decline of HRQoL if it is due to postmenopausal-estrogen insufficiency. In contrast, when MHT is recommended to asymptomatic younger and older climacteric women, no progress in HRQoL can be obtained. Health status and QoL are not linearly related. Recently, there has been a rising alertness of the features of QoL and aging. QoL is a subjective factor. Therefore, open enquiring is the most easy and proper way of adding data about how patients feel and function.

Existing measures of QoL try to quantify the effect of health deficiency through several physical, psychological, and social factors [1].

Symptoms experienced during menopause and sociodemographic characteristics affect quality of life in postmenopausal women. Hot flushes impact the daily activities of most postmenopausal women, especially those with more frequent/severe symptoms. The impact in daily life of menopause symptoms (hot flushes, vaginal dryness, cognitive function, anxiety and depression, urinary complaints, uterine bleeding, low sexual desire, among others) can be seen in work, social and leisure activities, mood, concentration, sleep quality, marital and sexual satisfaction, and the level of daily energy [1]. Vasomotor and sexual complaints have a major impact in the first 5 years after menopause and psychological, and physical symptoms have more effect on QoL in women with more than 5 years of menopause [19]. Quality of partnership, physical activity, weight changes, and education are particularly important for HRQoL during the menopausal transition. Women who decreased their physical activity had deterioration in HRQoL compared with women, whose physical activity remained stable. Inversely, women who increased their physical activity improved their HRQoL. These improvements are likely mediated through greater thermoregulatory control in response to increases in core temperature and enhanced vascular function in the cutaneous and cerebral circulations. Mechanisms involved include a decreased hypothalamic endorphin concentration and declining estrogen production, whereby the release of norepinephrine and serotonin is facilitated. Most likely, improvement of HRQoL by exercise is secondary to the reduction of hot flushes. Exercise may ameliorate vasomotor symptoms by increasing the presence of hypothalamic and peripheral b-endorphin production [1].

The decrease of HRQoL in women suffering from any severe acute or chronic disease may be superimposed on the decrease of HRQoL induced by menopause itself. The impact of coronary heart disease, a frequent disease in postmenopausal women, will serve as an example. Coronary risk factors are highly prevalent among older women and the main cause of death. About one-third of middle-aged women have hypertension. Over one-quarter of these are cigarette smokers, over one-quarter are also overweight. Modifiable coronary risk factors tend to predominate in populations of lower socioeconomic status as well as lower educational levels. Other long-standing metabolic consequences of the climacteric include osteoporosis and osteoporotic fractures skin changes, the general aspects of weight gain and obesity as well as degenerative disease of the central nervous system (CNS). Investigation on the effect of estrogen and other sex hormones on the vascular system, immunity, CNS performance, or musculoskeletal disease is constant, with particular allusion to the cellular level. Awareness of symptoms, nevertheless, and their effect on the everyday life of women, will support the care-giver in given women with proficient care and enduring specialized aid throughout the aging process. It will indeed be appropriately supportive to offer objective evidence about an individual's symptoms of the climacteric woman that might affect her QoL [1].

The effect of menopause on body fat distribution is uncertain, but some studies suggest that menopause is associated with an accumulation of central fat and intra-abdominal fat. Although weight gain during menopause is a normal phenomenon, few studies have proved the relationship between menopausal status and weight gain. The relationship between obesity and health-related quality of life (HRQoL) has been widely investigated that obesity has been associated with compromised HRQoL and psychological well-being. The prevalence of obesity and obesity-linked illnesses is increasing, particularly in the urban environment. Therefore, poor physical functioning and reduced QoL attributable to being overweight are

important in terms of public health and should be addressed by preventive measures and interventions to promote healthy living. Most general population studies conclude that QoL in many persons with obesity is suboptimal. The association between obesity and HRQoL is stronger in women than in men, in both physical and mental or psychosocial dimensions [21].

Many tools have been developed for the assessment of the HRQoL in aging and climacteric women. Myra Hunter developed her Women's Health Questionnaire (WHQ) as a self-reported measure of physical and emotional experience and functioning of women aged 45–65 years. The WHQ was used both in epidemiological and intervention studies. A revised WHQ comprises six domains with 23 items. The MENQOL was developed by a group of researchers from Canada during the mid-1990s. The final 32-item menopause-specific HRQoL instrument encompasses four subscales (physical, vasomotor, psychosocial, and sexual) plus one overall HRQoL item. As with the WHQ, no overall score can be obtained, because the relative contribution of each domain to such an overall score is unknown. The Menopause Rating Scale (MRS) was initially developed to provide the physician with a tool to document specific climacteric symptoms and their changes during treatment. The original physician-based scale was revised concerning the layout and some adjustments regarding the number, structure, and wording of items; these were made to support applicability as a self-administered questionnaire.

The MRS finally went through factor analysis of 11 standardized items encompassing 3 domains: psychological, somato-vegetative, and urogenital dimensions. The scoring is based on a five-point Likert scale, ranging from no symptoms to mild, moderate, marked, or severe complaints. It should be regarded as a brief and compact instrument, easy to complete and to score, and suitable for routine controls. It covers the key complaints of women during and after menopause. It is, however, not tailored to detail specific therapies to the needs of each individual woman. A large variety of linguistic validations of the MRS has created an excellent international response and acceptance [1]. Menopause-specific quality of life (MENQOL) talk about perceptions of women living with the menopausal change or premature postmenopause, employing methods to measure, bother and interference with aspects of daily living related to symptoms presented throughout the menopausal transition. The MENQOL questionnaire and the Women's Health Questionnaire (WHQ) clarify the menopause-detailed valuation of QoL [22].

Menopausal Hormone Therapy (MHT) for menopausal symptoms includes use of estrogens, alone or in combination with aprogestogen, tibolone or a blend of estrogens, and selective estrogen-receptor modulators (SERMs). Although MHT is the best effective treatment for menopausal vasomotor symptoms, it has no indication for all women, such as those with a personal history of breast cancer [23]. Despite the negative impact that the results of the WHI study had over patients' and clinicians' attitudes toward menopausal hormone therapy (MHT) [24]; to date, it is still the most effective option for the management of hot flushes and other symptoms related to the menopause. In fact, there is a current consensus to recommend the use of lower dosages and the non-oral route. Emerging data associated to effects of hormone therapy for MENQOL have continued to progress during this period, as well as a growth of novel investigations. Some search complementing evidence for MHT and QoL measure are the menopause strategies: finding lasting answers to symptoms and health (MS-FLASH) trials, the selective estrogens, menopause, and response to therapy (SMART) trials assessing results of combinations of conjugated estrogen therapy (CET) with bazedoxifene, a selective ET receptor modulator (SERM), and Kronos Early Estrogen Prevention Study trial. Besides, researchers

have conducted search analyzing use of MHT that contain a diversity of progestins (drospirenone) [22].

New and innovated technologies for hormonal delivery may have a better impact on MHT compliance shortly. Providing a combination of E/P in a parenteral monthly formulation with the presently suggested lower dosages and using a new technology that offers persistent plasmatic levels over time, will have a positive long-term outcome on compliance. It has just reported an optimistic pilot experience in taking care of vasomotor and urogenital atrophy symptoms with three low-dose continuous sequential monthly parenteral formulations of 17b-estradiol (E)/progesterone (P) employing innovative non-polymeric microsphere technology [25]. Later was presented the short-term effect of the same proposed schemes over secondary endpoints (menopausal symptoms and QoL). After 6 months, there was an improvement of menopausal symptoms for all groups [26].

The non-hormonal treatment of menopausal symptoms possibilities includes daily life modifications, régime and food supplements, non-hormonal drugs, and behavioral, alternative, or complementary therapies. While various are effective, for others the data are doubtful. Though, for women who cannot or do not desire to take estrogens, non-hormonal managing is now a real option. For instance, soy isoflavones, coumestans, and lignans are all phytoestrogen supplements that have been suggested as substitutes to MHT for vasomotor symptoms. Phytoestrogens are present in soybeans, hops, flaxseed, fruits, vegetables, whole grains, and legumes. These options have been proposed to have estrogenic or anti-estrogenic effects in human beings. Extracted or synthesized soybean isoflavones have been discovered to diminish hot flush occurrence and seriousness. Nevertheless, a latest meta-analysis establishes that there is no convinced evidence that phytoestrogen supplements successfully reduced the frequency or severity of vasomotor symptoms in perimenopausal or climacteric women. A non-hormonal pharmacological possibility is selective serotonin-reuptake inhibitors (SSRIs) and serotonin-norepinephrine-reuptake inhibitors (SNRIs), which have been suggested as an option to MHT for treatment of hot flushes. SSRIs, (paroxetine, escitalopram, citalopram, and sertraline) have been proven and are helpful in falling both frequency and severity of hot flushes. Paroxetine appears to have the best evidence base of efficacy and was approved by FDA for the treatment of menopausal hot flushes. SNRIs (venlafaxine, desvenlafaxine) have been tried to treat menopausal symptoms, mainly in women in whom MHT is not indicated, and desvenlafaxine is approved for vasomotor symptoms associated to menopause in Mexico [23].

## 4. Menopause and hormones

Menopause is a period of life when the ovaries are depleted of oocytes and the cyclical action of gonadotrophins, peptides, and steroids is disappeared. Age at menopause reveals the complex networks of health and socioeconomic aspects involving ethnicity, diet, education, oral contraceptive use, weight, occupation, exposure to endocrine disturbing substances, alcohol consumption, smoking, and physical activity [27]. Menopause is an indicator event in a woman's life that marks the end of reproductive capability. Although the age-related loss of vaginal bleeding in women has been described throughout history has been recognized the dramatic reduction in the amount of follicles within the ovary as a function of age, determining that the loss of both germ cells and the hormone-producing cells that help them is critical to the disappearing of menstrual function in women. Menopause is identified by the final menstrual period (FMP), but this diagnosis can only be made

retrospectively after a year of amenorrhea and happens at an average age of 51 [28]. In Mexico, the average age is 47.6 [29].

The development of reproductive aging, though, is slow, starts before the FMP, and can be defined as limiting (1) an early phase in which compensatory modifications in the hypothalamus, hypophysis, and ovary facilitate the preservation of both reproductive capability and gonadal hormone secretion; (2) an interval categorized by clear irregularity in follicle progress, ovarian secretion, and resulting symptoms precede to the FMP; and (3) constant and low ovarian hormone secretion [28]. The menopause has important effects on the functions of endocrine, cardiovascular, skeletal, immune, and genitourinary systems. Gonadal hormones affect much of the processes mainly by their effects on steroid binding proteins and receptors, but the changes in lifestyle with aging are also influential [27]. Detailed ultrasonographic show the changes in ovulatory function with reproductive aging largely define the hormonal changes, menstrual cycle patterns, and symptomatology that occur as the FMP approach [30].

Reproductive aging in women is mainly produced by the continuing, and finally quickening deficit of ovarian follicles. The related decay in inhibin B secretion from the ovaries ends in the disappearing of negative feedback on FSH. Inside the ovary, FSH stimulated follicle growth and estrogen synthesis and secretion. With additional follicle loss, these compensatory hormonal processes are no longer enough and follicle development come to be irregular in advance to additional loss of ovarian function results in the stable but very low estradiol levels that exemplify the postmenopause [28].

Several of the biochemical variations at climacteric period are due to estrogen and or progesterone diminution. Both steroids act through cytoplasmic receptors and two receptors for respectively steroid, alpha, and beta (ER-α and ER-β; PR-α and PR-β) are now recognized, occasionally antagonize each other. Isoforms of every receptor be present that have dissimilar tissue expression conformations and purpose which marks gene expression in normal and tumor tissue, therefore ligand treatment. ER-α is largely expressed in reproductive tissues, breast, kidney, bone, adipose tissue, and liver. ER-β is existent in ovary, CNS, lung, colon, kidney, and immune system. PR-α and PR-β are almost equal in configuration with the exception of PR-β having a supplementary 164 amino acids at the N terminus. PR-α and PR-β are expressed similarly in human tissues [27].

The 2001 Stages of Reproductive Aging Workshop (STRAW) and the 2011 STRAW + 10 proposed nomenclature and a staging system for ovarian aging including menstrual and qualitative hormonal criteria to define each stage. The STRAW staging system is extensively considered in the gold standard for describing reproductive aging through menopause. The menopausal shift signs a stage of physiologic changes as patients get close to reproductive senescence. Proof endorses the clinical significance of the transition for many patients as a phase of progressive fluctuations in health and QoL (i.e., vasomotor symptoms, insomnia, and MDD) and longer-term variations in numerous physical consequences (i.e., urogenital symptoms, bone, and lipids) that might impact women's QoL and the probability of healthy aging. As a standardized staging scheme for reproductive aging, STRAW is a huge influence to patient's health investigation by giving trustworthy categorization of menopause status for investigations of midlife patients. Significantly, STRAW helped investigation that proposed to differentiate the health effects of ovarian versus somatic aging. The STRAW staging system also helps as a clinical instrument for women and their healthcare providers to monitor the valuation of fertility, contraceptive needs, and healthcare decision making [31].

STRAW distributed the adult female life into three extensive phases: reproductive, the menopausal transition, and postmenopause. The late reproductive

phase indicates the time when fecundability starts to decay and during which a woman might observe variations in her menstrual cycles. Given that significant endocrine factors start to change before obvious variations in menstrual cyclicity and that these endocrine fluctuations are crucial to fertility assessment. Early menopausal evolution is discernible by amplified inconsistency in menstrual cycle extent, conceptualized as a persistent difference of 7 days or more in the length of consecutive cycles. Persistence is defined as recurrence within 10 cycles of the first variable length cycle [31].

Cycles in the initial menopausal transition are also defined by high but varying early follicular phase FSH levels and low antimüllerian hormone (AMH) levels and antral follicle count (AFC). The late menopausal transition is apparent by the manifestation of amenorrhea of 60 days or longer. Menstrual cycles in the late menopausal transition are exemplified by augmented inconsistency in cycle length, severe changes in hormonal amounts, and elevated frequency of anovulation. In this stage, FSH levels are occasionally raised into the menopausal range and sporadically within the span typical of the initial reproductive years, mainly in relationship with elevated estradiol levels. The elaboration of international criteria and the accessibility to fundamental population-based information now allow the definition of quantitative FSH criteria, with levels greater than 25 IU/L in a random blood draw typical of being in late transition, founded on actual international pituitary criteria that approximate more than 40 IU/L in the earlier used urine-based gonadotropin standards. First-hand analyses should be initiated to verify this reference, and investigators and clinicians should prudently estimate the proper FSH value, subject on the test they employ. Founded on investigations of menstrual calendars and on changes in FSH and estradiol, this phase is expected to persist, on average, 1–3 years. Vasomotor symptoms are probable to be present during this phase. Novel data on the routes of change in mean levels of FSH and estradiol indicate that FSH continues to rise and that estradiol continues to decline until around 2 years after the FMP, after which the levels of each of these hormones stabilize. The late postmenopause characterizes the interval in which supplementary variations in reproductive endocrine function are more delimited and processes of somatic aging become of principal worry. Symptoms of vaginal dryness and urogenital atrophy become progressively more prevalent at this time. Nevertheless, several years after menopause, it has been perceived that there may be an added drop in levels of FSH in very old women; forthcoming investigations will be required to define whether a supplementary stage is necessary close to the end of life [31].

Investigations in younger and older climacteric patients insinuate that consequences of aging on the hypothalamus and pituitary are present and those are autonomous of the disappearance of steroid feedback. Following menopause there is a 30–40% reduction in LH and FSH between the ages of 50 and 75. Lie beneath these gonadotropin differences are intricate consequences of aging on GnRH secretion, with a 22% reduction in GnRH pulse frequency that is slightly balanced by a 14% rise in the total quantity of GnRH secreted over that owing to the deficit of ovarian function only. There are also age-related outcomes at the pituitary, with a 30% lessening in both LH and FSH responses to GnRH in older in comparison with younger climacteric patients. Estrogen-negative feedback at the hypothalamic point continues complete in older contrasted with younger postmenopausal patients; low-dose estrogen prescription is related with a substantial descent in circulating levels of LH, FSH, and free alpha-subunit and a parallel reduction in the total concentration of GnRH, with no effect on pulse frequency. Adding of progesterone diminished pulse frequency in younger and older climacteric patients with an associated reduction in total quantity of GnRH.

The outcome of estrogen-negative feedback on the LH response to GnRH is not predisposed by aging even though the FSH response to GnRH is weakened with aging. Numerous reports have proposed that sensitivity to estrogen-positive feedback may be absent with aging in women [28]. Hormone measurements other than FSH during the perimenopause are usually considered to be of little diagnostic value. The transition may take four or more years [27].

In the late perimenopause, where extended cycles (≥60 days) predominate, 60–70% cycles are anovulatory. Regarding the steroid hormone secretion patterns, when ovulatory cycles do happen, the cycle may seem normal, overlaid on one another or have a prolonged follicular phase named as a lag phase. While the initial perimenopause is considered by instabilities in the timing and regulation of ovulation, the advanced perimenopause is distinguished by rareness of ovulation derived to the original ovarian follicle reduction. In the late perimenopause, although AMH has decreased to imperceptible levels, inhibin B frequently persists measureable, particularly if there is still residual follicle function. Both gonadotropins are considerably high and show substantial cyclical differences. FSH amounts can be at their most irregular throughout the late perimenopause. The function that very low AMH amounts to participate in the interference of ovulatory function in the perimenopause continues indeterminate but given its close link with the total non-growing follicle (NGF) pool and primordial follicle recruitment and the intricacy of underlying follicle wave action, it is likely to be crucial [30]. In the initial 1–2 years after the FMP, intermittent follicle growth is obvious in single women. Harmonious with these studies, epidemiologic reports employing sensitive estradiol assays prove a farthest decrease from the FMP to the estradiol lowest point 2 years ahead. Subsequently, estradiol levels persist low and stable. FSH levels also continue steady between 2 and 8 years after the FMP but decay over time such that FSH drops by 30% by around age 75, as does LH. Nevertheless women are no longer concerned by irregular bleeding or breast tenderness, hot flashes may continue for up to 7 years after the FMP, and with lengthy hypoestrogenism, the genitourinary syndrome (GSM) of menopause may appear as a novel clinical symptom [28].

## 5. Menopause and associated health problems

The transition to menopause is characterized mainly by elevated levels of follicle-stimulating hormone (FSH) and low serum levels of estradiol, which gives rise to the presence of the characteristic symptoms (hot flashes, menstrual irregularities, sleep disruption, mood swings, headache, and genitourinary syndrome) [32]. 80% of women suffer physical and psychological symptoms throughout menopause with different degrees of seriousness and influence on QoL [4]. Clinicians and women usually identify the transition to menopause by the onset of menstrual irregularities [5, 6]. This period called perimenopause is variable but can range from 5 to 10 years before menopause.

The Study of Women's Health Across the Nation (SWAN) is a longitudinal, epidemiologic study designed to examine the physical, biological, psychological, and social changes during their intermediate years when they are suffering from menopausal transition that evaluated a total of 3302 women from different ethnic among 42 and 52 years old with a follow up for 15 years. The scientific areas of study assessed: bone mineral density and body composition, cardiovascular measures/risk factors, ovarian markers, vaginal, urogenital and sexual health, physical functioning, sleep quality, psychosocial factors, and epidemiologic factors. The results of this study contributed to define The Stages of Reproductive Aging Workshop (STRAW),

a staging system that categories reproductive life stages of adult women en three main categories: reproductive, menopausal transition, and postmenopause [33].

During the late reproductive year's, progesterone levels in the luteal phase decrease and the follicular phase is shortened from 14 to 10 days, including the decrease in inhibin B and a slight increase in FSH levels with preserved levels of estradiol, which gives rise to menstrual irregularities. The levels of antimüllerian hormone (AMH) and the count of antral ovarian follicles diminish too [32]. As time goes (around 2 years since last menstrual period), the FSH levels continue to rise and estradiol levels start falling and for the next 3–6 years estradiol, AMH and inhibin B levels are even lower, at this time is when the symptoms of genitourinary syndrome (GSM) could be more severe [32, 34, 35]. Contraception should be a part of any counseling during the menopausal transition due to the presence ovulatory cycles that can still occur until 12 months of amenorrhea have occurred [32].

The body mass index (BMI), lifestyle factor like tobacco use could influence the timing of the physiologic changes, but not in the path of change in bleeding patterns or hormonal levels with reproductive aging [31]. Some situations like the surgical menopause caused after a hysterectomy may not let us know when is the patient is in transition to menopause, the only way we could evaluate objectively this stage of life is by endocrine markers of ovarian aging, it is necessary to mention that 3 months after surgery high levels of transient FSH may occur, so for an accurate diagnosis, a new measurement of estradiol or serum FSH is required [36].

The bleeding patterns may not be a reliable parameter for evaluating reproductive aging owing to different endocrine disorders like polycystic ovarian syndrome or any other chronic illness or medications like cancer treatment among other situations that can also affect menstrual patterns or even cause amenorrhea [32]. It is well known that alkylating agents used as chemotherapeutic medication may lead to temporary elevated levels FSH and a decline of AMH and ovarian antral follicle count (AFC), but with time menstruation may resume [37–39]. Women in treatment with tamoxifen may also have altered hormone levels and abnormal bleeding patterns [40].

During this life stage period, serum cortisol levels also increases as well as adrenal androgen levels (androstenediol, dehydroepiandrosterone sulfate). In thyroid function for the moment, there is no information about disorders related to menopause so far [32]. After the cessation of ovarian function, the production of estrogen comes from the aromatization of androgens in the ovarian stroma and, in less quantity, from extragonadal sites mainly the adipose tissue. Hence, it is expected that obese women present vasomotor symptoms more frequently and/or intensively.

Hot flashes, which may be accompanied with some other symptoms like flushing of the face, neck, and upper chest; palpitations; chills; and/or anxiety are some of the vasomotor symptoms [32] that occurs in up to 80% of women, frequently associated with diminished sleep quality [41, 42] irritability, difficulty concentrating, reduced quality of life (QoL) [43], and poorer health status [35]. Some researchers are looking for the relationship with the presence of hot flashes with markers of cardiovascular risk, in order to identify a vulnerable vascular phenotype [44].

Of all possible etiologies of headache, tensional headache is the most common. Migraine-type headache can increase during menopause due to hormonal changes. Tensional-type headache usually shows a favorable response to non-steroidal therapy and can be prevented altogether with tricyclic antidepressants instead of hormonal therapy alone. Non-cyclical hormonal therapies are recommended to minimize headache due to hormonal treatment. Women who suffer migraine headache with aura or other risk factors of CVD can benefit from

progesterone-only therapy, like the levonorgestrel intrauterine system, etonogestrel subdermal implant, depo-medroxyprogesterone acetate, or progestin-only contraceptives [32].

The symptoms of genitourinary syndrome (GUS), which may comprise signs and symptoms associated to the hypoestrogenism of the menopause involving changes to the labia, vagina, urethra, and bladder and includes vulvovaginal atrophy [45]. Symptoms are genital dryness, burning, and/or irritation; sexual symptoms of diminished lubrication and pain; and urinary symptoms of urgency, dysuria, and recurrent urinary tract infections (UTIs) [35]. Signs include changes in the skin consequently of the reduction blood flow to the vagina and vulva, the external genitalia reveals less pubic hair and less elasticity of the vulvar skin with introital narrowing and possible changes in the architecture, such as the loss of the labia minora, usually we could appreciate this changes about 3 years after menopause, although approximately 20% of women may report some symptoms in the early or late transition of menopause [46]. Topical estrogen is the best treatment for the relief of vulvovaginal symptoms and current therapeutic therapy, among the options for topical administration include creams, gel, vaginal tablets, or even vaginal ring [34]; other therapeutic options are vaginal lubricants and moisturizers. It is necessary to mention that also systemic estrogen preparations with or without progesterone provide excellent vaginal therapy [32].

Low-dose vaginal estrogen preparations are effective and generally safe treatments in women with actual diagnosis or history of breast cancer and treatment with tamoxifen, that with the non-hormonal treatments did not present relief of the symptomatology, there is lees information about treatment with aromatase inhibitors, taking into account that vaginal estrogen preparations can be absorbed systemically in a minimal amount. Less data are available on the creams containing conjugated estrogens than on those containing 17B-estradiol [47].

Menopause is associated with an increase in skeletal, joint, and muscle symptoms [43]. Estrogen binds on estrogenic receptor on joint tissues, protecting their biomechanical structure and function and maintaining overall joint health, but the exact effect of estrogen on osteoarthritis remains controversial [48–50]. Arthralgias increase with age, also rheumatic disorders incidence has an augment. Women who are obese or depressed may have marked symptoms, nevertheless it seems to be an association with joint pain or stiffness and menopausal transition, these symptoms could be alleviated with estrogen therapy alone or with combination therapy of estrogen and progestin, women in the WHI and some other studies have shown less joint pain or stiffness compared with those on placebo [32, 51].

In 2010, it was estimated that 21% of women in the European Union between 50 and 84 years old have osteoporosis. Osteoporosis, along with osteoarthritis, sarcopenia, and frailty, is considered a part of the so-called musculoskeletal aging phenotype. Adverse outcomes such as falls, fractures, functional deterioration, and increased morbidity can impact quality of life. The clinical complications of osteoporosis are fractures of the hip, wrist, and vertebral bodies. Worldwide, 8.9 million fractures occur annually due to osteoporosis, resulting in a fragility fracture every 3 seconds, which is associated with pain and decreased physical and social function in menopausal women [52].

Cardiovascular disease (CVD) is main etiology responsible of mortality in postmenopausal population. Menopause, itself, increases the risk of CVD no matter the age [53]. There is evidence that the use of estrogenic therapy has beneficial effects in cardiovascular mortality in many ways, some of them includes the reduction diminish of low-density lipoproteins levels and increased levels of high-density lipoprotein as well as the improved endothelial function in the coronary vasculature [32].

The reanalysis of older studies such as the WHI study and the recent studies suggest that in case of no contraindication, the benefits of hormone therapy outweigh its risks, with fewer CVD events in younger versus older women [54].

Venous thromboembolism (VTE) has an augmented incidence when is related to the usage of hormonal therapies for menopause, it is supposed to increase twofold or threefold the risk, presenting a higher risk with oral formulations. Transdermal preparations of estrogen or estrogen and progestins combined and vaginal estrogen preparations did not appear to increase the risks of VTE [55]. In a meta-analysis of women who started HRT less than 10 years following menopause beginning or who were younger than 60 years, robust sign of augmented jeopardy of VTE was seen in the horn therapy group related to placebo (RR 1.74; 95% CI, 1.11–2.73) [56]. Minor doses of oral ET may give reduced VTE risk than higher doses [57], but related RCT evidence is requiring.

Talking about hormone therapy and breast cancer may result controversial, the effect of hormone therapy on breast cancer risk may depend on the type of the formulation, dose, and duration regimen, route of administration, prior exposure, and individual characteristics [35]. In the WHI study, the incidence of breast cancer increased in the estrogen-progestogen cohort and decreased in the estrogen-only and placebo groups. Contrarily, hormone therapy users had more localized tumors and improved survival rates [32]. The NAMS do not recommended the prescription of systemic hormone therapy for survivors of breast cancer, although selected cases may be discussed in conjunction with an oncologist after non-hormone options have been unsuccessful. If the patient refers moderate to severe GSM symptoms, low-dose vaginal estrogens, may be considered after a failed trial of non-hormone therapies and with consultation of the oncologist in charge of the case [35]. Options for symptom management include non-hormonal moisturizers, vaginal estrogens, androgens, selective modulators of the estrogen receptor (SERM).

The skin is another target where the hypoestrogenism may have manifestations after menopause, it is altered by epidermal and dermal thickness, decreased collagen and elastin content, consequently more laxity and wrinkles, many women could also experience hair loss. Estrogen therapy may benefit wound healing through modifying inflammation, stimulating granulation tissue formation, and accelerating re-epithelialization. In studies, ET increased epidermal and dermal thickness, increased collagen and elastin content, and improved skin moisture, with fewer wrinkles [58]. It may be relevant to perform scrutiny studies to those women with hair loss like thyroid function, serum iron, and androgens in order to exclude other pathologies [32].

Cholelithiasis, cholecystitis, and cholecystectomy occur more frequently in women who take oral estrogen, presumably because of the first-pass hepatic effect after oral ingestion, so systemic hormone therapy should be prescribed with caution in women with known gallbladder disease [32, 35]. Estrogens increase biliary cholesterol secretion and saturation, promote precipitation of cholesterol in the bile, and reduce gallbladder motility, with increased bile crystallization [59, 60]. The transdermal route of administration could be the best option for this kind of patients [61].

In epileptic patients, menopause can present at earlier age. The cause of this could be related to the number of crisis the woman presents during her life and the anticonvulsants she uses as treatment, specifically the ones that are metabolized by the hepatic enzyme cytochrome p450, which also affects estrogen levels. It is common that women with epilepsy present seizures during the menopausal transition due to the hormonal fluctuations. It is important to note that some anticonvulsants agents may accelerate the metabolism of vitamin D, which possibly increasing the risks of osteopenia [32].

## 6. Menopause and psychiatric disorders

One of the most consistent findings in psychiatry and psychology is that from menarche onwards females are at higher risk than males of developing both depressive and anxiety disorders. This sex difference remains robust throughout the lifespan, including old age, in the years beyond the reproductive period. The extensively reported link between puberty, the perinatal period, and menopause and excessive amounts of anxiety and depressive symptoms has directed several researchers to suggest the concept of reproductive-related disorders (RRDs). These psychiatric conditions are said to include a collection of disorders categorized by their connection to reproductive processes and a maladaptive response by patients defined as being "genetically vulnerable" to normal hormonal variations. Other authors have examined not only the validity of such a construct, but also with respect to menopause, whether the marked cross-cultural changes in menopausal symptoms support this hypothesis [62]. While most women do not suffer negative mood consequences during menopausal transition, the risk to develop a major depression disorder (MDD) or depressive symptoms throughout perimenopause is greater than in the premenopausal stage. Nevertheless, estimates from individual studies are diverse and hence the true risk estimate is unknown [63].

Depression (at both the symptom and the disease level) was related with poorer QoL, and that this link appeared to be stable over time. Getting better from MDD after treatment resulted in higher QoL, and the QoL improved even in patients who did not fully recover from the depressive episode. Since MDD affects QoL negatively irrespective of medical health, it is imperative to identify MDD and treat MDD patients. Consequently, it is importantly suggested that the health personnel in specialist and primary healthcare settings have a dual treatment perspective, including both psychological and physical health [64].

MDD is an incapacitating disorder, which frequently directs to substantial personal, societal, and economic costs. It affects 20% of adults in the US, and women are known for being overly more affected than men. The roots of such increased risk (2-fold on average) have been the subject of discussion and research from diverse perspectives—from epidemiology to genetics, from copying strategies to hormone variations. Windows of risk for MDD—also known as reproductive-related depressive episodes—are probable linked with an augmented sensitivity suffered by several women to variations in the hormonal situation that happen throughout the luteal phase of their cycles, in the course of the postpartum phase, and/or throughout the menopause transition [65]. The odds-on depressive symptoms in perimenopause are doubled when associated to the premenopause and similar when compared to the postmenopause. Furthermore, throughout the perimenopausal phase, women describe a higher level of depressive symptoms severity when compared to the premenopause but not to the postmenopause. Moreover, there are signs for a positive connexion between vasomotor complaints and MDD during the perimenopause [63]. The presence of a menopause-associated depression, though, has been a more discussed issue. While it is irrefutable that variations in sex hormones and metabolism may affect QoL and overall functioning among certain women throughout midlife years, supplementary aspects—not connected to the menopause transition—may also influence MDD at this stage in life, involving comorbid medical illnesses, cardiovascular complications, vasomotor symptoms (VMS), sleep disorders, and stressful life events [65].

It is suggested that declines in estrogen around menopause are associated with declines in cognitive functioning as well as increased risk of depressive symptoms

and depressive disorders. Estrogen promotes neuronal growth and survival and acts on the cholinergic system, which is closely linked to cognitive functioning, particularly memory. Several studies suggest that cognitive function supported by the prefrontal cortex may be particularly sensitive to estrogen. Estrogen also has a role in neurotransmitter systems involved in depression. For instance, estrogen acts as a serotonergic agonist/modulator by increasing receptor binding sites, synthesis, and uptake in animal models and postmenopausal women and numerous longitudinal studies have demonstrated an increased risk of depressed mood in the menopausal transition compared to the premenopausal stage. The peri- and post-menopausal phases are linked with declines in delayed verbal memory compared to premenopause. Moreover, the postmenopausal stage is linked with reductions in phonemic verbal fluency contrasted to perimenopause. Evidences propose that women are at a meaningfully augmented risk of getting MDD, as determined either by symptom inventory or by structured clinical interviews, in the peri- and post-menopausal stages than in premenopause [66].

The strengthened burden related with depression, at any point in time, is undisputable. Thus far, the existence and perseverance of symptoms of depression over time—symptoms that do not reunite criteria for MDD—may furthermore trigger anyway psychosocial difficulties and negatively impact total health. It is, consequently, significant that physicians maintain a tighter surveillance and regularly re-evaluate the necessity for treatments to resolve depressive symptoms (e.g., low mood, reduced psychological energy and pleasure with habitual activities, and sleep problems), whether by employing pharmacologic options, behavioral/lifestyle modifications, or supplementary alternatives. An important amount of both cross-sectional and prospective reports have discovered a possible relationship between different menopause staging and the risks for depressive symptoms or MDD (new onset or recurrent). In general, information from cross-sectional trials show that symptoms of depression can be found by up to 70% of patients throughout perimenopause contrasted with almost 30% in premenopausal period. Longitudinal studies can describe the ideal approach for evaluating the link between reproductive staging and MDD, have also proposed an augmented risk (1.5- to 3.0-fold) for symptoms of depression during the menopause transition. This augmented risk was documented even between women with no preceding episodes [65].

Longitudinal trials have acknowledged possibility reasons for the presence of midlife MDD that appear persistent during the lifetime; they establish a continuum of risk for MDD and very likely function as regulating aspects. These aspects can be considered as: (1) demographic or socioeconomic (i.e., unemployment, low education, and being black or Hispanic); (2) health-related (e.g., greater body mass index, being a smoker, reporting poor health, and decreased functioning due to chronic medical diseases); and (3) psychosocial (e.g., reduced social care, record of anxiety, and one or more stressful life events). A prior MDD episode signifies the robust prognosticator for MDD throughout midlife years, while antecedents of mood symptoms with a hormone-related background (i.e., history of premenstrual syndrome/PMDD or postpartum depression) have been discreetly related to MDD during the menopause phase and initial postmenopausal years [65].

Investigators also explored the causative role of timing-related, context-related influences. Once more, results from cross-sectional and longitudinal investigation were valued foundations and helped to recognize in facilitating or triggering elements linked to menopause-related MDD. These elements include:
(1) hormone changes (i.e., the occurrence of wider variations in follicle-stimulating hormone [FSH] and estradiol [E2] levels over time); (2) menopause-related

symptoms (e.g., existence and seriousness of VMS and insomnia); and (3) global health (current poor health and low functioning because long-lasting diseases). Psychosocial stressors (including poor social help and stressful life events—the latter not only considered by the severity and number of episodes but also founded on the timing of their manifestation linked to the menopause transition per se) [65].

Nevertheless, symptoms of MDD such as insomnia and low energy in midlife women may be challenging to differentiate from menopausal symptoms and may not often reveal an MDD. They might also be associated to symptoms of the menopause such as VMS. This is reliable with the results of investigations of depressive symptoms, which demonstrate that they are more frequent throughout the menopausal transition in comparison with both pre and postmenopausal stages. It is too reliable with the remark that depressive symptoms could growth around the postmenopausal phase as somatic symptoms progressively become less frequent and/or severe, and that they can improve with the management of central menopausal symptoms such as VMS [67]. Also, psychological aspects as inter-personal relations, role, and sociocultural factors are defined as predictors for MDD during menopause [63].

Antidepressants are the first-line management of MDD around midlife years, mainly for women who had suffered numerous MDD episodes before (not always hormone-related) and women describing serious symptoms, important functional harm, and/or communicating suicidal thoughts. For recurrent episodes, a prior response to a particular antidepressant (agent or class) must lead the main resolution on what to use initially. For women facing MDD for the first time, women who never received treatment before, or women with antecedents of partial/no response to antidepressants before, current evidence confirmed the efficacy and tolerability of numerous SSRIs and SNRIs at typical doses; there are trials on fluoxetine, sertraline, venlafaxine, citalopram, escitalopram, duloxetine, and desvenlafaxine [65]. In a recent published paper, data support further study of vortioxetine for treating menopausal depression and associated symptoms (VMS) and was generally well-tolerated [68].

The association between depression and menopause has been extensively explored, but the study of anxiety remains largely neglected. This is surprising, since symptoms of anxiety in the community are more common than those of depression, and generalized anxiety disorder (GAD) is the second most prevalent psychiatric disorder in the primary care setting [62]. Peri- and post-menopausal phases represent a window of risk for emergence of anxiety symptoms and disorders in the life cycle of adult women. Compared to MDD, anxiety symptoms and disorders remain mainly unknown throughout this period of a woman's life, regardless of major impact on QoL if not identified and treated [69]. 'Anxiety' is a general term that can opaque the important difference between anxiety symptoms and anxiety disorders. Anxiety includes various symptoms such as feeling on edge, worrying, specific fears, and physiological arousal, and these may be distressing to the patient. Anxiety disorders, however, are defined by reference to specific criteria, and have much lower prevalence than anxiety symptoms. Most of the investigations reviewed measured anxiety symptoms, rather than anxiety disorders. There are physical correspondences between anxiety symptoms, particularly panic attacks and VMS. These include increasing sensations of heat through the chest and head, palpitations, and sweating connected with increased metabolic rate and noradrenergic dysregulation. It is not clear, however, whether body sensations of anxiety come first VMS or vice versa. The up-to-date data based on large community-based investigations proposes that psychological

symptoms during the menopause transition are related with known risk factors for anxiety and MDD, including stressful life events. An additional cognitive aspect that could be significant for comprehending the link between anxiety and VMS is that of catastrophic thinking. It is well-known that catastrophic thinking has a negative effect on perceived symptom seriousness in chronic health diseases. Those who report increased catastrophic thoughts also be likely to register poorer perceived control over their hot flashes [62].

Investigation has showed that sleep problems are frequent in middle-aged women, among whom the frequency of sleep problems has been observed to elevate in the period between pre- to peri- and post-menopause. While the precise process causing the connexion between elevated sleep troubles and the development of menopause is not completely recognized, it is probably linked to establish relationship between sleep disturbances. It has been found that VMS and depressed mood at this period in a woman's life are closely related, women who suffer from VMS and sleep troubles, 30% of them were severely depressed. The results of one study were that the findings of this study show that difficulty in initiating sleep (DIS) is meaningfully connected with anxiety and non-restorative sleep (NRS) is meaningfully related with MDD in peri- and post-menopausal women in a clinical scenery. Those who describe suffering DIS or NRS may be highly probable to likewise be experiencing anxiety or MDD, correspondingly, signifying that management of these problems might increase the related insomnia symptoms in this group [70].

Multiple randomized controlled trials (RCTs) support the efficacy of SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs) as first-line treatments for anxiety disorders. An analysis of 12 RCTs in panic disorder found a mean effect size for SSRIs relative to placebo of 0.55. In the case of GAD, response rates for SSRIs of between 60 and 75% are generally reported in RCTs, compared to response rates between 40 and 60% for placebo. Data suggest that post-traumatic stress disorder (PTSD) may be less amenable to current pharmacotherapy compared to other anxiety disorders. A Cochrane review of pharmacotherapy for PTSD including 35 RCTs and 4597 participants did support the use of SSRIs as first-line medication treatment. The benzodiazepines (BZD) play a significant position in the management of several anxiety disorders; but, these drugs are commonly kept for second-line or accessory utilization because of their tolerability and abuse danger issues. BZD possess the benefit of a fast onset of action, tempting their employment premature in the process of management preceding to the onset of action of a co-administered SSRI/SNRI. Information backing the longer-term efficacy of BZD is more inadequate [71]. BZD inappropriate use (i.e., misuse and overuse) is a global public health concern. Regardless of existing information about augmented sensitivity to adverse effects in the elderly that should guide to additional carefulness. Only 30% of BZD prescriptions in these women are believed correct. The largely prevalent deficient conditions are disproportionate length and/or dosage of a medical prescription or self-medication, particularly in a situation where it would be contraindicated, for example, long-acting BZD in the elderly. Polypharmacy and comorbidities are the main risk factors. Results of benzodiazepines incorrect employment are falls, delirium and other cognitive dysfunction, acute respiratory failure, traffic accidents, abuse, addiction, and withdrawal symptoms. A developing apprehension is a possibly elevated risk of dementia. Opposing many physicians' idea, discontinuation of long time BZD use in elderly patients is achievable, with acceptable psychotherapeutic or pharmacological options, and can direct to long-term abstinence [72]. Anticonvulsants, including gabapentin and pregabalin, have mixed data to support efficacy in

certain anxiety disorders. The data for second-generation antipsychotics (SGAs) in anxiety disorders are likewise mixed [71].

## 7. Menopause and sexual disorders

Female sexual dysfunction (FSD) and QoL are both multidimensional and have a bidirectional relationship across the reproductive life span and beyond. Methodological difficulties exist in assessing the actual prevalence of FSD because it is difficult to define the level of distress related to sexual symptoms. Around 40–50% of women present at least one sexual symptom, and various disorders related with hormonal variations at menopause, such as vulvovaginal atrophy (VVA) and hypoactive sexual desire disorder (HSDD), have an important influence on sexual function and QoL. Sexual troubles reach a highest point at midlife, decay with age, and are importantly partner-associated [73].

Although in human's sexual drive and performance are to some degree untied from sex hormones, menopause is the most studied medical condition in the framework of FSD from a biological perspective since there is a strong state of hormonal deficiency. Both the substantial descent in blood estrogen levels with natural menopause and the androgen reduction with age and, ultimately, with surgical menopause, have been exposed to back, to a distinct degree, to sexual complains such as low desire, reduced excitement, dyspareunia, orgasm difficulties, and diminished sexual gratification. In contrast, menopause impacts psychologic and cognitive characteristics of sexuality throughout the variation in blood sex hormones, but this could be partially related on the particular antecedents of the specific patient. The mainly important factors are age, global and mental health, and attainment of reproductive objectives, education, body image, self-esteem, values and experiences. Even length and quality of relationship, and global and sexual health of the sexual partner, are significant [73].

Sexual health and function are important goals in the management of menopausal women. The majority of these women wants their sexuality to be a significant part of their life and intensely desire to maintain a healthy and satisfactory sexual life. Nevertheless, the risk of having a disease that negatively affects sexual satisfaction and function as well as the risk for using prescription drugs that have an adverse impact in sexual function increases as women age. Although sexual dissatisfaction and dysfunction are highly predominant in peri- and post-menopausal women, few reveal their concerns to the health care provider. Age-related declines in sexual function may meaningfully reduce QoL [74].

Sexual function decays throughout midlife. The Study of Women's Health Across the Nation and other related observed that this drop links with the menopausal period, including in women who experience hysterectomy. Though symptoms such as vaginal dryness rise during the same interval, variations in sexual functioning are unrelated of other symptoms linked to the menopausal period. Decrease in sexual frequency throughout this period of life is multifactorial. One main factor that women do not participate in sexual activity is absence of a sexual partner. Women who are more sexually active previously menopause appear to remain to participate in sexual behaviors during midlife, even with reduced "functional sex." Lifestyle situations, including enough sleep and exercise, contribute to better sexual functioning during midlife [75, 76].

Vulvovaginal atrophy (VVA) is an important factor of genitourinary syndrome of menopause (GSM) and can end in postcoital vaginal bleeding, vaginal burning, irritation, and pain and distress with sexual behavior. Symptomatic GSM is frequently associated by reduced secretions from vulvar sebaceous glands and

decreased vaginal lubrication during sexual arousal. Hypo-estrogenic climacteric patients frequently face a change of the vaginal microbiome from lactic acid-producing lactobacilli to gram-negative and -positive bacteria. This change in the vaginal microbiome causes raising of the vaginal pH, local immune changes, and increased cytokine synthesis, which exacerbates symptoms of vaginal dryness and burning and raise the risk of sexual dysfunctions.

Pelvic organ prolapses (POP) consist of descent of one or more woman reproductive organs (anterior and/or posterior vaginal wall, the uterus or the apex of the vagina). The occurrence of pelvic floor relaxation rises with elderly and is theorized to appear from a mixture of connective tissue degradation, pelvic denervation, and devascularization, all of which prompt to prolapse. Dyspareunia, chronic pelvic pain, and poor self-image are related with POP. All of these undesirable physical alterations can destroy sexual desire and performance. Many medical problems, like diabetes, hypertension, and breast cancer, and their treatments, have been related with female sexual dysfunction. These conditions become more common as women move through midlife. Other medications have been associated with FSD. Among the most common responsible factors is the use of antidepressants. Although MDD itself is associated with sexual dysfunction, odds of sexual dysfunction are 4–6 times higher for women taking an antidepressant. Sexual side effects are less common with bupropion and mirtazapine [75].

The presence of MDD and anxiety symptoms during the menopausal period is frequent. Mood disorders and sexual dysfunction are significantly comorbid, with 25–75% of depressed women reporting sexual symptoms even when treating for other problems. It is important for health personnel to screen women with sexual complaints for MDD and anxiety disorders and be aware of that not all women with FSD have a MDD or an anxiety disorder. Common life stressors also have an undesirable influence. Midlife women may be look after for children of their own, may have adult offspring at home, and/or may attend to aging parents. Job-associated stress and economic worries are also frequent. Health personnel must be familiar to the costs of life stressors and convince patients to cultivate stress diminution approaches, like mindfulness meditation or exercise.

Patients who suffered or are victims of violence and abuse are at augmented risk for FSD, with those who suffered sexual abuse, up to 44% of women over their lifetime, at predominantly elevated jeopardy. The link between abuse antecedent and FSD is not totally explicated by psychiatric disorders, such as MDD, anxiety, and post-traumatic stress disorder (PTSD). It is significant to utilize evidence-based, trauma-informed management tools to ask for these experiences when treating patients with FSD. Helping women preserve healthy sexual function with aging is a crucial element of preserving QoL into older adulthood [75].

## Author details

César Velasco-Téllez*, Manuel Cortés-Bonilla, Guillermo Ortiz-Luna, Linda Sánchez-Zelayeta, Horacio Méndez-Serrano, Cinthya Salazar-Jiménez, Abraham Zavala-García and Alicia Sánchez-Cevallos
National Institute of Perinatology "Isidro Espinosa de los Reyes", Mexico City, Mexico

*Address all correspondence to: cesar.velasco@inper.gob.mx

## References

[1] Schneider HPG, Birkhäuser M. Quality of life in climacteric women. Climacteric. 2017;**20**:1-8. DOI: 10.1080/13697137.2017.1279599

[2] Ceylan B, Özerdoğan N. Menopausal symptoms and quality of life in Turkish women in the climacteric period. Climateric. 2014:1-8. DOI: 10.3109/13697137.2014.929108

[3] Potter B, Schrager S, Dalby J, Torell E, Hampton A. Menopause. Primary Care; Clinics in Office Practice. 2018;**45**: 625-641. DOI: 10.1016/j.pop.2018.08.001

[4] McKinlay SM, Jefferys M. The menopausal syndrome. British Journal of Preventive & Social Medicine. 1974;**28**:108-115

[5] Freeman EW, Sammel MD, Lin H, Gracia CR, Pien GW, Nelson DB, et al. Symptoms associated with menopausal transition and reproductive hormones in midlife women. Obstetrics & Gynecology. 2007;**110**(2 Pt 1):230-240

[6] Freeman EW, Sammel MD, Grisso JA, Battistini M, Garcia-Espagna B, Hollander L. Hot flashes in the late reproductive years: Risk factors for african american and caucasian women. Journal of Women's Health & Gender-Based Medicine. 2001;**10**:67-76. DOI: 10.1089/152460901750067133

[7] Freedman RR. Physiology of hot flashes. American Journal of Human Biology. 2001;**13**:453-464

[8] Kronenberg F. Hot flashes: Epidemiology and physiology. Annals of the New York Academy of Sciences. 1990;**592**:52-86. Discussion 123-33

[9] Freeman EW, Sammel MD, Lin H, Liu Z, Gracia CR. Duration of menopausal hot flashes and associated risk factors. Obstetrics and Gynecology. 2011;**117**(5):1095-1104. DOI: 10.1097/AOG.0b013e318214f0de

[10] Avis NE, Crawford SL, Greendale G, Bromberger JT, Everson-Rose SA, Gold EB, et al. Study of Women's Health Across the Nation (SWAN). Duration of menopausal vasomotor symptoms over the menopause transition. JAMA Internal Medicine. 2015;**175**(4):531-539. DOI: 10.1001/jamainternmed.2014.8063

[11] Gracia CR, Sammel MD, Freeman EW, Lin H, Langan E, Kapoor S, et al. Defining menopause status: Creation of a new definition to identify the early changes of the menopausal transition. Menopause. 2005;**12**(2):128-135. DOI: 10.1097/01.GME.0000141980.81159.B2

[12] Nelson DB, Sammel MD, Freeman EW, Lin H, Gracia CR, Schmitz KH. Effect of physical activity on menopausal symptoms among urban women. Medicine and Science in Sports and Exercise. 2008;**40**(1):50-58

[13] Greendale GA, Gold EB. Lifestyle factors: Are they related to vasomotor symptoms and do they modify the effectiveness or side effects of hormone therapy? The American Journal of Medicine. 2005;**118**(Suppl. 12B):148-154

[14] Munro MG, Critchley HO, Broder MS, Fraser IS; FIGO Working Group on Menstrual Disorders (2011) FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in non gravid women of reproductive age. International Journal of Gynecology and Obstetrics. 2011;**113**:3-13

[15] American College of Obstetricians and Gynecologists. ACOG committee opinion No. 440: The role of Transvaginal ultrasonography in the evaluation of postmenopausal bleeding. Obstetrics and Gynecology. 2009;**114**(2 Pt 1):409-411

[16] Lumsden MA. The NICE guideline menopause: Diagnosis and management. Climacteric. 2016;**19**(5):426-429. DOI: 10.1080/13697137.2016.1222483

[17] FSRH Clinical Effectiveness Unit. FSRH Guideline Contraception for Women Aged Over 40 Years. August 2017 (Updated October 2017)

[18] Power M, Kuyken W. The World Health Organization quality of life assessment (WHOQOL): Development and general psychometric properties. Social Science & Medicine. 1998;**46**(12):1569-1585

[19] Ceylan B, Özerdoğan N. Menopausal symptoms and quality of life in Turkish women in the climacteric period. Climacteric. 2014;**17**(6):705-712. DOI: 10.3109/13697137.2014.929108

[20] Utian WH. Psychosocial and socioeconomic burden of vasomotor symptoms in menopause: A comprehensive review. Health and Quality of Life Outcomes. 2005;**3**:47. DOI: 10.1186/1477-7525-3-47

[21] Ghazanfarpour M, Abdolahian S, Zare M, Shahsavari S. Association between anthropometric indices and quality of life in menopausal women. Gynecological Endocrinology. 2013;**29**(10):917-920. DOI: 10.3109/09513590.2013.819078

[22] Woods NF. Quality of life, menopause, and hormone therapy: An update and recommendations for future research. Menopause. 2018;**25**(7):713-720. DOI: 10.1097/GME.0000000000001114

[23] Mintziori G, Lambrinoudaki I, Goulis DG, Ceausu I, Depypere H, Erel CT, et al. EMAS position statement: Non-hormonal managementof menopausal vasomotor symptoms. Maturitas. 2015;**81**(3):410-413. DOI: 10.1016/j.maturitas.2015.04.009

[24] Blümel JE, Castelo-Branco C, Chedraui PA, Binfa L, Dowlani B, Gómez MS, et al. Patients' and clinicians' attitudes after the women's health initiative study. Menopause. 2004;**11**(1):57-61. DOI: 10.1097/01.GME.0000075503.60230.61

[25] Cortés-BonillaM,Bernardo-EscuderoR, Alonso-Campero R, Francisco-Doce MT, Hernández-ValenciaM,Celis-GonzálezC, et al. Treatment of menopausal symptoms with three low-dose continuous sequential 17β-estradiol/ progesterone parenteral monthly formulations using novel non-polymeric microsphere technology. Gynecological Endocrinology. 2015;**31**(7):552-559. DOI: 10.3109/09513590.2015.1019853

[26] Cortés-Bonilla M, Alonso-Campero R, Bernardo-Escudero R, Francisco-DoceMT,Chavarín-GonzálezJ, Pérez-Cuevas R, et al. Improvement of quality of life and menopausal symptoms in climacteric women treated with low-dose monthly parenteral formulations of non-polymeric microspheres of 17β-estradiol/ progesterone. Gynecological Endocrinology. 2016;**32**(10):831-834. DOI: 10.1080/09513590.2016.1183628

[27] Honour JW. Biochemistry of the menopause. Annals of Clinical Biochemistry. 2018;**55**(1):18-33. DOI: 10.1177/0004563217739930

[28] Hall JE. Endocrinology of the menopause. Endocrinology and Metabolism Clinics of North America. 2015;**44**(2015):485-496. DOI: 10.1016/j.ecl.2015.05.010

[29] Blümel JE, Chedraui P, Calle A, Bocanera R, Depiano E, Figueroa-Casas P, et al. Age at menopause in Latin America. Menopause. 2006;**13**(4):706-712. DOI: 10.1097/01.gme.0000227338.73738.2d

[30] Hale GE, Robertson DM, Burger HG. The perimenopausal woman: Endocrinology and management. The Journal of Steroid Biochemistry and Molecular Biology. 2014;**142**:121-131. DOI: 10.1016/j.jsbmb.2013.08.015

[31] Harlow SD, Gass M, Hall JE, Lobo R, Maki P, Rebar RW, et al. STRAW + 10

Collaborative Group Executive summary of the stages of reproductive aging workshop + 10: Addressing the unfinished agenda of staging reproductive aging. The Journal of Clinical Endocrinology and Metabolism. 2012;**97**(4):1159-1168. DOI: 10.1210/jc.2011-3362

[32] Bacon JL. The menopausal transition. Obstetrics and Gynecology Clinics of North America. 2017;**44**(2):285-296. DOI: 10.1016/j.ogc.2017.02.008

[33] Sowers M, Crawford S, Sternfeld B, Morganstein D, Gold E, Greendale G, et al. SWAN: A multi-center, multi-ethnic, community-based cohort study of women and the menopausal transition. In: Lobo RA, Kelsey J, Marcus R, editors. Menopause: Biology and Pathobiology. San Diego: Academic Press; 2000. pp. 175-188. ISBN 0124537901, 9780124537903

[34] Lethaby A, Ayeleke RO, Roberts H. Local oestrogen for vaginal atrophy in postmenopausal women. Cochrane Database of Systematic Reviews. 2016;(8):CD001500. DOI: 10.1002/14651858.CD001500.pub3

[35] The NAMS 2017 Hormone Therapy Position Statement Advisory Panel. The 2017 hormone therapy position statement of the North American Menopause Society. Menopause. 2017;**24**(7):728-753. DOI: 10.1097/GME.0000000000000921

[36] Qu X, Cheng Z, Yang W, Xu L, Dai H, Hu L. Controlled clinical trial assessing the effect of laparoscopic uterine arterial occlusion on ovarian reserve. Journal of Minimally Invasive Gynecology. 2010;**17**(1):47-52. DOI: 10.1016/j.jmig.2009.10.001

[37] Broekmans FJ, Soules MR, Fauser BC. Ovarian aging: Mechanisms and clinical consequences. Endocrine Reviews. 2009;**30**(5):465-493. DOI: 10.1210/er.2009-0006

[38] Irene Su H, Sammel MD, Green J, Velders L, Stankiewicz C, Matro J, et al. Antimullerian hormone and Inhibin B are hormone measures of ovarian function in late reproductive-aged breast cancer survivors. Cancer. 2010;**116**(3):592-599. DOI: 10.1002/cncr.24746

[39] Sukumvanich P, Case LD, Zee KV, Singletary SE, Paskett ED, Petrek JA, et al. Incidence and time course of bleeding after long-term amenorrhea after breast cancer treatment. Cancer. 2010;**116**(13):3102-3111. DOI: 10.1002/cncr.25106

[40] Welt CK, Pagan YL, Smith PC, Rado KB, Hall JE. Control of follicle-stimulating hormone by estradiol and the Inhibins: Critical role of estradiol at the hypothalamus during the luteal-follicular transition. The Journal of Clinical Endocrinology and Metabolism. 2003;**88**(4):1766-1771. DOI: 10.1210/jc.2002-021516

[41] Randolph JF Jr, Sowers M, Bondarenko I, Gold EB, Greendale GA, Bromberger JT, et al. The relationship of longitudinal change in reproductive hormones and vasomotor symptoms during the menopausal transition. The Journal of Clinical Endocrinology and Metabolism. 2005;**90**(11):6106-6112. DOI: 10.1210/jc.2005-1374

[42] Thurston RC, Joffe H. Vasomotor symptoms and menopause: Findings from the study of women's health across the nation. Obstetrics and Gynecology Clinics of North America. 2011;**38**(3):489-501. DOI: 10.1016/j.ogc.2011.05.006

[43] Nelson HD. Menopause. Lancet. 2008;**371**(9614):760-770. DOI: 10.1016/S0140-6736(08)60346-3

[44] Thurston RC, Chang Y, Barinas-Mitchell E, Jennings JR, Landsittel DP, Santoro N, et al. Menopausal hot flashes and

carotid intima media thickness among midlife women. Stroke. 2016;**47**(12):2910-2915. DOI: 10.1161/STROKEAHA.116.014674

[45] Portman DJ, Gass ML, Vulvovaginal Atrophy Terminology Consensus Conference Panel. Genitourinary syndrome of menopause: New terminology for vulvovaginal atrophy from the International Society for the Study of Women's sexual health and the north American menopause society. Menopause. 2014;**21**(10):1063-1068. DOI: 10.1097/GME.0000000000000329

[46] Tang MX, Jacobs D, Stern Y, Marder K, Schofield P, Gurland B, et al. Effect of oestrogen during menopause on risk and age at onset of Alzheimer's disease. Lancet. 1996;**348**(9025):429-432

[47] ACOG committee opinion No. 659: The use of vaginal oestrogen in women with a history of oestrogen dependent breast cancer. Obstetrics and Gynecology. 2016;**127**:e93-e96

[48] Xiao Y-P, Tian F-M, Dai M-W, Wang W-Y, Shao L-T, Zhang L. Are oestrogen-related drugs new alternatives for the management of osteoarthritis? Arthritis Research & Therapy. 2016;**18**:151. DOI: 10.1186/s13075-016-1045-7

[49] de Klerk BM, Schiphof D, Groeneveld FP, Koes BW, van Osch GJ, van Meurs JB, et al. Limited evidence for a protective effect of unopposed oestrogen therapy for osteoarthritis of the hip: A systematic review. Rheumatology. 2009;**48**(2):104-112. DOI: 10.1093/rheumatology/ken390

[50] Watt FE. Hand osteoarthritis, menopause and menopausal hormone therapy. Maturitas. 2015;**83**:13-18. DOI: 10.1016/j.maturitas.2015.09.007

[51] Barnabei VM, Cochrane BB, Aragaki AK, Nygaard I, Williams RS, McGovern PG, et al. Women's Health Initiative Investigators. Menopausal symptoms and treatment related effects of oestrogen and progestin in the women's health initiative. Obstetrics and Gynecology. 2005;**105**(5 Pt 1):1063-1073. DOI: 10.1097/01.AOG.0000158120.47542.18

[52] Ciubean AD, Ungur RA, Irsay L, Ciortea VM, Borda IM, Onac I, et al. Health related quality of life in Romanian postmenopausal women with osteoporosis and fragility fractures. Clinical Interventions in Aging. 2018;**13**:2465-2472. DOI: 10.2147/CIA.S190440

[53] LaCroix AZ, Chlebowski RT, Manson JE, Aragaki AK, Johnson KC, Martin L, et al. WHI Investigators. Health outcomes after stopping conjugated equine oestrogens among postmenopausal women with prior hysterectomy: A randomized controlled trial. Journal of the American Medical Association. 2011;**305**(13):1305-1314. DOI: 10.1001/jama.2011.382

[54] Manson JE, Chlebowski RT, Stefanick ML, Aragaki AK, Rossouw JE, Prentice RL, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the women's health initiative randomized trials. JAMA. 2013;**310**(13):1353-1368. DOI: 10.1001/jama.2013.278040

[55] Bergendal A, Kieler H, Sundström A, Hirschberg AL, Kocoska-Maras L. Risk of venous thromboembolism associated with local and systemic use of hormone therapy in peri-and postmenopausal women and in relation to type and route of administration. Menopause. 2016;**23**(6):593-599. DOI: 10.1097/GME.0000000000000611

[56] Boardman HMP, Hartley L, Eisinga A, Main C, Roqué i Figuls M, Bonfill Cosp X, et al. Hormone therapy for preventing cardiovascular disease in post-menopausal women.

Cochrane Database of Systematic Reviews. 2015;(3):CD002229. DOI: 10.1002/14651858.CD002229.pub4

[57] Speroff L. Transdermal hormone therapy and the risk of stroke and venous thrombosis. Climacteric. 2010;**13**(5):429-432. DOI: 10.3109/13697137.2010.507111

[58] Emmerson E, Hardman MJ. The role of estrogen deficiency in skin ageing and wound healing. Biogerontology. 2012;**13**:3-20. DOI: 10.1007/s10522-011-9322-y

[59] Everson GT, McKinley C, Kern F Jr. Mechanisms of gallstone formation in women. Effects of exogenous estrogen (Premarin) and dietary cholesterol on hepatic lipid metabolism. The Journal of Clinical Investigation. 1991;**87**(1):237-246. DOI: 10.1172/JCI114977

[60] Cirillo DJ, Wallace RB, Rodabough RJ, Greenland P, LaCroix AZ, Limacher MC, et al. Effect of estrogen therapy on Gallblader disease. Journal of the American Medical Association. 2005;**293**(3):330-339

[61] Marjoribanks J, Farquhar C, Roberts H, Lethaby A, Lee J. Long-term hormone therapy for perimenopausal and postmenopausal women. Cochrane Database of Systematic Reviews. 2017;(1):CD004143. DOI: 10.1002/14651858.CD004143.pub5

[62] Bryant C, Judd FK, Hickey M. Anxiety during the menopausal transition: A systematic review. Journal of Affective Disorders. 2012;**139**(2):141-148. DOI: 10.1016/j.jad.2011.06.055

[63] de Kruif M, Spijker AT, Molendijk ML. Depression during the perimenopause: A meta-analysis. Journal of Affective Disorders. 2016;**206**:174-180. DOI: 10.1016/j.jad.2016.07.040

[64] Sivertsen H, Bjørkløf GH, Engedal K, Selbæk G, Helvik AS. Depression and quality of life in older persons: A review. Dementia and Geriatric Cognitive Disorders. 2015;**40**(5-6):311-339. DOI: 10.1159/000437299

[65] Soares CN. Depression and menopause: Current knowledge and clinical recommendations for a critical window. The Psychiatric Clinics of North America. 2017;**40**(2):239-254. DOI: 10.1016/j.psc.2017.01.007

[66] Weber MT, Maki PM, McDermott MP. Cognition and mood in perimenopause: A systematic review and meta-analysis. The Journal of Steroid Biochemistry and Molecular Biology. 2014;**142**:90-98. DOI: 10.1016/j.jsbmb.2013.06.001

[67] Judd FK, Hickey M, Bryant C. Depression and midlife: Are we overpathologising the menopause? Journal of Affective Disorders. 2012;**136**(3):199-211. DOI: 10.1016/j.jad.2010.12.010

[68] Freeman MP, Cheng LJ, Moustafa D, Davies A, Sosinsky AZ, Wang B, et al. Vortioxetine for major depressive disorder, vasomotor, and cognitive symptoms associated with the menopausal transition. Annals of Clinical Psychiatry. 2017;**29**(4):249-257

[69] Siegel AM, Mathews SB. Diagnosis and treatment of anxiety in the aging woman. Current Psychiatry Reports. 2015;**17**:93. DOI: 10.1007/s11920-015-0636-3

[70] Terauchi M, Hiramitsu S, Akiyoshi M, Owa Y, Kato K, Obayashi S, et al. Associations between anxiety, depression and insomnia in peri- and postmenopausal women. Maturitas. 2012;**72**(1):61-65. DOI: 10.1016/j.maturitas.2012.01.014

[71] Murrough JW, Yaqubi S, Sayed S, Charney DS. Emerging drugs for the treatment of anxiety. Expert Opinion on

Emerging Drugs. 2015;**20**(3):393-406. DOI: 10.1517/14728214.2015.1049996

[72] Airagnes G, Pelissolo A, Lavallée M, Flament M, Limosin F. Benzodiazepine misuse in the elderly: Risk factors, consequences, and management. Current Psychiatry Reports. 2016;**18**(10):89. DOI: 10.1007/s11920-016-0727-9

[73] Nappi RE, Cucinella L, Martella S, Rossi M, Tiranini L, Martini E. Female sexual dysfunction (FSD): Prevalence and impact on quality of life (QoL). Maturitas. 2016;**94**:87-91. DOI: 10.1016/j.maturitas.2016.09.013

[74] Thornton K, Chervenak J, Neal-Perry G. Menopause and sexuality. Endocrinology and Metabolism Clinics of North America. 2015;**44**(3):649-661. DOI: 10.1016/j.ecl.2015.05.009

[75] Thomas HN, Neal-Perry GS, Hess R. Female sexual function at midlife and beyond. Obstetrics and Gynecology Clinics of North America. 2018;**45**(4):709-722. DOI: 10.1016/j.ogc.2018.07.013

[76] Avis NE, Colvin A, Karlamangla AS, Crawford S, Hess R, Waetjen LE, et al. Change in sexual functioning over the menopausal transition: Results from the study of women's health across the nation. Menopause. 2017;**24**(4):379-390. DOI: 10.1097/GME.0000000000000770