

Long-Term Consequences of Menopause

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Article Info

Received: January 03, 2021

Accepted: January 11, 2021

Published: January 18, 2021

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Citation: Vargas Hernandez V M. "Long-Term Consequences of Menopause". International Journal of Clinical Gynaecology and Obstetrics, 2(1); DOI: <http://doi.org/03.2021/1.1005>.

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Abstract

The dramatic changes in sex hormone levels that occur during the transition to menopause and beyond are responsible for the long-term consequences, which are of primary importance to healthy aging in women. Sex hormones have a vital physiological role in maintaining the health and normal functioning of various organs; like bone, heart and brain. Disease activity is highly dependent on estrogen exposure; cardiovascular and musculoskeletal disorders frequently occur during postmenopause. Even cognitive decline is related to hypoestrogenism during the menopausal transition. Several lines of evidence indicate that the presence, duration and severity of menopausal vasomotor symptoms, especially hot flashes, not only have an impact on quality of life, but are biomarkers of increased risk of chronic conditions, which require prevention strategies, including menopausal hormone therapy. Nutrition, exercise, and other lifestyle measures, use of appropriate hormonal treatments in symptomatic women during the "window" of opportunity (under 60 years or within 10 years after menopause) can significantly counteract the process of aging of the female body. Meanwhile an individualized menopausal hormone therapy helps postmenopausal women overcome the burden of symptoms, including those related to Genitourinary Menopause Syndrome.

Key Words: Aging, Osteoporosis; Fractures; Metabolic síndrome; Diabetes; Cardiovascular risk; Cognition; Dementia; Quality of life; Genitourinary menopause síndrome

Background

The current classification system for the stages of reproductive aging, STRAW + 10, is validated to identify when reproductive aging begins and to try to separate the effect of menopause on women's health from the senescence process. Menopause means the date of the last menstruation (LMP), which corresponds to the absence of menstruation for at least 12 months, neuroendocrine phenomena associated with reproductive aging begin long before LMP, the menopause transition (MT), that is variable and lasts up to 10 years. Early postmenopause represents the period of endocrine difference from menopause with increased high follicle stimulating hormone (FSH) and low estradiol (E2) levels and stabilizes, lasts 5 to 8 years, MT is quite long with symptoms and signs that depend on a wide range of biopsychosocial determinants, which are under investigation [1,2].

Menopause occurs between 48 and 52 years of age with little geographic variation, possibly reflecting genetic and climatic factors. Entering menopause at a certain point in life has been an advantage to humans, and the long-term consequences of ovarian depletion have been less apparent until recently. [3]. Today, in developed countries, women expect survive more than 30 years after spontaneous menopause and can manifest a number of pathological conditions associated with decreased estrogen production [4]. The complex interaction between genetics and epigenetic factors are responsible for the negative health impact of menopause. The evidence that menopause accelerates biological aging, especially it occurs prematurely [5,6]. The deprivation of androgens, produced by both ovaries and adrenal glands contribute to the deterioration of health, including bone, metabolism, cardiovascular system and cognitive performances, sexual function and quality of life [7], the impact of the symptoms of menopause on The chronic conditions that



occur in MT and later in menopause, the long-term consequences, are separated from the short-term ones, including the common symptoms observed around LMP, such as vasomotor symptoms (VMS), hot flashes, changes in sleep, adverse mood and vaginal dryness, and long-term consequences of hypoestrogenism and, reduction of androgens. Even aging itself contributes to long-term manifestations such as osteoporosis, increased cardiovascular disease and cognitive decline, changes related to menopause significantly reflect the individual pattern of health improvements in a wide range of mechanisms [2,4], there is a link between short and long-term consequences of menopause, which implies the presence, duration and severity of symptoms that are "red flags" for medical care for special care of symptomatic women [6]; addressing VMS, particularly hot flashes, is not only to improve quality of life but to prevent risk of cardiovascular disease, osteoporosis and cognitive impairment [6]. If these conditions coexist as a common marker of a multi-organ response to changes in sex hormones or, alternatively, some etiopathogenic mechanisms involved in VMS that influence long-term sequelae. Symptoms, such as sleep disorders and mood swings, are part of the menopausal syndrome and are risk factors for cardiovascular and cognitive problems. [4]. In general, there is a "window" of opportunity to establish preventive strategies for future healthy longevity through proper treatment of women. Hormone therapy for menopause has shown a benefit than a risk in those women with moderate to severe symptoms, less than 60 years of age or within 10 years of menopause (with an age range of 50 to 64 years). In women with premature menopause, Hormone therapy for menopause is indicated up to the time that LMP occurs. [8]. Even vaginal dryness has clearly been associated with hypoestrogenism during and after MT, hot flashes can occur early in the LMP time. Vaginal dryness is the cardinal symptom of vulvovaginal atrophy, or genitourinary syndrome of menopause (GSM). [9]; chronic conditions that progress due to the deficiency of sex hormones, chronological aging, and medical morbidity [10], with great impact on sexual function and quality of life in post-reproductive life. The presence and severity of vaginal dryness at menopause represents an early biomarker of long-term pathological conditions associated with GSM

Bone health

MT is a critical period of change in bone health, there is acceleration of bone loss depending on age, for the development of osteoporosis and susceptibility to fractures in older women. Changes in estradiol and follicle-stimulating hormone (FSH) levels during MT related to changes in bone mass with a rate of decrease in white women of 2.5% per year in the lumbar spine and 1.8% per year in the femoral neck. In women (50 to 79 years). With moderate / severe VMS she had lower BMD (in the femoral neck and lumbar spine) and increased rates of hip fractures during more than 8 years of follow-up compared with women without VMS [11]. Estrogen deficiency causes decreased bone mineral density (BMD) and alterations in bone microarchitecture. Estrogens stimulate osteoblast proliferation and differentiation, cessation and mineralization of the bone matrix by binding isoforms of the estrogen receptor alpha ER- α and ER- β ; induce apoptosis in osteoclasts, and their absence results in an environment of pro-inflammatory cytokines with increased oxidative stress, which further induces bone resorption, and

explains the link with hot flashes [12]. Circulating levels of bone resorption markers, such as N-Type 1 collagen telopeptide, type 1 collagen C-terminal telopeptide, and pyridinoline crosslinks increase 90% after menopause, while bone marker formation increases 45% [13]. About 3 years of LMP, a rapid phase of bone loss is the result of the imbalance of bone remodeling with a greater increase in the level of osteoclast-mediated bone resorption than osteoblast-mediated bone formation. BMD begins to decline 1 year before LMP and continues to decline in early postmenopause, with a slight reduction in the rate of loss about 2 years after LMP. The trabecular bone thins and there the connectivity is lost, with the reduction of the load capacity.

There is less rapid cortical bone loss in long bones and vertebrae after menopause, and after 10 years, age-related bone loss is slower, becomes prominent, and continues for the rest of life. At the age of 50 years, the lifetime risk of hip fracture is 15% and vertebral deformity is 25%, many fractures occur in postmenopausal women with normal or slightly reduced BMD indicating that many other additional risk factors are important. Race/ethnicity, low socioeconomic status, obesity, diabetes, certain types of drugs (psychoactive agents, angiotensin converting enzyme inhibitors, thyroid replacement, etc.), smoking, and low vitamin D intake are associated with increased risk of fracture [12]. Osteoarthritis is affected by hypoestrogenism with a significant increase in deformity and pain because estrogens are directed to cartilage, periarticular bone, synovial lining, ligaments and joint capsule. A special group of women are those with ER-positive early breast cancer, who start adjuvant endocrine therapy with aromatase inhibitors in postmenopause or selective estradiol receptor modulators such as tamoxifen in premenopause due to accelerated bone loss and increased risk of fracture [14].

At the onset of menopause, assessing the subsequent risk of fracture is not easy and screening tools are not accurate to identify who will fracture in the next 10 years. A history of previous fracture and low bone mineral density; the only important predictors for fracture risk; for the detection of osteoporosis during the "window of opportunity" recommends using the fracture risk assessment (FRAX) to estimate the 10-year risk of osteoporosis fracture as a first step and proceed only if the estimated 10-year risk exceeds 9.3% ; unfortunately, in women between 50 and 64 years of age, only a third who met treatment criteria for BMD (T 2.5 score) and 25% who experienced a fracture in the next 10 years would reach the threshold based for FRAX screening [15] , prevention of bone loss in postmenopausal women through the use of Hormone therapy for menopause is the true primary prevention strategy to reduce the risk of future fracture, the benefit / risk balance is favorable in early postmenopause in women who require Hormone therapy for menopause to alleviate VMS ; The use of Hormone therapy for menopause has recently been supported and they are indicated in postmenopausal women with low BMD and high risk of fractures with osteoporosis, calcium and vitamin D as a supplement or alternative to prevent hip fractures are indicated for women who cannot tolerate other specific treatments. The dietary intake with calcium is the safest and most appropriate for osteoporosis and the recommended dose of calcium per day in the diet and/or in supplements is 1000-1200 mg and there is no consensus on vitamin D as a supplement, postmenopausal women with a confirmed diagnosis of osteoporosis should be screened with a



serum level of 25-hydroxyvitamin D, and ingest 1000IU of vitamin D per day, or at least 20ng / mL (50nmol/L), (or a threshold of 30ng/ml (75nmol/L). , resistance and balance exercises, stopping smoking, limiting alcohol use, drug use and improving comorbidities that can damage bones is recommended [16].

Metabolic Syndrome

Women have a higher risk of metabolic syndrome (MS) compared to men, due to polycystic ovary syndrome (PCOS), pregnancy and MT; MS in postmenopausal women indicated a prevalence of 37.17% (95% confidence interval [CI]: 35.00% -39.31%), ranging from 13.60% (95% CI 13.55%) -13.64%) to 46.00% (95% CI 1.90% -90.09%), depending on the diagnostic criteria used. The overall pooled OR for MS in postmenopausal women, compared to premenopausal women, was OR 3.54 (95% CI 2.92-4.30), but ranged from OR 2.74 (95% CI 1.32-5.66) to OR 5.03 (95% CI 2.25-11.22), depending on the criteria used, the odds of fasting blood glucose (OR 3.51, 95% CI 2.11-5.83), low high-density lipoprotein cholesterol (OR 1.45, 95% CI 1.03-2.03), systemic blood pressure high (OR 3.95, 95% CI 2.01-7.78), high triglycerides (OR 3.2, 95% CI 2.37-4.31) and high waist circumference (OR 2.75, 95% CI 1.80-4.21) are higher in women postmenopausal women than premenopausal women 17. MS includes at least three of the following findings: obesity, systemic blood pressure high, hyperglycemia, hypertriglyceridemia and low high-density lipoprotein cholesterol (HDL-C) in plasma levels; events related to menopause, weight gain, changes in lifestyle and endocrines are related to the prevalence of MS, which is more common in women with VMS [18], women with VMS increase in body mass index, waist circumference larger, dyslipidemia and higher prevalence of MS compared to asymptomatic women.

Race/ethnicity is strongly linked to the hormonal pattern of MT in women that is related to SVM over time and accumulation of visceral abdominal fat. VMS are associated with insulin resistance, obesity and type 2 diabetes mellitus (DM2), components of MS; even a lifetime history or current major depressive episode at baseline was associated with a higher risk of developing MS during follow-up; Also, sleep disorders have been related to MS due to circadian alterations and neuroendocrine rearrangements, which involve oxygenic and anorectic mediators that regulate caloric intake and energy expenditure. The absolute weight gain in women in MT is more related to aging than with menopause itself, throughout the MT there was a cumulative absolute period of 6 years of increase in fat mass of 3.4kg and 5.7cm in waist circumference with a rate of increase decreasing 1 year after LMP. The prevalence of MS is higher in women with excessive weight or visceral adiposity, but it can also occur in individuals with fat, and it is one of the main contributors to the pathogenesis of cardiovascular diseases (CVD) [19,20]. An imbalance of the sympathetic nervous system, also increased as a proinflammatory and thrombotic state as well as oxidative stress, may also play a role in the development of cardiovascular risk [20]. MS doubles the risk of CVD increases 1.5 times mortality from all causes, MS affects cognition, especially if there are risk factors, such as DM2. Hyperglycemia and elevated blood pressure have been strongly associated with cognitive impairment [18]. Risk factors assessment is

recommended in MT, which allows the timely introduction of lifestyle, hormonal, and therapeutic interventions to modify or reverse adverse changes; mainly reduction in total fat mass with estrogen-progestin therapy, estrogens, improved insulin sensitivity and a lower rate of developing DM2 this positive effect positively influences quality of life related to health and sexual function.

Cardiovascular Risk

There is a strong connection between MS and CVD, the main cause of death mainly after menopause. Compared with men, there is a 10-year delay in the clinical manifestation of CVD due to the strong protection exerted by estrogens until LMP [21]. The prevalence of CVD in women after 75 years exceeds that reported in men, mortality In the short and medium term after acute myocardial infarction is greater in women than in men, and the impact of classic risk factors CVD is also likely to differ in men and women, DM2 is related to higher morbidity and mortality due to CVD in both genders, but women with DM2 are at a higher relative risk of CVD than men [21,22]. There is no clear evidence of an association between estradiol levels and glucose balance during MT [23]. CVD risk factors are affected by hormonal status and other common female-specific comorbidities, including the duration of the decline in reproductive life , onset of reproductive disorders such as PCOS, miscarriage, and a positive history of hypertensive disorders of pregnancy and gestational diabetes [22]. Menopause is an independent risk factors of CVD, a finding more corroborated by evidence in women with premature menopause; bilateral salpingo-oophorectomy is an independent intervention as relative risk of CVD with a relative risk of 4.55, while early menopause was associated with a relative risk of 1.25. Predictions of future early menopause of coronary heart disease and stroke, women with a history of early menopause had more severe coronary disease and less impaired stroke-free survival.

The cardioprotective role of vascular estradiol shows a pattern over time, and its function is involving a wide range of mechanisms, from vasodilation to anti-inflammatory activity, antioxidant properties, and neuroendocrine modulation. Increased visceral fat deposition in postmenopausal women, especially heart fat, is associated with low estradiol levels that increase women's CVD risk later in life. Even FSH controls fat deposition, insulin resistance, and the development of DM2, dyslipidemia, and atherosclerosis. Dyslipidemia in the blood tends to become atherogenic in women one year after LMP, with significant increases in total cholesterol, LDL cholesterol and apolipoprotein B, regardless of ethnic origin, age or weight, the antiatherogenic effect of HDL cholesterol it is less effective after menopause, although it is still a good predictor of cardiovascular mortality in women. Elevated triglycerides are independent factor risk for coronary heart disease mortality in women, particularly with low HDL cholesterol. Hypoestrogenism during menopause exerts a negative effect on endothelial cell function, resulting in reduced release of cardioprotective nitric oxide and influencing the growth and proliferation of vascular smooth muscle cells, also leading to the activation of the renin system. angiotensin, up-regulation of the potent vasoconstrictor endothelin, and even the prevalence of sensitivity to salt increases, contributing to the greater risk of developing systemic blood pressure high with more than twice the prevalence of premenopausal women [4,19]. The higher



frequency of VMS is correlated with the increase in systolic independent if awake or as leep during the menopausal state. In late postmenopausal women with VMS have a higher prevalence of previous diagnosis of systemic blood pressure high and VMS is an early marker of endothelial dysfunction that presides over CVD risk in women [24], the severity of VMS is associated with a decreased vascular response to mediated dilation due to endothelium, this decrease in endothelial function and vascular fall. Surgical menopause causes imbalance in the autonomic nervous control of the CVD system with decreased cardiac vagal modulation and increased sympathetic activity, similar to women in MT during VMS, in women with frequent VMS, the thickness of the median intimal artery of the carotid is larger, and in those with hot flashes during MT, there is a higher incidence of arterial endothelial dysfunction, with flow-mediated dilation of the brachial artery. VMS are associated with a procoagulant hemostatic profile and an unfavorable hemodynamic profile with a lower overall cardiac index and stroke volume index; es, evidence that women with current signs and symptoms of myocardial ischemia who present VMS during MT have higher CVD mortality and reduced endothelial function compared to women in late menopause with VMS [4]. Other aspects of menopausal well-being, such as disorders of the sleep, mood, are risk factors of CVD. The short duration and general low quality of sleep are associated with a higher degree of aortic calcification and increased carotid atherosclerosis in MT [20]. Health and nutrition showed that women with depression had a higher relative risk of developing CVD than women without depression. The menopausal period and early menopause present an ideal opportunity to assess cardiovascular risk and establish strategies for preventive measures, from reducing body weight to eliminating other traditional risk factors such as smoking and sedentary lifestyle. The use of Hormone therapy for menopause may be beneficial in women who report VMS in MT, and should be initiated during this "window of opportunity of time" [17].

Cognitive Impairment

Cognitive decline and dementia are a growing public health problem, the global prevalence of dementia will triple by 2050. Alzheimer's disease (AD), the most common cause of dementia, occurs more frequently in women than in men. This difference could be due to a longer life expectancy of women, but sex-specific differences in the incidence of AD exist, the increased risk of late-onset AD in women suggests pathophysiological changes that may be mediated by the MT of endocrine problems of menopause, which is female-specific and age-related. MT is a neuroendocrine transition state and symptoms are neurological in nature, including disruption of estrogen-regulated systems such as thermoregulation, sleep, circadian rhythms, and sensory processing, depression, and impairment in multiple cognitive domains [25]. Estradiol may play an important role in cognitive performance because estrogens target the central nervous system, such as the hippocampus and prefrontal cortex, which mediate episodic and working memory, estrogens modulate the synthesis, release, and metabolism of various neurotransmitters (serotonin, dopamine and acetylcholine) and a wide range of neuropeptides (β -endorphin and neurosteroids), can influence the electrical excitability, function, and morphological characteristics of synapses [4]. Estrogens can be neuroprotective in several

mechanisms, including the promotion of cell growth and survival of neurons, increased density of the column Dendritic activity, synaptogenesis, and attenuation of associated neurodegenerative processes, despite the fact that brain aging and neurodegenerative diseases have a multifactorial effect, estrogen dysregulation during MT significantly affects the brain bioenergetic system, which reflects neurodegenerative processes [26]. Levels Fluctuating estradiol during MT cause clinically evident transient cognitive deficits, especially when VMS is present [25,27] It has been shown that MT induces a hypometabolic state associated with neurological dysfunction due to increased catabolism of fat, acid, β -amyloid (main component of senile plaques, a distinctive marker of AD), and decreased synaptic plasticity in vulnerable women; These changes negatively influence the microglial function, antioxidant and clearance mechanisms, exacerbating neuroinflammation and finally neurodegeneration. Even the high levels of FSH and LH in postmenopausal women have been linked to AD these hormones could be responsible for the increased production of β -amyloid [25], both the compromised bioenergetic system of menopause and chronic low-grade inflammation of aging contribute to neurodegenerative diseases, together with increased metabolic and vascular risk, explaining the difficulties in linking Hormone therapy for menopause with cognitive benefits, MT represents a "window of opportunity" to prevent age-related neurological diseases with decreases in cognitive function, reduction of " learning effects "on repeated cognitive assessments rather than a decline in cognitive performance. A lack of improvement in verbal memory in early and late MT, and deficits in processing speed with repeated tests were observed at the end of the MT stage compared to premenopausal and postmenopausal. Despite evidence that cognitive deficits observed during MT are independent of mood symptoms, the SWAN showed that women with depressive symptoms showed poorer processing speed and those with higher degrees of anxiety had poor verbal memory [25], supporting the association between depression and AD. VMS, in addition to poor sleep quality, favors the appearance of depressive symptoms that are very frequent during MT [28-30]. Even sleep disorders are associated with increased risk of cognitive decline in menopausal women, particularly with regard to attention, episodic memory, and executive function, early postmenopausal women at high risk of obstructive sleep apnea showed significant impairment of cognitive function in compared with those at low risk of sleep apnea [25]. In surgical menopausal women, with bilateral salpingo-oophorectomy before the age of natural menopause, hypoestrogenism in cognitive function is more conclusive and the widespread use of Hormone therapy for menopause to prevent deterioration should be supported cognitive and reduce AD 29%; although, it is reported that Hormone therapy for menopause for the prevention of AD doubled the risk of dementia from all causes. Parallel to cardiovascular risk, with Hormone therapy for menopause the age at onset, which in the general population is 52 years.

Discussion

There is no statistically significant relationship between physiological menopause and the presentation of chronic diseases [5,31,32-35], such as diabetes mellitus, cardiovascular or cerebrovascular disease, lung disease, depression, anxiety,



dementia, osteoporosis or cancer; however, patients with early menopause have a higher incidence of chronic diseases at a younger age than in patients with physiological menopause [36]. Physiological menopausal patients with chronic comorbidities share socioeconomic and reproductive risk factors, in addition to genetic and environmental factors, which in turn can condition early menopause and chronic diseases [37,38,39]. Previous conditions such as insulin resistance, dyslipidemia or metabolic syndrome in premenopausal women lead to the appearance of related chronic diseases [33,34].

Genetic predisposition to physiological or early menopause causes an alteration in the aging processes at the cellular and organic level, which can lead to the development of chronic diseases with increased cardiovascular risk [40]. The premature loss of estrogens, whether physiological or surgical, in addition to genetic or environmental risk factors leads to the development of chronic diseases [36, 38,39].

La menopausia prematura es un marcador de aceleración del proceso de envejecimiento y vinculados con menor sobrevida [5,38]. Se debe considerar un problema de salud pública y prevención primaria, deben establecerse recomendaciones integrales para la prevención y manejo de enfermedades crónicas, particularmente en los primeros 10 años después de la menopausia y antes de los 60 años de edad [41,42], ya que, a partir de esta edad, el riesgo de muerte por complicaciones cardiovasculares se incrementa [36].

Premature menopause is a marker of acceleration of the aging process and is associated with lower survival [5,38]. It should be considered a public health problem and primary prevention, comprehensive recommendations for the prevention and management of chronic diseases should be established, particularly in the first 10 years after menopause and before 60 years of age, [41-43] since, From this age on, the risk of death from cardiovascular complications increases [36]

Comprehensive strategies that are part of caring for women such as nutritional habits, healthy lifestyle, body weight control, stimulating mental activity, cancer screening and reproductive conditions; can elucidate some prevention against chronic diseases in patients with physiological menopause [32,41]. Therefore, the importance of identifying risk factors early, even during reproductive age, will have an impact on the reduction of cardiovascular morbidity and mortality. The incorporation of genetic signatures in search of multifactorial pathology has not been established as a prevention strategy, since the disparity that exists between single pathologies may not be a determining factor due to menopause. 26; for example, death due to cardiovascular conditions is increased in menopausal patients, but not diseases such as colorectal cancer [35,40,44,45]. Until now, there are no trials of genetic signatures that can predict the risk of chronic diseases that can be incorporated into the evaluation of patients in menopause, [32,36] mental health evaluations in menopause should be considered as part of the comprehensive evaluation strategy [36,46,47]

Conclusión

Menopause is a time of anguish for most women and its symptoms have a great impact on quality of life and general health; Changes that depend directly or indirectly on hypoestrogenism is crucial for the early recognition of risk factors for chronic diseases, which

are prevented with comprehensive strategies that include personalized treatments.

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