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Review Article

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Neuroprotection in Perimenopause New Insights for Hormone Therapy

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Abbreviations

FMP: Final Menstrual Period
HPOA: Hypothalamic-Pituitary-Ovarian Axis
MT: Menopausal Transition
VMS: Vasomotor Symptoms
MHT: Menopausal Hormone Therapy
ERT: Estrogen Replacement Therapy
PCC: Posterior Cingulate Cortex
MCI: Mild Cognitive Impairment
AD: Alzheimer 's disease
PD: Parkinson's Disease
Aβ: Beta Amyloid
CVD: Cerebrovascular Disease
CAA: Cerebral Amyloid Angiopathy
HS: Hippocampal Sclerosis
17ß-E2: 17ß-Estradiol
CEE: Conjugated Equine Estrogens
ERs: Estrogen Receptors
Pg: Progesterone
PRs: Progesterone Receptors
mPRs: Membrane Progesterone Receptors
Allo: Allopregnanolone
DHEA(S): Dehydroepiandrosterone (Sulphate)
DHT: Dihydrotestosterone
ARs: Androgen Receptors
PET: Positron Emission Tomography
PiB: Pittsburgh Compound B
WHI: Women's Health Initiative
KEEPS: Kronos Early Estrogen Prevention Study
SWAN: Study of Women's Health across the Nation

Introduction

Endocrine and Neural Senescence overlap by intertwined complex feedback loops. The variable levels of estradiol, progesterone, DHEA(S), and neurotransmitters -GABA, serotonin, dopamine and glutamate dependent on sexual steroids make women's brain to suffer from the menarche to menopause, perimenopause being a "critical period", "a neurological transition state" offering to the scientific and medical communities a "window of opportunity" to delay the onset of brain aging, The modern medical communities are moving from focusing on the treatment of already identified dementia to develop strategies for accurate depiction of predementia conditions/risk factors for brain aging, for prevention and slowing a demented status to progress from early stages of endocrine aging process [1].

Update on the importance of Hormone Therapy in perimenopause

The menopausal transition (MT) or perimenopause– 4 to 6 years duration [2]. with reproductive and dynamic critical changes in hypothalamic-pituitary-ovarian axis (HPOA), and entire women's body, biology and psychology, starts with menstrual irregularities from the stage -3b/-3a in the late reproductive ages, with ethnic differences in symptoms, hormones and their receptors and actions [3, 4].

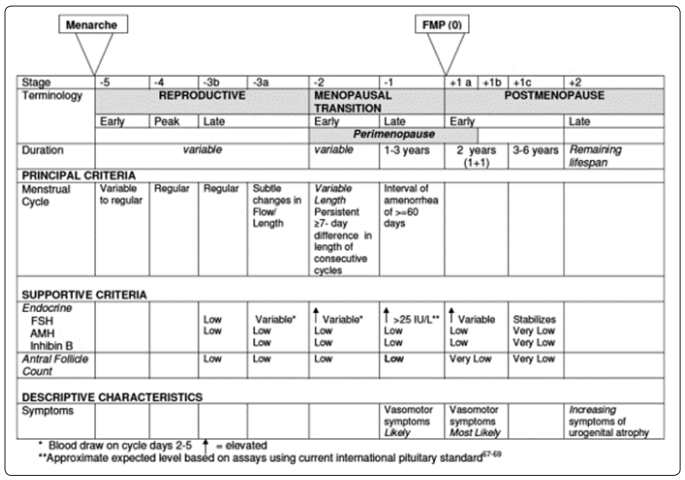

Figure 1: The Stages of Reproductive Aging Workshop + 10 staging system for women's reproductive aging (Adapted from [3] Harlow SD, Gass M, Hall JE, Lobo R, Maki P, Rebar RW, Sherman S, Sluss PM, de Villiers TJ, STRAW +10 Collaborative Group-. Executive Summary of the Stages of Reproductive Aging Workshop + 10: Addressing the Unfinished Agenda of Staging Reproductive Aging. J Clin Endocrinol Metab, 2012 Apr;97(4):1159-68)

The characteristic menopause symptoms connected to thermoregulation, sleep, circadian rhythms, and sensory processing have a neurological nature, besides the controverted changes in cognition and mood [5]. Vasomotor symptoms (VMS) and genitourinary syndrome are the recommendations for menopausal hormone therapy (MHT), which may prevent the cardiovascular, and neurological disorders, and reduces global women's mortality

if MHT is started in perimenopause/early postmenopause, "What is good for our hearts is also good for our heads", a statement at the "end of an era", after fears and confusions induced by Women's Health Initiative (WHI) [6, 7]. The "Study of Women's Health across the Nation" (SWAN) gives another image on perimenopause health, emphasizing the assessment and prevention of asymptomatic disturbances with onset during midlife [4].

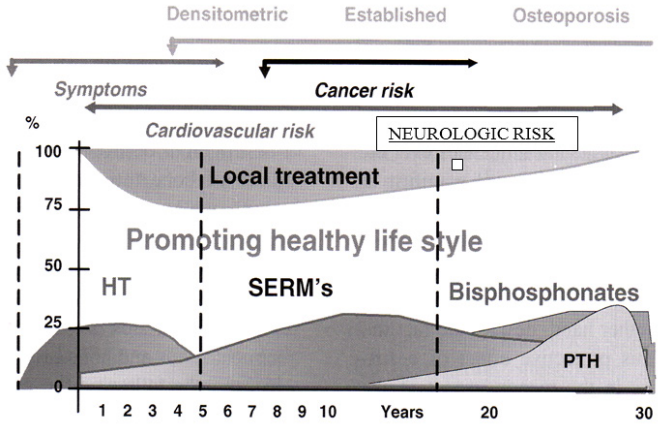

Figure 2: Peri and Menopausal Symptoms and Risks. according to time since last period. The NEUROLOGIC RISK is added at the same range to the cardiovascular risk, in the figure of Castelo- Branco C, Palacios S, Calaf J, Vazquez A, Lanchares JL (2005)-Available medical choices for the management of menopause. Maturitas. 15;52 Suppl 1:S 61-70. [8]

Perimenopause to menopause transition - a neurological transition state. Cognitive and mood performances in menopause transition. Cerebrovascular disease. Imaging and biomarkers in brain aging

Perimenopause to menopause transition- a neurological transition state

Menopause-associated hormonal effects on aging brain functions are potentially relevant to various neurologic and psychiatric disorders, women seeking treatment for their alleviation/heal. Estrogen loss is the major difference between pre- and postmenopause, between women and men of the same age. Dementia, its most severe entity- the Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis, amiotrophic lateral sclerosis are the most frequent contemporary neurodegenerative disorders, connected by neural cells loss, and neuroinflammation. Cognitive decline is aging associated, but severe loss of cognitive abilities are attributed to pathological AD alterations. Estrogen deprivation or disruptors are associated from MT with episodic memory troubles, and brain impairments are associated with increased risk of AD, being less known the other neurodegenerative disorders onset, and long term estrogen deprivation (LTED) is the cause of AD severe symptoms [8, 9]. The subtype of mild cognitive impairment (MCI) has 10-15% risk per year to progress to AD [10, 11]. The multiple comorbid pathologies are the norm, with substantial interindividual variation in neuropathological phenotypes; the causes begin, interact and co-occur [12]. The aging brain has depositions of many misfolded proteins, identified with new pathological markers: β-amyloid (Aβ), tau, and TDP-43. The pathological hallmarks of AD- Aβ protein, neurofibrillary tangles (NFTs), and chronic gliosis are laid down during a 20-year prodromal period before symptoms onset, coincidental to MT, around 45- 54 years. Hippocampus, frontal, medial temporal and parietal cortical regions, posterior cingulate cortex (PCC) are damaged by AD; frontal cortex is affected by Aβ depositions earlier in MT compared to men of similar ages [13-16]. The toxicity of intracellular Aβ induces neuronal apoptosis and cell death, events that HT may prevent before intracellular misfolded protein appearance. The marked fluctuating estrogen levels with periods of irregular hormone- receptor interaction characterizing MT, and the associated AD phenotype (brain Aβ deposition and hypometabolism) may act as an accelerator of brain aging, which can be stopped or slowed by HT [16, 17]. Animals experiments have shown a persistency of estrogen neuroprotection for 40 days after therapy termination, fact appreciated with short- term estradiol therapy after oophorectomy in early ages, as is the concept of long term potentiation [18].

Cognitive and Mood Performances in Menopausal Transition

MT cognitive performances are controverted. Cross-sectional and longitudinal studies in midlife women are examining the association between ovarian hormones serum levels and cognition, and mood (mainly anxiety). There are studies in Australia (Melbourne Women's Midlife Health Project, 2009; episodic memory performance on a word-list learning task was similar for women reporting good and poor memory, with small differences between MT, early and late postmenopause), UK (Whitehall II prospective cohort study, 2012- demonstrating longitudinal declines in midlife cognitive performance, higher when low education level, albeit at a slower rate than at older adults), USA (Rochester Investigation of Cognition Across Menopause, 2013): cognitive function does not change linearly across perimenopause, and the decrease in attention/working memory, verbal learning, verbal memory, and fine motor speed may be most evident in the first year after the FMP [5, 7, 19]. SWAN duration of 23 years allowed the upgrade of tests for cognition assessment, with a protocol in-person serial tests of cognitive processing speed, verbal episodic memory, and working memory [4]. The initial SWAN 4-year longitudinal analysis of the relation between MT and cognitive performance disclosed a temporary decrement in processing speed and verbal episodic memory during perimenopause, with the resolve of decrement in postmenopause [20]. The negative MT effect was subtle, manifest as the absence of a learning effect, meaning that cognitive test scores did not get better when repeated at regular intervals, did not drop after recent recall, but the third one shows decline, even after 2 normal tests; 54 years was the median age for onset of cognitive disturbance, and 60% of women had reached menopause. Another SWAN remark is the missing connection between VMS, depressive symptoms, anxiety, and sleep disturbance to cognition difficulties observed during perimenopause. The SWAN subsequent 6-year, longitudinal analysis evaluated the direct relation between these four symptoms and cognitive performance, and did not uphold this thesis: no association between cognitive performance and either VMS or poor sleep, but women with depressive symptoms did score lower in the cognition processing speed domain, and when more anxiety the episodic memory was worse, as mentioned earlier [21, 22]. When all four symptoms were added to the models of MT stage and cognition, the negative effect of late, perimenopause on cognitive performance was unaltered, suggesting that the presence of these symptoms does not account for the perimenopause learning decrement [21]. SWAN debates whether age-related cognitive decline starts in midlife parallel to ovarian hormones decline or it is a normal part of aging [23, 24]. Cognitive processing speed and verbal episodic memory declined with time, adjusted for MT stage, symptoms, diabetes,

race/ethnicity, education, and attrition. The results are supporting the thesis that the decline in cognitive processing speed and verbal memory per year of chronological age are not related to menopause, but rather are a function of chronological aging.

Cerebrovascular Disease and Cognition Impairment

The geriatricians know that perimenopause increases the risk for cardiovascular and cerebrovascular diseases (CVD), including ischemic stroke, and underlying CVD (embolism, hemorrhage, neuroinflammation, impaired perfusion, hypertension, hypoxia, vascular malformations, glycemic fluxes) were observed in humans with AD [14, 25]. LTED starting after MT may enhance women's risks to develop MCI, which may progress to vascular dementia or AD [26]. The dementia risk following a stroke increases 4- to 12-fold [27]. CVD causes more rapid cognitive deterioration in patients with coexisting AD vs patients without AD [28]. There are an ischemic and a hemorrhagic type of stroke (known as cerebral amyloid angiopathy- CAA), and hippocampal sclerosis (HS) - in patients with CVD around 80s [14]. The CAA- a rate of 12-15% in the elderly with lobar intracerebral hemorrhage has common inheritance of familial patterns, being discussed along the role of genetic screening in relatives of patients with CAA: the APOE-ε4 alleles alter Aβ plaque burden in a dramatic fashion; the Aβ depositions are associated to recurrent and multiple superficial cortical and meningeal hemorrhages [29]. The ischemic stroke is known as a tauopathy; it leads to hyperphosphorylation of the microtubule-associated to protein tau, which regulates neurotransmission by stabilizing axons, and hyperphosphorilated tau proteins are inducers for insoluble aggregates called neurofibrillary tangles, one pathological hallmark of AD. Cerebral ischemia is a driver for hypometabolism, the switch of glucose metabolism to ketogenic profile, oxidative stress, and mitochondrial Aβ deposition, known as favorable condition for Aβ depositions, neuronal cells and microglia damage and demise specially from hippocampal CAl region- the most damaged area [30, 31].

The studies on rodents have revealed that E2 replacement immediately not after 10 weeks from oophorectomy, and ischemic damage following global cerebral ischemia (GCI) is restoring neuroprotection in the rat damaged hippocampal CAl region [25]. LTED is differentially supported by hippocampus zones after GCI. Hippocampal CAl is "estrogen sensitive" and hippocampal CA3/CA4 is "estrogen hypersensitive" to E2 supplementation after LTED and GCI. The rat hippocampal CAl region is estrogen insensitive at estrogen supplement in condition of LTED, and after GCI, different from endometrium, which reacts to E2 many postmenopausal years [25]. This condition is associated to the loss of ER-ά by proteasomal degradation in hippocampal CAl, ER-ά is a key mediator of E2 neuroprotection at cerebral ischemia [32, 33]. CA3/CA4 region is normally resistant to ischemic insult, and not significantly damaged during GCI in comparison to CAl region The experiments of Scott E, et al showed that after LTED, the CA3/CA4 region becomes extensively damaged by the same ischemic insult that caused little to no damage in animals that have not LTED [25]. This is intriguing because long-term after human oophorectomy (surgical menopause) there is an increased risk of cognitive decline, and dementia, PD, and mortality from neurological disorders [34, 35]. The mechanistic explanation for the increased risk of CA3/CA4 region is the "hypersensitivity" to injury after prolonged hypoestrogenicity in conditions of GCI.

Table 1: Oophorectomy in premenopause and neurological mortality and morbidity (cognitive impairment/dementia and parkinsonism) after non- malignant uni/bilateral oophorectomy during 1950-1987, and vital status at follow-up (2001-2006) in 2390 patients (95 are from the referent cohort, suffering oophorectomy during study development) compared to referent cohort [2390 women; from the number of 574*(the asterisk marks 95 patients who underwent oophorectomy during study, and they were counted only in the first group, even they were in both groups)] Mayo Clinic Cohort Study of Oophorectomy and Aging (part of Rochester Epidemiology Project in Olmsted County, Minnesota (USA). Adapted from Rocca AW, Grossardi RB, Maraganore MD - The Long-Term Effects of Oophorectomy on Cognitive and Motor Aging Are Age Dependent. Neurodegenerative Diseases. 2008, Mar; 5(3-4);257-260 [36]

Oophorectomy Cohort (2390)	**Unilateral**		**Bilateral:**	
	1293		**1097 (including 110 who had a second unilateral oophorectomy)**	
Follow up study 2001-2006	Followed for Dementia	Followed for Parkinson Disease	Alive	Deceased
	1498	2327	1758	569
Referent cohort (2390)	Followed for Dementia	Followed for Parkinson Disease	Alive	Deceased
	1472	2368	1699	574*

Clinic Cohort Study of Oophorectomy and Aging (part of Rochester Epidemiology Project in Olmsted County, Minnesota (USA). Adapted from Rocca AW, Grossardi RB, Maraganore MD - The Long-Term Effects of Oophorectomy on Cognitive and Motor Aging Are Age Dependent. Neurodegenerative Diseases. 2008, Mar; 5(3-4);257-260 [36]

Adjusted Odd Ratio for dementia after unilateral or bilateral oophorectomy			
Age at surgery (yrs)	**Hazard Ratio**	**CI 95%**	**P value**
< 38	2.79	0.97– 3.14	0.06
383 – 45	1.57	1.06 – 2.66	0.03
> 45	1.19	0.74 – 1.61	0.66
Adjusted Odd Ratio for Parkinson Disease after unilateral or bilateral oophorectomy			
< 38	2.79	1.28 – 6.35	0.001
38-45	1.54	1.28 – 6.35	0.42
> 45	1.54	0.92 – 3.03	0.09

Imaging and Biomarkers in perimenopause brain aging

Neuroimaging and biomarkers changes precede any evidence of clinical AD symptoms, predicting cognitive impairment accompanied by plaques and tangles, and neuronal volume loss in premenopausal women compared to men of the same age, providing clearer evidence that MT increases risk of AD-related brain changes [37]. Recent imaging studies emphasize the importance of earlier assessment of women neuroaging vs men, for prodromal/ preclinical changes depiction at ages lower than 65s, which was the rule. The Aβ depositions are in vivo depicted by three methods: positron emission tomography (PET)– showing increased retention, reduced depositions levels in cerebrospinal fluid obtained by lumbar spinal puncture (in prodromal stages), and MRI, with discordant results in younger adults, as previously shown [38]. After bilateral oophorectomy ≤45 years, brain images changes are an early alarm signal for future serious cognitive disorders, and the decision of HT is critical [35, 39]. The changes are located in medial temporal lobe, with smaller amygdala volume, thinner para-hippocampal-entorhinal, and lower white matter fractional anisotropy values in the entorhinal cortex compared to referent women [40]. Women's hippocampus is larger than men's relative to cerebrum size are, with significant differences in the covariance matrices in perimenopause versus postmenopause [41]. Hippocampal atrophy is more predictive for incipient AD than whole brain atrophy [42].

The researches from Weill Cornell Memory Disorders Program reported that the frontal cortex and PCC present consistent biomarker abnormalities in peri- and postmenopause, and reduced gray matter volume in parietal, temporal, and medial temporal cortex regions versus men [16, 43]. The white matter loss is associated with tau protein and/or Aβ depositions in defined brain regions, but the white matter hyper intensities (representing primarily the small vessels in CVD) are considered of no predictive value for degenerative Aβ depositions progression in a longitudinal study [44, 45]. The 3-year longitudinal follow-up observational study (2010–2016) in Weill Cornell Memory Disorders Program characterized the progression of well- established AD biomarkers (FDG- PET for neurodegeneration and PiB-PET for Aβ load), and structural MRI, plus cognitive tests repeated at 2 years apart, in normal cognitive midlife women (pre- as control, peri and postmenopausal without any MHT all study duration) vs men (40 to 60 years) [16]. They discovered that neurodegenerative changes arise at an earlier age in women vs men, during perimenopause to MT, and CMRglc decline exceeded Aβ and atrophy changes in all female groups vs men; higher Aβ depositions (p<.01) in PCC and frontal cortex in menopause (restricted to PCC in men) is suggesting a more widespread distribution vs premenopause. The memory decline was higher in menopausal and perimenopausal groups vs males (p<.02), the menopausal group exhibited the highest rate of hippocampal volume loss (p ≤.001). Over 3 years with no MHT, frontal PiB uptake increased by 6.3% in postmenopause group, and by 4.5% in perimenopause group, no significant increase of frontal PiB uptake in premenopause/control and male groups. PCC PiB uptake increased by 8.6% in postmenopausal group, by 6.2% in male group, and no significant changes in the premenopause/control and perimenopausal groups (<1.3% change).

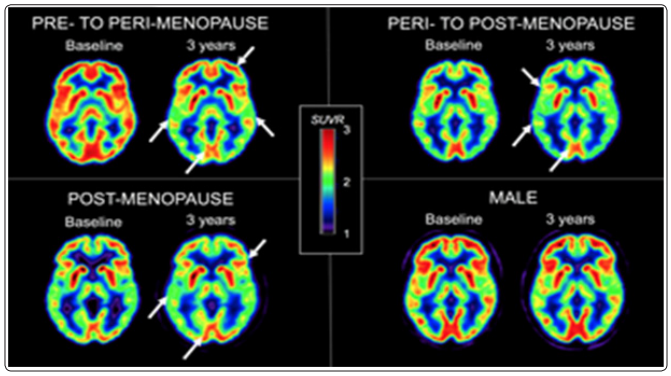

Figure 3 : Brain and Hippocampus volumes loss and cortex metabolism changes in women vs men . Baseline and 3 yrs follow-up of 4 representative cases: women in PRE (control) to PERI, PERI to POST and POSTMENOPAUSE and MALE. Top right: A 43 year-old woman (16 years education, APOE 3/3 carrier, CDR:0, perimenopausal at baseline and postmenopausal by the follow-up exam. Bottom left: A 59 year-old woman (16 years education, APOE 3/3 carrier, postmenopausal at baseline. Bottom right: A 55 year-old man (14 years education, APOE 3/4 carrier). Arrows point to areas of progressive CMRglc reductions in the follow-up vs. baseline scans. FDGPET for neurodegeneration measures are standardized uptake volume ratios adjusted for global uptake. CDR: clinical dementia rating; CMRglc: cortical metabolism rating glucose Adapted from [16] Mosconi L, Rahman A, Diaz I, Wu X, Scheyer O, Hristov HW, Brinton DR, et al (2018)- Increased Alzheimer's risk during the menopause transition: A 3-year longitudinal brain imaging study. PLoS One. 2018; 13(12): e0207885 This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution,

The cerebral blood flow assessment is very important for perimenopausal complete diagnosis, considering the possible role of cell membrane-derived microvesicles in the blood that may negatively influence endothelial function and sex-specific differences in cerebral blood flow regulation, as potential mechanism mediating changes of cognition [46].

Whole brain, hippocampal and ventricular volumes assessment by MRI is considered a surrogate for neurons structural integrity, and it is used for cognition assessment [47]. 0.2% is the annual decrease rate of whole-brain volumes after 54 years, with onset from the 40s, similar to brain weight reduction, which are due to cell shrinkage, through senescence degenerative processes [48]. The Kronos Early Estrogen Prevention Study (KEEPS) during 2008- 2012 presents a brain volume reducing in average by 0.30- 0.35%/year, and a ventricular volume increasing in the first 18 months of menopause by 3.59- 3.73% [49]. The rate of brain volume decrease is comparable to the baseline brain volume previously observed when was done cognition analysis for women with two decades elder – 79 years [47]. KEEPS examined during 4 years the effects of HT (randomization on oral, transdermal, placebo) on cognition and mood in recently postmenopausal healthy women [average age 52.6 yrs (42 to 58), within 6 to 36 months of natural menopause]. The ancillary MRI brain study of KEEPS found greater ventricular expansion in oral E2 group than the *placebo* group, and the trends for white matter hyperintensities increased in both treated groups in that time: 0.4% at elder women vs 0.35% in KEEPS cases. The ventricular volume increase was 2 higher than in KEEPS cases (1.7% elderly vs 3.7% KEEPS subjects). A pilot study was done on 98 cases from KEEPS, who were retested [Pittsburgh compound B (PiB) PET scans; MRI and the cognitive tests] at 3 years after MHT phase (7 years from randomization) [50]. At the 7-year point, the rates of change in global brain volumes and cognitive function in either treatment group did not differ from *placebo*, but the volume of white matter hyperintensities tended to increase in both studies during, and after the end of ERT in both treatment groups. Although the magnitude of increase from baseline to month 84 was similar in the oral E2 (mean increase 0.08cm^3) and transdermal estradiol (mean increase 0.07 cm^3) groups, the rate of increase in white matter hyperintensities volume was statistically significantly greater than *placebo* only in oral estrogen users. The pilot study conclusion is that transdermal ERT in recently postmenopausal women was associated with a reduced Aβ deposition, with dorsolateral prefrontal cortex volumes preservation, particularly in APOEϵ4 carriers, fact very important for AD prevention in postmenopause.

Estrogen exposure and women's brain aging. The ovarian continuum.

Timing hypothesis/ Critical period hypothesi s. The "estrogen action hypothesis"/"healthy-cell bias"

Estrogen exposure and women's brain aging

The cortical and sub-cortical structures are targets for estrogens, with receptors in and outside the nucleus, including plasma membrane, mitochondria, and endoplasmic reticulum, where they activate different signaling cascades exerting the actions through a classical and/or non-classical pathway [51]. The brain synthetizes its own steroid hormones, the "neurosteroids" starting from cholesterol, or by local metabolism from intermediate peripheral steroids [51, 52]. The mean serum concentration of the mainly estrogen 17β-E2, begins to decline about 2 years before FMP, and reaches a permanent nadir about 2 years later; progesterone deficiency/absence is usually in early ages, if 51 is the average menopause age. Estrogens are a „master regulator" of brain's glucose metabolism in multiple areas involved in cognition: glucose transport, aerobic glycolisis, insuline resistance, mitochondrial function to generate ATP [53]. Estrogen decline is jeopardizing the neurones structure and functions, and indirectly brain synapses, being favorized brain bioenergetic crisis with misfolding, aggregation and deposition of proteins, and hippocampal volume loss during perimenopause to MT. There are controverses between brain ageing and cerebral amyloid angiopathy and AD pathogenesis [14, 54].

Ovarian continuum

One considers an ovarian continuum during women's life [55]. Women are influenced by ovarian hormones from fetal life, childhood to puberty, an adequate production of estrogens and progesterone, androgen, inhibin starting at/after ovulation, inducing cyclic periods in reproductive years, up the stage -3b (STRAW+10), when high levels of FSH try to correct ovarian deficiency [56]. Each woman has her own ovarian continuum, being ethnic differences regarding E2 and FSH levels around FMP, and actually one tries to find which ovarian continuum is the most neuroprotective type [56]. Aging jeopardizes the morphology and function of hypothalamic GnRH neurons; ovarian hormones production failure is followed by changes in neurotransmitters, neuropeptides, and neurosteroids, driving to deterioration of many central nervous system activities [57-59].

A trial on dementia risk of Kaiser Permanente members with the diagnosis of dementia at mean age 76.5 years, demonstrated that ovarian continuum is covering the aspect that women's brain exposure to estrogens is crucial for brain health in elder ages [60]. The risk is correlated to a less exposure to estradiol according to age of menarche [when the menarche began at age ≥16 years, a 23% higher risk for dementia than when the menarche started at 13 yrs (HR 1.23; 95% CI 1.01-1.50)], menopause [when natural menopause began at age < 47.4, a 19% elevated risk of dementia versus women whose natural menopause began at ≥ 47.4 years (HR 1.19; 95% CI 1.07-1.31)], and shorter reproductive span [when last pregnancy < 34.4 years a 20% greater risk for dementia (HR 1.20; 95% CI 1.08-132)]. Hysterectomy has a marginal, but not insignificant association with elevated dementia risk (HR 1.08, 95% CI 0.99-1.18). The brain damages are also associated to gestational hypertension: preeclampsia and future chronic hypertension are discussed to increase the risk of brain atrophy- mainly white matter of occipital lobes, and cognitive decline decades after pregnancy, and MT is the early moment of dementia onset when women claim verbal memory decrease [46, 22, 61].

The initiation of HT is actually added to ovarian continuum; HT changes the data of estrogens' loss effects on brain, as Rochester Epidemiology Project (REP), and Mayo Clinic Specialized Center of Research Excellence (SCORE) on Sex Differences are analyzing [40].

The long-term potentiation is an important concept on estrogens action to slow AD progression. The increase in synaptic strength, mainly in hippocampus persists in time and correlates with the processes of memory and learning, with a change in estrogen-induced plasticity, and consolidation of short term memory to long

term memory, and spatial memory, and a global improvement of cognition [62, 63].

Timing hypothesis/Critical period hypothesis. The "estrogen action hypothesis"/"healthy-cell bias"

Current data shows the discrepancy between clinical symptoms and signs of dementia and the pathological condition of Aβ load in brain of younger healthy adults. Menopausal changes coincide with the timespan between average age of menopause (mid-50s) and average age of AD diagnosis (mid-70s). The use of PET and ligands that adhere to Aβ (as PiB) allow its visualization in younger healthy brains, and in the cerebrospinal fluid, and the apolipoprotein E (APOE) ε4 status, which influences Aβ load, but not the neurodegenerative changes [38, 16]. A meta-analysis found that Aβ appears approximately 20 years before any clinical sign, and approximately 20% of adults without dementia show significant Aβ accumulation in the brain [64]. According to these data, the "window of opportunity" for neuroprotection means to move the focus to the MT age from an elder age, when dementia is diagnosed, and its progression is inexorable. The differences between observational studies and the results of WHI -which demonstrated estrogen induced brain damages, pushed to new concepts as the "estrogen action hypothesis" known also as "healthy-cell bias" elaborated in the North American Laboratories for Neuroscience Research. This hypothesis tries to explain the differences between the estrogens effects on normal/healthy and aged neurons, already damaged ones [30, 65]. The "estrogen hypothesis" is becoming widely accepted because it posits that sex steroids, particularly 17ß-E2, exert a neuroprotective effect by shielding females' brains from AD progression. Many recent findings are supporting the theory that the onset of MT is associated with the emergence of AD-related brain changes in contrast to men at the similar age.

After WHI results, initially the North American, and later the Chinese researchers had elaborated, and tried to confirm the hypothesis of "critical period" of estrogen neuroprotection, which appreciates the risk of duration of estrogen deprivation It was suggested a "critical period" or a "critical window of opportunity" for the beneficial protective effect of E2 on human brain, and that estrogens have to be administered at perimenopause or earlier to observe their beneficial protective effect on the neural system, as it is recently again proved for the subclinical progression of atherosclerosis in early vs late postmenopause [66-74]. The ERT initiation timing is critical; close to the time of menopause (within about 3 years) is more effective than delay of up to 5 years, in order to maintain their neuroprotective effects, and to avoid brain's damages of LTED; this period was named "window of opportunity", being important for cardiovascular and brain protection, fact that also works when oophorectomy is done around 35s [36, 75, 76]. The mechanisms governing the duration of the "critical period" include depletion of E2 receptors, the switch to a ketogenic metabolic profile of neuronal mitochondria, and a decrease in acetylcholine that accompanies E2 deprivation. The LTED is inducing ER-ά and later ER-β loss (mainly in hippocampal CAl region), which cannot be restored by E2 replacement, as shown on basic research using rodents models [25]. E2 protects against changes resulting from serotonin withdrawal, and defends against changes from cholinergic depletion, and on the increase with 30% of axospinous synapses density in young rats' CAl compared to age ones [76]. The E2 use around menopause predicts decreased rates of dementia in later life compared to never users [77-79]. Experiments on rats with different E2 doses (10 ng/ml- low dose, 200 ng/ml- large dose) and on different schedules (acute vs. continuous vs. intermittent) demonstrated a possible prevention of neurodegeneration in hippocampal neurons exposed to Aβ, when E2 is administered before or during Aβ exposure. The strongest effect is on continuous administration, and the effects are worsened up to neuronal death, when larger doses or when Aβ is already present [77].

The reinterpretation and stratification of adverse events from WHI considering a MHT delayed administration made increasingly apparent that MHT has cognitive and cardiovascular benefits provided it is initiated in perimenopause, within the "window of opportunity" <10 years postmenopause, when it has better outcomes. The paper on what WHI has taught us about MHT discusses the optimal therapy duration for cognition preservation [78-80]. The Cache County Memory Study Investigators suggested that TH of >10 years provides better protection against AD than <10 years duration, or < 5 years (with beneficial effects on mood), being evidences that more women are continuing MHT for more than a decade, fact that is beneficial in cases with bilateral oophorectomy at ages < 34- 38 years (hazard ratio reached statistical significance in cases with bilateral oophorectomy at age < 34s for dementia, and < 38s for PD), as shows Table 3, and as demonstrates the Danish cohort and North American study, when therapy is up to the natural age of menopause [81,83].

Table 3: Oophorectomy in premenopause and hazard ratio for neurological disturbances, according to age at surgery. Cases of cognitive impairment/dementia and PD in women with uni (813) and bilateral (676) oophorectomy for a non-malignant disease, in Olmsted County, Minnesota (USA) during 1950 – 1987, followed up to death or finish of study at 2001-2006. Adapted from Rocca WA, Grossardt BR, de Andrade M, Malkasian GD, Melton LJ, 3rd (2006)-Survival patterns after oophorectomy in premenopausal women: a population-based cohort study. Lancet Oncol.; 7:821–828) [34]

Adjusted Odd Ratio for dementia after unilateral oophorectomy			
Age at surgery (yrs)	Hazard Ratio	CI 95%	P value
< 43	1.74	0.97– 3.14	0.06
43 – 48	1.68	1.06 – 2.66	0.03
> 48	1.09	0.74 – 1.61	0.66
Adjusted Odd Ratio for dementia after bilateral oophorectomy			
< 34	4.61	2.52 – 8.43	< 0.0001
34-41	1.23	0.67 – 2.26	0.51
> 41	1.50	1.05 – 2.13	0.03

Adjusted Odd Ratio for Parkinson's Disease after bilateral oophorectomy			
< 38	2.85	1.28 – 6.35	0.001
38-45	1.38	1.28 – 6.35	0.42
> 45	1.38	0.92 – 3.03	0.09

Age at surgical menopause influences cognitive decline, with a rapid decline rate; the deletorious effect of each year of earlier surgical menopause matched the effect of 6 months of aging in relation to the rate of "natural"cognitive decline [84]. MHT slows significantly cognitive decline and future risk of AD when is administered during perimenopause "window of opportunity" in contrast to a worsening and risk of AD with delayed initiation after 65 years [85, 86]. Natural/iatrogenic premature ovarian deprivation needs systemic HT at least until average age of natural menopause, according to the Global Consensus Statement on MHT [87].

The Nationwide Exposure-Matched Cohort Study, Finland (2005-2011) assessed initiation and discontinuation of systemic ERT among community-dwellers with AD versus a matched cohort without AD, with follow-up started on the matching date (AD diagnosis date from prescription register, and index case). It revealed that 3.1% cases with AD and 4.3% without AD used estrogen (E2 valerate/17β-E2) during the follow-up [88]. Only < 0.5% initiated use during the follow-up, and 3.7% continued HT until death. The AD diagnosis age was 35–54.9, 55–64.9, and 65–105 years. The mean age at the beginning of follow-up was 80.8 years (range 34.5–104.6), and the mean users age was 74 years in both cohorts. The prevalence of ERT use 1 year after AD diagnosis declined in 2005–2011, as it was after WHI results. Nearly 3% of Finnish women used/initiated ERT after AD diagnosis. The conclusion was that there were no major differences in systemic ERT among Finnish women with AD vs without AD, and although some cases initiated ERT after AD diagnosis and/or at an advanced age, the observed use patterns were consistent with current recommendations–NAMS HT Position Statement (2017) [6].

One must consider the individualized or personalized HT, after a correct assessment of each woman genetic/epigenetic variability, risk factors and vulnerabilities, type of MT disorder, resistance and reevaluation of benefits and harms [4]. As the presence and severity of midlife VMS varies widely among women, women differ greatly in their risk for brain aging and dementia. Pharmacogenomics is an important part of such personalized approach, being possible to tailor pharmacology, optimal dose, duration, formulation, and route of HT delivery- oral, transdermal, nasal [89].

Progesterone/Progestogens potential cognitive performances. Brain nuclear and membrane Progesterone Receptors. Progesterone/Allopregnanolone and Neurotransmitters

Progesterone/Progestogens potential cognitive effects

During MT on assists at reduced progesterone (Pg) blood levels, and later in peri and postmenopause to Pg absence, and Pg was mandatory for women with intact uterus (oral, vaginal, intrauterine devices, nasal) [89,90]. At the beginning of TH history, fact still actual. Similar to estrogens, Pg is a potent regulator of neurogenesis, cell survival and bioenergetic systems [88, 89]. Estrogens and Pg do not have synergistic actions, and their co-administration was controverted about a lower response compared to a single compound [90-92]. Available progestins- progesterone/progestogens differ largely in their hormonal pattern and, in addition to their progestogenic and antiestrogenic actions on the endometrium, they can exert androgenic, antiandrogenic, glucocorticoid and/or ant mineralocorticoid effects depending on their formulation. There are pure/natural progesterone (synthesized in large amount from the plant diosgenin by the chemist Russell Marker in 1940), and Pg metabolites [allopregnanolone (Allo), dihydroprogesterone (DHP)], and progestogens or synthetic progestins with different chemic and pharmacologic proprieties [93]. There were intensive efforts to develop Pg neurobiology in the hippocampus and cortex, and current discoveries are sustaining Pg administration for more than endometrial protection, for brain aging protection, besides the much analyzed Pg "therapeutic window" in brain trauma. It was proved that within 6 years of menopause and without HT, progesterone levels are positively associated with verbal memory, and global cognition, and at 10 years of postmenopause, the reported association is null in healthy women [94].

The new compound Allo is a neurosteroid, which was extensively experimented on rodents, being experimented now in humans for central and peripheral nervous system damages. Pg is active on cognition through its 5α-reduced metabolite, 3α, 5α-tetrahydroprogesterone or Allo, fact that differentiates Pg from the progestogen MPA, which jeopardizes brain and cognition in postmenopause. Pg is neuroprotective by various mechanisms such as reduction of neuronal vulnerability to neurotoxic molecules, reduction of cell loss, inhibition of lipid peroxidation, and expression of pro-inflammatory genes [95, 96].

Brain Nuclear and Membrane Progesterone Receptors. Progesterone/Allopregnanolone and Neurotransmitters

Pg acts both through the classical/genomic pathway, binding to its estrogen induced nuclear receptors [PR-A, and PR-B (PR-B is the positive regulator of Pg; PR-A antagonizes PR-B)] regulating gene, and together with Allo and DHP through the non- classical membrane Pg receptors [(mPRs) ά, β, γ, and δ, very important for neuroprotection] to signal the cascades and the transcription of various genes [97]. The novel reported mPRs resemble and function as G-protein-coupled receptors. The brain is a major site of rapid actions of Pg, and progestins neurosteroids, and the isoform mPRδ (PAQR6) is exclusively expressed in the brain, intermediating Pg rapid effects [98]. One supposes a cross-talk between steroid signaling pathways involving membrane receptors with transactivation of Pg nuclear receptors. The G-protein-coupled receptor 30 (GPR30) is an intermediary in the rapid, nongenomic actions of estrogens; this proposed function of GPR30 as a membrane ER has been challenged by several research groups in Western Europe, North America with contradictory results on the basis of European negative results [99-101]. The main effects of the 2 pathways are anti-apoptosis promotion, cell survival, bioenergetic, and a significant neural cell proliferation, and white matter generation. Allo induces the generation and survival of new hippocampus neurons, which was associated with restoration of learning and memory function in aged mice and transgenic mouse models of AD [102, 103]. Pg and mainly Allo are active on glial cells, promoting proliferation and action of oligodendrocytes, which can produce Pg and transform bloodstream Pg into Allo and DHP, regulators of myelinization and

modulators of GABA-A receptors [104]. Pg and Allo are promoters for GABAergic system, by using the mPRs to inhibit synaptic transmission, with rapid down-regulation of GnRH hypothalamic secretion, and have an anti- anxiety effect similar to benzodiazepines, a benefit for depression and anxiety control in MT [98, 105-107]. The Allo positive modulation on the release of dopamine may have a possible effect on menopausal depression [108]. The GABAergic role of Pg in hippocampus explains why exogenous administration of progestins has a negative impact on working memory tests in healthy women [109]. Pg and Allo influence the dopaminergic systems with an improvement in motor sensory functions during menstrual cycle phases when Pg is high [105]. Pg and Allo have an inhibitory role on glutamatergic synapses [110]. Allo inhibits dopamine induced glutamate release in the prefrontal cortex, by decreasing the efficacy of glutamate receptor, and inhibits L-type Calcium channel [111-113].

One might select Pg over other progestogens or recommend cyclic HT over continuous combined estrogen-Pg/progestogen therapy. Some model systems may prefer an estrogen alone to an estrogen plus a progestogen, regimen accepted in hysterectomized cases. Some studies pretend that neuroprotective estrogens' actions are modulated by Pg [114-115]. Specifically, continuous Pg exposure is associated with inhibition of estrogen actions whereas cyclic progestogens delivery may enhance estrogens' neural benefits [116]. The dosage and duration of therapy with Pg, Allo is critical, because there is internalization (endocytosis or caveolae) of mPRs [117]. Preclinical studies recommend promotion of endogenous regeneration of damaged brain with Allo once per week, over several months, for brain safety; Allo doses, and frequency of exposure are determinant factors for therapeutic efficacy [103].

Androgens and cognitive performances. DHEA and Intracrinology

Androgen supplementation in women has received enormous attention regarding neuroprotection, sexuality, muscle mass, bone mineral density, physical functioning, and well-being, parameters analyzed in SWAN [4]. Androgen deficiency has no clear-cut definition: impaired sexual function, low energy and depression; a total testosterone level of <15ng/d, which is the lower limit of normal range in some North American laboratories, and measurement of free testosterone is ideal, providing a better estimation of biologically active fraction, but with methodological difficulties [118]. During MT plasma and brain androgens are within physiological limits, the decline of testosterone and DHEA(S) becomes apparent in the decade prior to menopause, being gradual and progressive, after the fourth decade; at 60s testosterone is 50% of women at 20s [119, 120]. One discusses the adrenopause, in conjunction to androgens adrenal gland source, besides ovaries [121]. Relative hyperandrogenemia is a risk of MT, because ovarian stromal hyperplasia under high MT gonadotropins levels, and the change of E2/T ratio predicts incident metabolic syndrome in midlife and postmenopause; the E2/T ratio was not changed by CEE supplementation, which is analyzed in WHI [122-124].

Androgens prevent intracellular amyloid 1-42 (the most damaging form of Aβ) depositions in hippocampus, and entorhinal cortex neurons, preceding amyloid plaque formation, and neuronal death [125]. Androgens support cell survival, axonal regeneration, and dendritic maintenance. Proteomic analyses demonstrated high levels of heat shock protein 70 in testosterone- treated human hippocampus neurons- a sign of Aβ toxicity inhibition, via a rapid estrogen-independent mechanism [10, 126]. Androgen neuroprotective effects are mediated by direct activation of androgen receptors (ARs) pathways, and indirectly by aromatization to E2, and initiation of protective estrogen signaling mechanisms, a controverted action [127-129].

DHEA(S) – a neurosteroid, named the "youth" hormone- the human body does not have receptors, but it is a source of intracrinology, with different enzymes for steroid-forming and/or steroid-inactivating, permitting each cell/tissue to synthesize a small amount of androgens and/or estrogens in order to meet the local physiological needs without affecting other tissues [130]. DHEA(S) is precursor for E2, testosterone, and when DHEA(S) supplemented it is no change on E2/Testosterone plasma levels. The serum estrogen level is at sub-threshold or in biologically inactive concentrations when DHEA(S) is supplemented.

There are controversies about DHEA longitudinal blood and tissue concentrations in humans and rodents; some studies show no differences between pre and postmenopause, other studies discovered high serum DHEA concentrations in normal postmenopause, and some studies show a more rapidly decline in the brain- mainly in hippocampus, than in the rest of the body [131]. It was proposed a short-term DHEA supplement (5 mg/day for 7 days) in perimenopause female rhesus macaques. The comparison of serum and hippocampus levels in treated and controls at same ages revealed that despite elder animals' serum estrogens concentrations were lower, the hippocampus concentrations did not show any differences due to age or DHEA supplementation. The results suggest a brain de novo estrogen synthesis that may compensate perimenopause estrogens' serum loss even without DHEA supplement [132].

Biological actions of DHEA(S) in the brain involve neuroprotection, neurite growth, neurogenesis and neuronal survival, apoptosis, catecholamine synthesis and secretion, as well as anti-oxidant, anti-inflammatory and antiglucocorticoid effects, positive effects on neurosteroidogenesis and endorphin synthesis/release [133].

There are controversies on DHEA de nevo synthesis in human brain and neuroglial cells (astrocytes, and oligodendroglia) from an unknown "precursor" molecule other than pregnenolone [134]. DHEA levels in the normal human brain are higher than serum [131-135]. The decline of DHEA(S) was associated to cognition decline because of neuroinflammation as a part of the immunosenescence process, which favorizes microglia "activation" from a quiescent to a "primed" state with synthesis of pro-inflammatory mediators, known to be involved in hippocampal Aβ increased densities [136].

Besides binding to ERs and ARs, there is a plethora of cell membrane receptors, mitochondrial and reticulum endoplasmic receptors used by DHEA [137]. The effects are mediated via GABA-A cell membrane receptors, probably by metabolizing DHEA into a GABA-A receptor agonist, as androsterone/androstanediol, N-methyl-D aspartate from the glutamate neurotransmitter receptors class, and sigma-1 receptors [138, 139]. DHEA may stimulate nitric oxide (NO) production and NO synthetase activity, inducing a brain anti-oxidant effect [135].

Patients with AD have DHEA lower serum levels than matched cases without AD, and DHEA(S) supplement may have both therapeutic and preventive benefits to limit neuroinflammation, by

anti-inflammatory and antiglucocorticoid effects, and reduction of microtubule-associated protein MAP2 [140-142]. Perimenopausal DHEA(S) supplements are much analyzed from the beginning of this century; concentrations of DHEA(S) are important with respect to the final effect. Low concentrations may be neuroprotective, while high concentrations are ineffective or neurotoxic, and lead to the inhibition of complex I of the mitochondrial respiratory chain [143].

The testosterone supplement in MT may be discussed for cognition maintenance after bilateral oophorectomy in ages < 4 years, when it is an abrupt loss of all ovarian steroids and a disruption of the HPOA, and epigenetic changes induced by oophorectomy may be the cause of accelerated accumulation of multimorbidity, as does natural menopause for biological aging [37, 144, 145]. Besides these conditions, testosterone supplement has no rationale for prevention of cognition impair during perimenopause to MT.

Perspectives for Perimenopause Neuroprotection

Brain aging and neurodegenerative diseases have a multifactorial nature, vascular, metabolic and inflammatory changes from the moment of perimenopause to menopause transition; blood-brain barrier disruption, and aberrant microglial activation can be modulated or prevented in a moment prior to their onset in the "critical period of opportunity," if the clinicians, health care practitioners and the patients are aware of this knowledge, and have a good understanding of very early perimenopausal symptoms, before appearance of any symptom of cognition alteration, earlier or at least at the stage of MCI. Some conditions may predict hippocampus atrophy- hypoxia, hypoperfusion, hypoglycaemia, stress, and seizures, in cases with genetic or familial characteristics, and epigenetic changes of each woman. Endocrine events that signal less exposure to estradiol, such as shorter reproductive span, elder age of menarche, and young age at menopause, and oophorectomy, hysterectomy may increase a woman's risk of cognitive disorders, and dementia. While these risk factors are not modifiable, knowing their timing could help ob/gyns identify patients who could benefit most from preventive measures.

The differences between estrogens, between progesterone and progestogens, between MHT regimens (sequential or continuous combined), between classes of steroid receptors agonists—NeuroSERMs (novel neuro-selective estrogen receptor modulator) and PhytoSERMs (phyto-selective estrogen receptor modulator), and the new molecules tested in high-tech laboratories, will help clinicians/health providers to recommend the best neuroprotective molecule without any harmful action from women's early sex steroids disturbances.

Conflict of interest: None

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