



# Alzheimer's Disease and Premature Ovarian Insufficiency

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**Abstract:** Estradiol promotes neuronal growth, transmission, survival, myelination, plasticity, synaptogenesis, and dendritic branching and it improves cognitive function. Alzheimer's disease (AD) is characterized by amyloid plaques, neurofibrillary tangles, and the loss of neuronal connection in the brain. Genomic analysis has concluded that hypoestrogenism influences the APOE gene and increases the risk of AD. Premature ovarian insufficiency (POI) is defined as oligo/amenorrhea in women below 40 years of age, low estradiol, and high-gonadotropin levels. Early symptoms and signs of POI must be detected in time in order to prevent subsequent complications, such as Alzheimer's disease. Meta-analysis has shown favorable effects of estrogen in preventing Alzheimer's. We measured some of the typical markers of AD in women with POI such as interleukin 6 (IL-6), interleukin 8 (IL-8), tissue necrosis factor  $\alpha$  (TNF $\alpha$ ), TAU1, TREM2, and amyloid precursor proteins (APP). While FSH, LH, and IL-8 were significantly higher in POI group, compared to controls, testosterone and DHEAS were lower. A significant decrease in IL-6 was found in the POI group during a 6-month therapy, as well as an increase in amyloid precursor proteins. **CONCLUSION:** Neurological complications of POI, such as declining short-term memory, cognitive function, and dementia, have to be promptly stopped by initiating estrogen-progestogen therapy in POI. A long-term continuation of the therapy would be strongly advised.

**Keywords:** premature ovarian insufficiency; Alzheimer's disease



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## 1. Introduction

It is predicted that by 2050 the number of people over 60 years of age will increase fivefold compared to 1950 [1]. One billion women will be menopausal in the next 25 years and 80% of them will have some typical menopausal symptoms. A meta-analysis of the global prevalence of premature ovarian insufficiency (POI) found a rate of 3.7% [2]. They all deserve good life quality defined as psychological and physical wellbeing depending on influences of genetic and environmental factors.

## 2. Premature Ovarian Insufficiency (POI)

Premature ovarian insufficiency is characterized by oligo/amenorrhea and hypergonadotropic hypogonadism in women younger than 40 years of age. The cutoff point of follicle-stimulating hormones (FSH) changed from 40 IU/L [3] to 25 IU/L [4] so as to make a diagnosis on time. We proposed four grades of POI: I (FSH: 10–20 IU/L), II (FSH: 21–30 IU/L), III (FSH: 31–40 IU/L), and IV (FSH > 40 IU/L).

### 2.1. Early Symptoms and Signs

Typical symptoms and signs of POI are hot flushes, night sweating, irritability, anxiety, depression, mood swings, loss of concentration, insomnia, loss of libido, vaginal dryness, dyspareunia, and gaining weight.

### 2.2. Late Symptoms and Signs

Late symptoms and signs of untreated POI include the following: cardiovascular (endothelial dysfunction, ischemic heart disease, myocardial infarction, etc.), metabolic syndrome, diabetes mellitus, osteoporosis, bone fractures, cognitive impairments, urogenital and sexual disorders, infertility, lower quality of life, and twofold age-specific mortality rate [5].

In such a disbalance of homeostasis and a loss of adaptive mechanism, resistance and resilience, POI is correlated with inflammatory aging. Oxidative stress refers to an imbalance between oxidation and antioxidation leading to neutrophil infiltrations. An increase in interleukin 6, interleukin 8, interleukin 1  $\beta$ , interleukin 10, tissue growth factor beta (TGF $\beta$ ), interferon  $\gamma$ , and prostaglandin E<sub>2</sub>, and a decrease in tumor necrosis factor  $\alpha$  (TNF $\alpha$ ), and interleukin 2 have been detected in POI. Antioxidants help the organism to fight free radicals.

Known etiological factors inducing POI include chromosomal abnormalities, enzyme changes, autoimmune diseases, FSH receptor gene polymorphism, inhibin B mutation, infectious diseases, adnexectomy, radiotherapy, uterine artery embolization, etc. Unknown factors include stressors, inflammation, telomerase shortening, biological clock acceleration, etc. Stress, as a disease, develops when adaptive mechanisms are broken under the influence of too strong stressors or stressors that have been present for a long time [6].

## 3. Alzheimer's Disease

Premature ovarian insufficiency can cause some neurological diseases. Conversely, some neurological diseases and symptoms may be related to an increased earlier risk of POI [7]. An increased risk of neurological disorders appears to be most apparent in the field of global cognitive and verbal memory. Neurodegenerative diseases, such as Alzheimer's disease, are characterized by sustained cell cycle arrest and the production of a continuous senescence-associated secretory phenotype due to structural and functional changes in neurons [8].

In 1838, Etienne Esquirol first wrote "Menstrual disorders and sequelae of delivery are causes of dementia" in the book "Des Maladies Mentales" [9], Paris. He described typical clinical signs and symptoms of Alzheimer's dementia.

Alzheimer's disease (AD) is a neurodegenerative disease occurring when amyloid beta is accumulated extracellularly and then intracellularly as neurofibrillary tangles. This altered protein clearance ability is age related and regulated by brain cholesterol. Numerous studies have been performed in menopausal women confirming the role of hypoestrogenism in AD. A higher incidence of AD was detected in women who had entered menopause at an earlier age.

There are about 47 million people with AD nowadays. Two-thirds of 5.4 million Americans with AD are women. Scheltens N. study [10] showed that 32% of all people with AD were older than 85 years of age. The severity of AD confirmed the data about the mortality rate which increased 71% in the period between 2000 and 2013 [11]. The situation has been found to be even worse in women with surgical ovariectomy. They have a doubled lifetime risk of dementia [12]. After surgery, hormone therapy appears to be most beneficial if initiated close to the average natural age of menopause [13]. Some typical characteristics of AD are shown in Table 1.

Amyloid beta (peptides and oligomers) and tau hyperphosphorylation, mitochondrial damage and oxidative stress, alterations in calcium signaling and glucose metabolism [14], metal ions and neuropeptides deregulation, apo epsilon polymorphism, and neuroinflammation are typically found in AD.

**Table 1.** Typical characteristics of Alzheimer's disease.

1.	Distinct temporospatial brain pathological changes.
2.	Amyloid plaque accumulation.
3.	Neurofibrillary tangles deposition.
4.	Synaptic loss.
5.	Neuronal death with brain atrophy.

Genetic, epigenetic, environmental, and lifestyle factors are important for AD. Sex hormones play a neuroprotective role. Hypogonadal status can trigger Alzheimer's disease.

Hypoestrogenism and hypoprogesteronism in women and low testosterone in men increase beta amyloid, tau phosphorylation and neuron death, decrease spine density, and impair cognition leading to AD.

### 3.1. Etiology of AD

#### 3.1.1. Genetic Hypothesis

Ratnakumar A. et al. [15] compared neuronal genes upregulated by estrogens in ovariectomized female rhesus macaques with a database of over 17,800 diverse gene sets and applied a rare variant burden test to exome sequencing data from 1208 female AD patients with the onset age below 75 years and 2162 female AD controls. They found an overlap between the genes upregulated by estrogen in macaques and the gene downregulated in the human postmortem AD brain. Estrogen upregulates the APOE gene and progesterone acts antagonistically to estrogen genome-wide. They found that female patients with AD had an excessively rare mutation in the early menopausal gene MCM8.

Apolipoprotein  $\epsilon$  allele is the strongest known genetic factor for AD [16] and is presented in 40–65% of patients with AD. (vs. 15% in healthy-age-matched group). ApoE transports cholesterol to the neurons on apo E receptors and is involved in amyloid deposition. Estrogen receptors are present on the ApoE gene which can modify the expression of the ApoE gene in the cerebral cortex by  $17\beta$  estradiol [17].

#### 3.1.2. Amyloid Hypothesis

Amyloid plaques are aggregates of amyloid  $\beta$  peptide derived mainly from the cleavage of a transmembrane protein named amyloid precursor protein (APP) by sequential action of two aspartic protease enzymes. The insoluble A  $\beta$  aggregates start to appear 15–25 years prior to the onset of cognitive decline or tau pathology. Monomeric, oligomeric, protofibrils and mature insoluble APP are present. Normally, the ratio is as follows:  $A\beta_{42}:A\beta_{40} = 1:9$ . An increase in the ratio is the cause of A  $\beta$  accumulation [18] which induces neuronal injury, a synaptic loss and has neurotoxic effects. APP, under the influence of  $\beta$  and  $\gamma$  secretases, forms amyloid  $\beta$  fibrils which activate microglia and neuronal damage and death. It increases oxidative stress inflammation, alters kinase and phosphatase increases neurofibrillary tangles and further damaging neurons and AD progression.

#### 3.1.3. Tau Hypothesis

Tau pathology (including neurofibrillary tangles, neuritic plaques, neuropil threads, intraneural deposition) is assumed to be a consequence of amyloid accumulation. Tauopathies result in marked synaptic disturbances and impaired selective autophagic clearance [19].

Marker for tauopathies is P-Tau. Neurogranin is a marker of synaptic dysfunction. NFL and FABP are signaling markers influencing axon damage, membrane disruption, and neurodegeneration. Neuroinflammation can be measured by astrogliosis and microgliosis markers MCP-1, YKL-40, TREM2. Amyloidosis is characterized by accumulations of -amyloid  $\beta$  peptide with marker  $A\beta_{1-42}$ .

Microglial-expressed genes associated with AD are: TREM2, CD33, CR1, etc. The mediators of inflammation are reactive oxygen species, interleukin 1, interferon 1, interferon

gamma, TNF alfa leading to disturbed AD clearance, increased levels of TAU, promoting neurofibrillary tangles accumulation and cognitive decline. Microglia expresses sex hormone receptors. Receptors modulate microglial activities producing anti-inflammatory actions that resist the development and progression of AD [20].

#### 4. The Effects of Estrogens on Alzheimer's Disease

##### *Cognitive Health and Brain Function*

Two-thirds of brain weight are blood vessels with receptors for estradiol, progesterone, and androgens. Estradiol is involved in all brain functions and studies have been conducted including hippocampus, striatum, prefrontal cortex controlling language abilities, verbal fluences, memory, sleeping, learning, and the evaluation process. Estradiol influences neuroprotection on the level of cerebral microvascularization, mitochondria, anti-inflammation, synaptic plasticity, neurogenesis, cholinergic neurotransmission, cellular maintenance, and survival. In the basal forebrain, estrogen increases choline acetyltransferase activity and decreases deposition of amyloid. Declining short-term memory and cognitive function and the increased incidence of Alzheimer's disease have been reported in patients with POI, but this phenomenon has not been observed before or after the age-appropriate menopause. Oophorectomy before the age of menopause increases the risk of cognitive impairment or dementia nearly two-fold [21].

Rocca WA et al., using the data from Mayo Clinic, studied oophorectomy and aging in 813 women with unilateral adnexectomy, 676 with bilateral oophorectomy, and 1472 controls. They found that women who underwent surgery before the age of natural menopause had increased cognitive impairment or dementia compared to controls [22]. They found that women who underwent bilateral oophorectomy before the age of 45 experienced increased mortality for neurological and mental disorders.

These data suggest that early estrogen deficiency has deleterious effects on the brain and correlates with nervousness, anxiety, depression, irritability, lack of concentration, insomnia, restlessness, etc., in POI.

The 5-year-long study by the Women Health Initiative (WHI) established a twofold increased risk of all-cause dementia with CEE/MPA [23]. CEE alone had no effect on the risk [24]. Contrasting findings were reported in the 18-year-long follow-up study by WHI, where CEE led to a 26% decrease in deaths from AD whereas CEE/MPA led to no effect [25]. Regarding the formulation, estradiol therapy initiated at the onset of menopause or one to five years after the onset of menopause was associated with a reduced risk of AD [26]. Maki P. [27] concluded that the use of menopause-replacement therapy early on in menopause appears to save cognitive function.

A meta-analysis (21 articles) confirmed that estrogen replacement therapy significantly decreased the risk of the onset and/or development of AD independently of age, sample size, hormone therapy, the duration of the treatment, or the route of administration [28].

KRONOS early Estrogen prevention study showed that taking hormone replacement therapy between 50 and 60 years of age is not cognitively detrimental, whereas taking it over 75–79 years of age was associated with a reduction in global cognition, working memory and executive function [29].

There are positive effects of estrogen on cognitive functions leading to a 20–40% decrease in AD [30]. The genes associated with neurodegenerative diseases are also known to be regulated by estrogens [31]. Brain-derived neurotrophic factor (BDNF) gene contains an estrogen response element (ERE) which confirms that ER $\beta$  affects the maturation and plasticity of synapses through the BDNF-TrkB signaling pathway [32].

Estradiol has many favorable effects on AD (Table 2).

Estrogen therapy improves synaptic plasticity acting on the level of dendritic spines in hippocampus. It improves cerebral blood flow and glucose metabolism. Bioinformatics gene network analysis revealed that insulin-like growth factor 1 (IGF-1) appeared as a central driver leading to the overall reduced energy metabolism associated with early aging in the female brain [33].

Estrogen therapy inhibits amyloid beta accumulation and prevents from AD by:

1. The inhibition of tau hyperphosphorylation and the promotion of tau dephosphorylation in E-receptor-dependent mode through the promotion of protein phosphatase 2A enzyme activities [34].
2. Decreasing A  $\beta$  production by the enhancement of non-amyloid degeneration APP pathway through the activation of negative inhibition of  $\beta$ -secretase and the stimulation of APP-containing vesicle budding by the trans-Golgi network [35].
3. Promoting A  $\beta$  clearance by stimulating microglial A  $\beta$  phagocytosis and enzymes involved in A  $\beta$  degradation, including metalloproteases-2 and 9, insulin-degrading enzyme and neprilysin [36].
4. Increasing the expression of antiapoptotic BclL and Bcl-w and suppressing the expression of proapoptotic Bim lead to the prevention of neuronal loss from A  $\beta$  toxicity [37].
5. Monk D. [38] showed that estrogen prevented amyloid formation from inducing a rise in intracellular calcium and from mitochondrial damage.
6. In the presence of estradiol heat shock protein 70 (HSP70) accumulate at heat shock factor 1—regulated noncoding regions, leading to the deactivation of HSF1 and the abrogation of the heat shock transcriptional response [39].
7. Kalaitzidis D. et al. [40] showed that ER mediates inhibition of nuclear factor—kappa B activity at several levels. Such crosstalk between this important regulator of the endocrine and immune systems is important. Whilst NF-kappa B activity has been shown to be required for the progression of severe inflammatory and autoimmune diseases, ER activity lessens the severity of the same diseases, like AD.

**Table 2.** Some estrogen effects on AD.

Anti-glutamate	Enhances non-amyloidogenic pathway
Anti-apoptotic	Promotes microglial A $\beta$ clearance
Inhibits amyloidogenic pathway	Stimulates enzymatic A $\beta$ degradation
Reduces microvascular resistance	Enhances cholinergic neurotransmitter
Prevents chronic microglia activation	Promotes tau dephosphorylation
Inhibits tau hyperphosphorylation	Promotes synaptogenesis

The role of progesterone was controversial temporarily. It reduces A  $\beta$  production and decreases the pool of soluble A  $\beta$  by:

- Enhancement of the non-amyloidogenic alfa-secretase pathway;
- Modulation of  $\gamma$  secretases activities;
- Increasing A  $\beta$  clearance by the enhancement insulin-degrading enzyme expression and downregulation of beta-secretase gene expression [41].

Progesterone decreases tau hyperphosphorylation and serum progesterone is inversely correlated with tau accumulation.

The ageing process is associated with neurodegeneration, AD, diabetes, obesity, glucose intolerance, decreasing insulin signaling. Genazzani AD et al. recently found that familial diabetes, higher basal insulin levels, and elevated transaminase levels should be considered a consistent clinical suspect of liver impairments that might trigger compensatory hyperinsulinemia [42]. Inflammation and mitochondrial dysfunction, in the case of non-treated early menopausal women or men with low testosterone, can be triggering factors for many diseases.

## 5. Conclusions

All doctors should be obliged to start hormone replacement therapy early, in order to prevent diseases and improve life quality. Long-term therapy for hypogonadal status is advised.

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