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Claudia Barth, Ann-Marie G. de Lange

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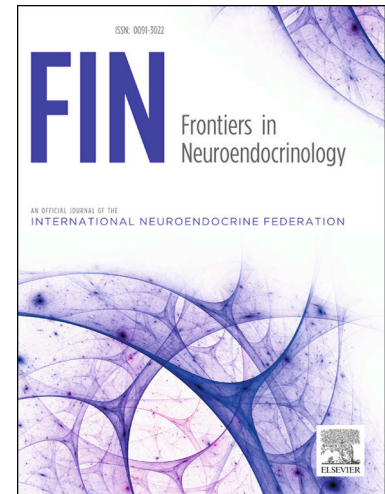
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Towards an understanding of women's brain aging: the immunology of pregnancy and menopause

Claudia Barth^{*a}, Ann-Marie G. de Lange^{*b,a,c}

^a*NORMENT, Institute of Clinical Medicine, University of Oslo, & Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway*

^b*Department of Psychology, University of Oslo, Oslo, Norway*

^c*Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford, UK*

Abstract

Women are at significantly greater risk of developing Alzheimer's disease and show higher prevalence of autoimmune conditions relative to men. Women's brain health is historically understudied, and little is therefore known about the mechanisms underlying epidemiological sex differences in neurodegenerative diseases, and how female-specific factors may influence women's brain health across the lifespan. In this review, we summarize recent studies on the immunology of pregnancy and menopause, emphasizing that these major immunological and hormonal transition phases may play a critical part in women's brain aging trajectories.

Keywords: Women's brain aging; Immunology; Estrogen; Pregnancy; Menopause

*correspondence: claudia.barth@medisin.uio.no & a.m.g.d.lange@psykologi.uio.no

1. Introduction

The prevalence of Alzheimer’s disease (AD) is higher in women compared to men in most regions of the world [1, 2], particularly in older age [3, 4, 5]. AD pathogenesis involves inflammatory processes [6] and autoimmune activity [7, 8, 9], and several types of autoimmune diseases have been linked to increased risk for AD [10]. Women are in general more frequently affected by autoimmune diseases than men [11, 12], and the female to male ratio has been shown to be 3:1 for multiple sclerosis (MS), 7:1 for rheumatoid arthritis (RA), and up to 16:1 for Sjögren’s syndrome [13]. Some autoimmune diseases have considerable impact on brain structure [14, 15, 16, 17, 18, 19, 20], and may accelerate neural aging processes [21, 22, 23, 24].

Despite the known sex differences in prevalence, as well as symptoms, severity, and treatment responses [25, 26], there has been limited focus on how sex-specific immunology affects brain aging [27, 25]. Recent studies have shown that pregnancy-related endocrinological fluctuations influence neural plasticity and brain structure in animals [28, 29, 30, 31, 32] and humans [33, 34, 35, 36], and that biological processes related to menopause can have significant effects on brain health [37]. During pregnancy and menopause, the female immune system undergoes substantial changes [38, 39], and evidence suggests that the immune regulations that occur during these major transitional phases may play an important part in women’s brain aging trajectories [40, 41, 42]. However, the long-term implications of these complex immune processes are far from fully understood. In this *perspective* article, we provide an overview of the current status of knowledge, and potential directions for future research.

2. Pregnancy

When pregnancy occurs, the maternal immune system develops a tolerance to the fetus [43], and adapts a state of low-level inflammation characterized by a fine-tuned balance between anti-inflammatory and pro-inflammatory cytokines [44]. The immune system fluctuates between three immunological stages with unique inflammatory profiles, each corresponding to the stages of gestation: a pro-inflammatory stage that is associated with implantation and placentation; an anti-inflammatory stage that is linked to fetal tolerance and growth; and a final pro-inflammatory stage that initiates parturition [38, 45]. As the normal milieu created by

microbiota can be disrupted by external influences such as infections, a successful pregnancy depends on the ability of the immune system to adapt to each immunological stage [45]. In combination with endocrinological modulations, pregnancy-related immune adaptations may influence maternal brain plasticity during pregnancy and postpartum, potentially affecting the course of neurobiological aging later in life.

2.1. Neural adaptations

During pregnancy and postpartum, neural brain plasticity is instigated to support maternal adaptation and ensure protection of the offspring [32, 40, 44, 46, 47]. In rodents, brain adaptations across pregnancy and postpartum include changes in volume, dendritic morphology, and cell proliferation [44, 48], as well as altered neurogenesis in the hippocampus [46, 49]. Hippocampal neurogenesis has also been shown to increase during middle age in primiparous rats and decrease in nulliparous rats over the same period, indicating enduring effects of maternal experience on the brain [46]. Alternations in microglia, the brain's innate immune cells, have been detected in female rats, with a significant reduction in microglial density and count during late pregnancy and early postpartum in the amygdala, medial prefrontal cortex, nucleus accumbens, and hippocampus [50], indicating a central role of neuroimmune mechanisms in maternal brain plasticity. Hippocampal concentrations of the cytokines interleukin (IL)-6 and IL-10 have been shown to increase in rats after parturition [50], and distinct changes in IL-6 and IL-1 β expression have been observed in the hippocampus and medial prefrontal cortex during pregnancy and postpartum [51].

In humans, reduction in total brain volume has been observed during pregnancy, with reversion occurring within six months of parturition [52]. A study by Hoekzema and colleagues showed reductions in gray matter volume after pregnancy, primarily in regions subserving social cognition; the anterior and posterior midline, the bilateral lateral prefrontal cortex, and the bilateral temporal cortex [34]. The gray matter changes overlapped with brain regions showing activation in response to the women's babies in a functional magnetic resonance imaging (MRI) task, and endured for at least 2 years post-pregnancy. A positive association has also been observed between postpartum months and cortical thickness in prefrontal regions [53]. Conversely, a recent study by Luders and colleagues found no evidence of any significant decrease in gray matter volume following childbirth, but instead detected a

pronounced gray matter *increase* in both cortical and subcortical regions [36]. Alterations in brain structure may thus depend on region and time since delivery [36, 29, 34, 53, 54], and while some maternal brain changes revert postpartum, others may extend beyond this phase [29, 34, 44, 55] and influence neurobiological aging trajectories later in life [56].

2.2. Endocrine-modulated immune adaptations

The brain plasticity that occurs during and after pregnancy is linked to endocrinological modulations [31, 57]. Changes in hormones such as progesterone, estrogen, prolactin, oxytocin, and cortisol are known to regulate brain plasticity [31, 58, 59, 60, 61, 62], and can influence brain structure through regulation of neuronal morphology [58]. Estrogen and progesterone are critically involved in the successful establishment, maintenance, and termination of pregnancy [63]. Four major endogenous estrogens are present in women: estrone (E1), 17β -estradiol (E2), estriol (E3), and estetrol (E4), with E2 being the most prevalent and potent circulating estrogen [64]. Early in pregnancy, progesterone, E1, and E2 levels rise and influence transcriptional signaling of inflammatory responses to suppress detrimental maternal alloresponses, and to favor gestational immune tolerance [63]. For instance, increased levels of progesterone foster the differentiation of CD4+ T cells into T helper type 2 (Th2) cells, which releases anti-inflammatory cytokines including IL-4, IL-5, and IL-10 [65]. E2 also mediates CD4+ T cell activation and IL-10 secretion, via its control of immunosuppressive regulatory B cells [66]. As such, both progesterone and E2 play an important part in creating an anti-inflammatory immune environment to promote fetal growth [67, 68]. The shift towards a Th2 anti-inflammatory phenotype also modulates disease pathogenesis, such that symptoms of diseases that are characterized by inflammatory responses (e.g. MS) improve during pregnancy, while the severity of diseases that are mitigated by inflammatory responses (e.g. influenza) may increase [67]. The recently proposed ‘*pregnancy-compensation hypothesis*’ [13] suggests that the female immune system ramps up throughout adulthood to prepare for a sequence of pregnancies, as from an evolutionary perspective and before birth control, the majority of women would have been pregnant during most of their adult years. In this view, autoimmune activity may arise when the ‘expected’ pregnancies fail to occur; without a frequent push-back from the placenta, the immune system can become overly elevated and start releasing auto-antibodies that attack healthy cells [13]. While endocrine-modulated

immune changes in pregnancy are substantial, some evidence indicates that ovarian hormone fluctuations across the menstrual cycle may involve smaller-scale immune changes that are reminiscent to those observed during pregnancy. One study found a shift towards a Th2-type response in the luteal phase of the menstrual cycle, when both progesterone and E2 are high [69]. Rapid decline in ovarian hormone levels occur both premenstrually and postpartum, and both phases are associated with increased symptom severity of Th1-related diseases such as MS [70, 71]. However, reports on immune cell modulation throughout the menstrual cycle are limited (see [72] for a review).

While hormonal fluctuations and their interactions with immune processes contribute to maternal brain adaptations, their long-term effects on brain aging are not fully understood. For instance, endogenous E2 exposure has been suggested to be neuroprotective [73, 74] and to lower the risk for AD [75], but a recent population-based study found no evidence of an effect of endogenous E2 exposure on incident dementia [76]. Endogenous sex-hormone exposure can be estimated based on factors such as length of reproductive span (time from menarche to menopause) [76] and parity, including age at first birth [77] and duration of breastfeeding [75]. Some studies also include postmenopausal weight or body mass index, number or occurrence of abortions and miscarriages, as well as duration of oral contraceptive (OC) use and hormonal replacement therapy (HRT) to approximate cumulative estrogen exposure [75, 77]. Hence, study-specific variations in the variables included, as well as different compound compositions and modes of administration for OCs and HRT, may contribute to discrepancies in findings observed in the literature. A recent study found that higher cumulative time spent pregnant in first trimesters, but not third trimesters, conferred a protective effect against AD, indicating that immune processes such as the proliferation of regulatory T (Treg) cells, which is highest in the first trimester, could be more relevant for AD risk relative to general estrogenic exposure [40]. Treg cells are T lymphocytes that do not activate the immune system, but rather arrest immune responses when no longer needed - a mechanism that is vital for the maternal tolerance to the fetus [78]. The proliferation of Treg cells during pregnancy could potentially influence brain-aging trajectories later in life, and less evident brain aging in midlife and older age has been observed in parous relative to nulliparous women [79, 55]. However, parity has also been linked to Alzheimer's-like brain

pathology such as neurofibrillary tangle and neuritic plaque [80, 81], as well as increased risk of AD [80, 82], with a higher risk in women with five or more completed pregnancies [83]. A recent study also found a J-shaped relationship between parity and mortality with longevity peaking at 3-4 births [84], indicating that the influence of pregnancies on disease trajectories could depend on the number of children a woman gives birth to.

2.3. Fetal microchimerism

Another mechanism through which pregnancy may influence brain aging is fetal microchimerism - the long-lasting presence of fetal cells in the maternal body [85, 32, 47, 86]. Microchimerism stems from the bi-directional transfer of cells across the placental barrier during pregnancy [87], and involves biological interactions between fetal and maternal cells long after delivery [88]. Fetal chimeric cells are initially undifferentiated and can mature into various cell types in the maternal body [89, 90], including functional T lymphocytes such as T helper cells (CD4+) and T killer cells (e.g. CD8+) that respond to infection [91, 92], as well as glial cells and neurons [93, 94], and pregnancy-related adaptations in blood brain barrier (BBB) permeability may provide the opportunity for microchimeristic cells to establish in the brain [81, 93, 95].

The effects of fetal microchimerism on neural health and disease are debated. Detection of Y chromosomes originating from previous pregnancies with a male fetus has been associated with systemic sclerosis (SSc) [96, 97], which has a peak onset in post-reproductive years. In connection with this, it has been suggested that microchimerism could trigger allogeneic inflammation - an inflammatory response to genetically dissimilar, hence immunologically incompatible, cells [96, 97]. While some types of inflammation can promote cancer formation, allogeneic inflammation can also be therapeutically used to treat certain cancer types [98], which could explain the protective effect of microchimerism on breast cancer documented by several studies [99, 100, 101]. However, persistent fetal microchimerism is also common in healthy women [88, 92], and while some studies suggest that parity involves an increased risk for autoimmune disease [96, 97, 102, 103], other studies report no evidence for such relationship [104, 105, 106, 107, 108, 109, 110, 111, 112, 113]. One study found that the correlation between parity and autoimmune risk disappeared when correcting for several factors including disease history, age, ethnic background, smoking status, and iodine levels [114].

Another study found that in women with MS, a higher proportion were nulliparous at disease onset [115]. There are also studies suggesting that parous women have a *decreased* risk of developing autoimmune disease compared to nulliparous women [13], and that the risk further decreases with multiparity [116, 117]. While fetal cells could be a potential target of inflammatory activity, emerging evidence indicate that these cells are involved in tissue repair processes [117, 90, 118, 119], and lower prevalence and concentration of fetal cells has been found in the brains of women with AD relative to healthy controls [81].

A possible explanation for the inconclusive findings is that microchimerism may involve both cooperation and conflict: a woman's reproductive success depends on the number of children she raises, and while investment in one offspring has evolutionary benefits, providing resources at the expense of the maternal system may compromise future reproduction [120, 121]. Maternal and offspring fitness interests may be conflicting in some domains and aligned in others, and fetal cells may produce chemicals that can manipulate maternal tissues [47, 122, 123]. Conflict over resources has been proposed as a possible explanation for several pregnancy-related conditions such as preeclampsia and gestational diabetes [123, 124], as well as recurrent miscarriage [125]. When the mother-offspring negotiation involves maternally sub-optimal resource allocation, countermeasures including immune targeting of fetal cells in the brain may be initiated [47]. This process is likely to cause inflammatory activity in the maternal brain, which, in addition to its relevance for autoimmune conditions, provides an intriguing link to maternal mental health: postpartum depression, affecting approximately 10-15% of mothers [126], has been associated with increased levels of pro-inflammatory cytokines [127], as well as multiparity and shorter intervals between births [128]. A recent study showed that a composite inflammatory marker score was ranked as the second most predictive factor for postpartum depression, following history of depression as number one [129]. In combination with genetic risk and environmental triggers, inflammatory processes may contribute to an increased susceptibility to pregnancy-related psychopathology including depression, which is known to influence brain health [130, 131, 132]. Fetal microchimerism may thus provide a link between pregnancy-related immunology, maternal mental health, and neural aging processes through common mechanisms [47, 133, 134, 135]. While the implications of pregnancy-related immunology on brain aging are far from fully understood [136, 137],

emerging evidence provides a promising avenue in the search for an understanding of women's brain aging, as well as sex differences in the prevalence of autoimmune disease.

3. Menopause

Aging has been linked to a plethora of broad systems-level effects on human biology including extensive and complex effects on immune responses [39]. *Immunosenescence*, a term coined to describe the deterioration of human immunity with aging, comprises both increased inflammation and diminished protective immunity [138]. Uniquely to women, chronological aging is concomitant with endocrine aging, which is characterized by decreases in reproductive function during the transition to menopause (average age 51.4 years [37]). Menopause is defined as the absence of a menstrual period for one year, and is characterized by marked declines in ovarian hormone levels, as well as desynchronized secretion of pituitary gland hormones [139]. Preceding the last menstrual period, women undergo perimenopause, which lasts 4 years on average [140] and involves gradual, but highly fluctuating withdrawal of E2 [141]. The cessation of ovarian hormone function during perimenopause is associated with rises in chronic low-grade inflammation, which has been shown to promote ovarian insufficiency [142], and to increase the risk for developing obesity, AD, and autoimmune disorders [143]. For instance, the incidence of RA increases with menopause [143], and MS-related symptoms worsen after menopause [144]. The peri-menopausal decline in ovarian hormone function can also increase the risk for osteoporosis, induce metabolic changes that predispose women to cardiovascular diseases and diabetes, and cause physical and psychological symptoms that may be debilitating, including hot flashes, night sweats, urogenital atrophy, sexual dysfunction, as well as mood, sleep, and cognitive disturbances [139, 37]. The majority of women (80%) will experience such symptoms during perimenopause [37], and altered immunoregulation represents a prominent mechanism underlying this constellation of effects also known as *menopausal syndrome* [145].

3.1. Neural adaptations

While some women transition through perimenopause without long-term adverse effects beyond normal aging processes, this period may also involve an increased risk of accelerated

neurological decline [37]. The transition to menopause is characterized by neural changes such as decline in brain glucose metabolism [42], reduction in gray and white matter volume in brain regions vulnerable to AD [146, 147, 148, 41], increased amyloid-beta deposition [149], and a wide array of changes in neurological function [37]. All of these processes are highly intertwined. For instance, to compensate for the decline in brain glucose metabolism, the female brain starts catabolising white matter as an endogenous lipid source of ketone bodies as bioenergetic fuel to generate energy in form of adenosine triphosphate [150]. The catabolism of white matter as an alternative energy source may contribute to the described *menopausal syndrome*. For instance, greater white matter hyperintensity burden has been linked to more hot flashes during sleep among peri-menopausal women without clinical cardiovascular disease [151]. White matter hyperintensities has been shown to be more common among women relative to men, particularly in both deep and periventricular regions [152]. Such sex-differences may not be significant before the age of 50 [153], suggesting that the transition to menopause may have considerable influence on white matter integrity in the female brain. The extent to which white matter is preserved in aging may depend on women's estrogen exposure during reproductive years [154]. For instance, high E2 levels during women's menstrual cycle have been associated with increased hippocampal white matter integrity [35], and long-term usage of unopposed E2 has been linked to greater white matter volumes relative to non-users [154]. Use of OCs may also modulate white matter microstructure during reproductive years [155], but despite their widespread use [156], only a few studies have systematically investigated the effect of OC use on brain structure (see [157] for a review), and reports on the long-term effects of OCs on the female brain are largely missing [157].

Estrogen is a master regulator of metabolic function [158], and the menopausal decline in E2 coincides with a bioenergetic deficit in the brain [42]. Activated by E2, nuclear estrogen receptors, ER- α and ER- β , promote the expression of nuclear encoded genes that are required for glucose transport, glucose metabolism, and mitochondrial functions, while simultaneously suppressing expression of genes required for ketone body metabolism, inflammation and β -amyloid generation [37, 159, 160]. E2 further regulates the bioenergetic system in the brain through transmembrane G-protein coupled estrogen receptor 1 (GPER) and their activation of PI3K and downstream Akt and MAPK-ERK rapid signaling path-

ways [161, 162]. During perimenopause, the estrogen receptor network of ER- α , ER- β and GPER may become uncoupled from the bioenergetic system, resulting in a hypometabolic state associated with neurological dysfunctions [37]. Furthermore, new estrogen receptor splice variants may emerge [163], leading to reduced binding affinity to E2. Alterations in estrogen receptor degradation [164] as well as epigenetic reconfigurations [165] have also been reported. While the brain may be able to adapt to perimenopausal changes in estrogen receptor networks [166], these processes may also give rise to neurological symptoms, such as cognitive dysfunction [37], particularly in women with lower capacity for neuroplastic adaptation [167].

3.2. Endocrine-modulated immune adaptations

Estrogen receptors are widely expressed in most cells in the immune system, and E2 has been implicated in all aspects of immune function including innate and adaptive, humoral, and cell-mediated immune responses [78]. Changes in these E2-regulated immune mechanisms may augment the vulnerability to immune-mediated diseases including autoimmune disease and AD. More specifically, the menopausal transition may potentiate inflammation by changes in T cell biology and increases in cytokine levels [168]. E2 has been shown to impact T cell activation, proliferation, and pathogenic potential [169, 170]. T cells are a type of lymphocyte, which play pivotal roles in adaptive immune functions, and are a major source of cytokines. Two main subtypes of T lymphocytes have been defined, based on the presence of cell surface molecules: CD4+ and CD8+ [171]. While CD8+ cells are T killer cells, T lymphocytes expressing CD4+ are known as T helper cells, which directly regulate B cell recruitment. CD4+ cells can be further subdivided into T helper type 1 (Th1), which produce interferon (IFN)- γ , IL-2 and tumor necrosis factor (TNF)- β [172], and T helper type 2 (Th2), which produce IL-4, IL-5, IL-9, IL-10, and IL-13 [172]. Th1-type cytokines have been associated with pro-inflammatory action linked to perpetuating autoimmune responses [171], and may in excess lead to uncontrolled tissue damage such as seen in MS. Th1-type actions are counteracted by Th2-type responses, and an intricate balance between Th1/Th2 responses seems to be key for healthy immune functions [171]. During reproductive years, women have higher CD4+ counts than men [169]. With menopause, the numbers of CD4+ T as well as B2 cell involved in antibody production, decline, leading to diminished immune adaptation [173]. Another vital category of CD4+ cell are Treg cells. E2

enhances Treg numbers and function [174], and the menopausal decline in E2 levels might lead to a depletion of Treg cells, subsequently increasing the risk for autoimmune disorders. Indirect evidence for this claim stems from research in women with premature ovarian insufficiency, who show decreased numbers of Treg cells and increased CD4+CD69+ activated T cells, indicative of autoimmune activity [175]. In sum, the menopausal decline in E2 levels may result in lower levels of anti-inflammatory cytokines, which in combination with increased pro-inflammatory cytokine levels [176, 177, 178, 138] perturbs the Th1/Th2 balance. Menopause may thus promote a Th1-dominant environment, which entails an increased susceptibility to pro-inflammatory and autoimmune activity [169, 179]. The imbalance towards a Th1 response during menopause may be reversed by HRT, as E2 may help to shift the T-cell population towards a Th2 phenotype [180]. Work by Porter and colleagues showed higher numbers of circulating B-cells, a lower proportion of activated CD4+ T-cells, higher mitogen-induced stimulated T-cell proliferation, an enhanced ability to produce TNF- α , and a trend toward higher T-cell apoptosis in postmenopausal women treated with HRT relative to non-treated women [181]. These findings suggest a preservation or improvement of immune function by replenishing E2. Interestingly, the estrogen-lowering effects of certain OCs have been associated with higher levels of pro-inflammatory markers such as C-reactive protein (CRP) in OC users vs non-users [182], and may increase the risk for specific autoimmune disease such as MS [183]. However, research on the impact of OCs on the female immune system is limited, and future studies integrating endocrine and immune factors are needed to understand how OCs influence brain structure and function during reproductive years and in aging.

Besides the recruitment and activation of T cells as well as production of cytokines, E2 also impacts other cells in the central nervous system. For instance, the cessation of E2 has been linked to increased microglial and astrocyte reactivity in the brain [184, 185, 186]. Microglia are immunocompetent brain-resident tissue macrophage, which are, *inter alia*, involved in the removal of debris from degenerating neurons. However, persistently activated microglia may increase neuronal injury through up-regulating MHC class II molecules, inflammatory cytokines, reactive oxygen and nitrogen species [187], that exacerbate the primary insult [188], and may foster the development of neurodegenerative diseases such as AD [189].

For instance, pro-inflammatory marker IL-1 β is expressed by activated microglia, and may promote the production and metabolism of amyloid precursor protein, augmenting amyloid deposition and plaque formation [9]. Estrogen receptors are present in microglia, and E2 seems to exert anti-inflammatory effects on microglia activation in a dose-dependent manner [190]. One *in vitro* study showed that while high concentrations (1 μ M) of E2 exacerbated LPS-induced microglial activation, concentrations between 0.1–10 nM resulted in reduced activation. However, the effects of E2 were blocked by the anti-estrogen ICI 182,780, suggesting that activation of estrogen receptors is crucial in mediating microglial activation [190]. The menopausal decline in estrogen may lead to an up-regulation in microglial markers CD14, CD18, and CD45, as well as TLR4 and MHC-II markers CD74 and C3 [191], which could cause neuronal damage. The concept that exaggerated responses of activated microglia may contribute to neurodegeneration in aging women could be of importance for treatments targeting systemic neuroinflammation to slow down or halt degenerative processes.

Synergistically with dose-dependent anti-inflammatory properties, E2 further exerts neuroprotective activity in the brain via the modulation of other cell types such as: i) neurons, through anti-apoptotic and neurotrophic actions; ii) neural stem cells, by inducing their proliferation; iii) astroglial cells, by fostering the secretion of neuroprotective molecules instead of neurotoxic agents; iv) endothelial cells, on which E2 acts to reduce adhesion molecule expression and other factors that recruit circulating leukocytes [192, 193, 187]. The latter may be of particular importance for the integrity of the BBB. Formed by astrocytes, endothelial cells and pericytes, the BBB works as a physical barrier between the central nervous system and circulating immune cells. Animal research suggests that changes in estrogen levels increase the permeability of the BBB [194, 195]. The peripheral transfer of inflammatory cytokines and pathogens into the brain due to breaches in the BBB can potentially affect neuronal health, and has been reviewed as a potential cause for AD [196].

In summary, estrogen displays multiple effects on the regulation of immune responses, including the activation of T cells, microglia, and astrocytes, as well as the secretion of cytokines. The menopausal cessation of estrogen coincides with the emergence of a bioenergetic deficit in the brain and may promote a plethora of processes constituting a female-specific *immunosenescence*, which can increase the risk for neurodegenerative diseases such as AD,

as well as autoimmune diseases such as MS and RA. However, E2 does not act in isolation: menopause-related reductions in levels of other hormones such as E1, androgens, and progesterone, as well as increases in FSH and LH, may also influence immune function. E1 is the most prevalent, but least potent, endogenous estrogen during menopause, and is produced by the peripheral aromatization of androgens (androstenedione and testosterone) [197]. Low levels of E1 have been associated with greater all-cause mortality [198], as well as reduced bone mineral density in postmenopausal women [199]. While the effects of E1 on inflammatory processes and women's brain aging are largely unknown, studies indicate potent anti-inflammatory effects of both androgens [200] and progesterone [201] on humoral and cellular immune responses.

Although androgens are continuously produced by both the ovaries and the adrenal gland throughout the postmenopausal period, their levels steadily decline with increasing age [197]. Reduced androgen levels have been reported for Th1-mediated autoimmune diseases such as RA and MS in both male and female patients [202], particularly during active phases of the disease [203]. This is in line with research showing that testosterone has the ability to enhance Th2 cytokine production and inhibit Th1 differentiation [204]. However, effects of androgens differ between the sexes. Uniquely to women, androgens are capable of directly converting peripheral T cells into Treg cells [200], which obstruct immune responses when no longer needed. In combination with low levels of E2, accelerated reduction in androgen levels after menopause may exacerbate a Th1-dominant environment, increasing the risk for autoimmune activity. Conversely, high levels of androgens in postmenopausal women have been linked to increased risk of cardiovascular disease [205]. Hence, similar to the dose-dependent effects of E2 on the immune system [190], adequate and balanced levels of androgens may contribute to preventing negative health outcomes in women after menopause. Similarly to E2 and androgens, high levels of progesterone may also suppress the activity of RA and MS via the inhibition of Th1 pathways [206, 207]. On a neural level, one study demonstrated that a single 100 mg progesterone implant, increasing levels to those of pregnancy, mitigated demyelination and microglia reaction in a focal demyelination mouse model [208]. During perimenopause, progesterone levels decline rapidly, likely contributing to the emerging Th1 immune environment through a loss of inhibitory control over Th1 pathways.

Menopausal decline in E2 is also accompanied by increased levels of FSH and LH, which are both associated with T-cell maturation, T-cell activation, and cytokine production [209, 210]. Elevated FSH may contribute to the genesis of postmenopausal osteoporosis by directly stimulating TNF- α production from bone marrow granulocytes and macrophages [211]. One study found that the number of B cells and CD4+ T cells correlated positively with LH and negatively with FSH serum levels [212]. This finding could indicate that high LH levels may be detrimental, while high FSH levels may lower the risk for autoimmune diseases during and after menopause by reducing the number of B and CD4+ T cells [212]. Another study showed an association between increased LH and FSH levels and an increase in key pro-inflammatory cytokines such as TNF- α and IL-1 β in postmenopausal RA patients, contradicting any beneficial effects of high FSH levels [213]. However, no significant associations were found between hormonal or cytokine fluctuations and changes in disease activity [213], and more research is needed to understand the impact of menopausal LH and FSH levels on women's immune function, risk for autoimmune diseases, and brain health.

To summarize, the effects of sex steroid and pituitary hormones on the female immune system are highly intertwined. Combined with the immunosuppressive actions of androgens and progesterone, dose-dependent immunostimulatory effects of E2 modulate the intricate balance between Th1 and Th2 responses needed to successfully defend against pathogens, immunological tolerance, and autoimmunity [214]. However, the precise molecular mechanisms of how sex steroid and pituitary hormones regulate the immune system to influence brain aging are still to be elucidated. Prospective studies focusing on the dynamic interplay between inflammation, age, and endocrine transition states may foster the development of inflammation-based biomarkers and preventive treatment strategies to improve health outcomes for women.

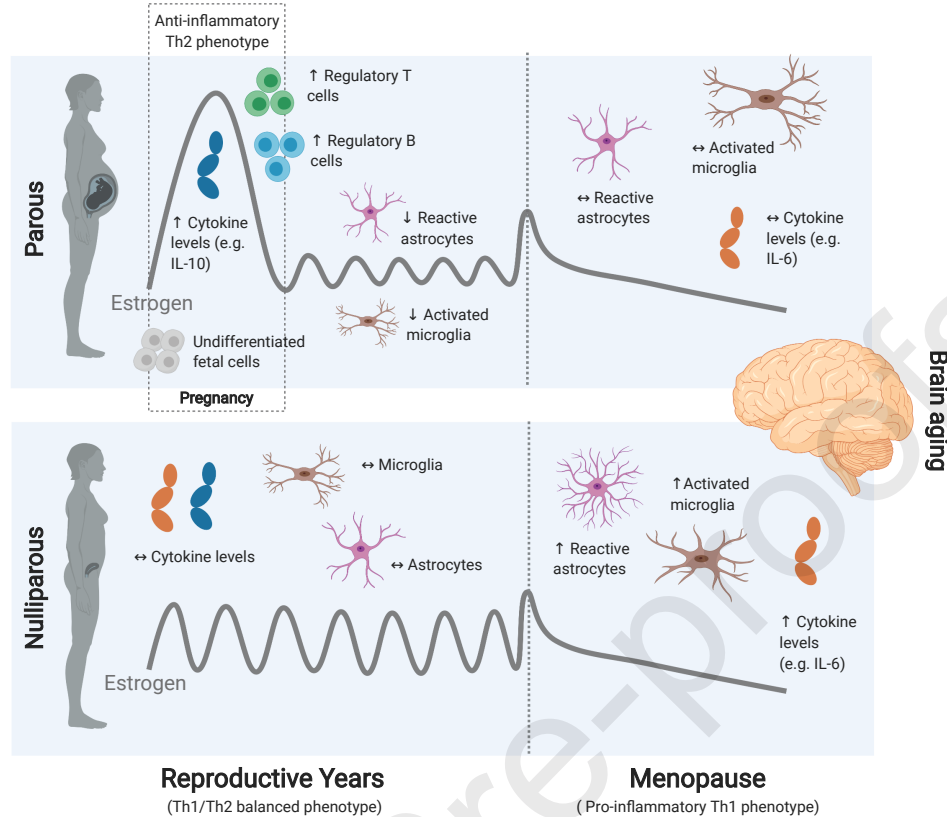


Figure 1: **Conceptual framework for potential effects of parity on menopausal inflammatory processes and subsequent brain aging.** In healthy women, pro- (Th1) and anti-inflammatory (Th2) responses are balanced during reproductive years. While pregnancy fosters a Th2-phenotype (cytokines in dark blue), menopause can be associated with increased low-grade inflammation (Th1-phenotype, cytokines in orange). Pregnancy-related immune adaptations such as the elevation of regulatory T (green) and B cells (blue), and the transfer of fetal cells (gray) may confer protective effects on menopausal inflammatory processes and brain aging later in life. For instance, microglia and astrocytes may be less reactive in parous compared to nulliparous women. In addition, pregnancy and menopause are characterized by marked changes in estrogen levels (gray solid lines): during reproductive years, women's estrogen levels fluctuate across the menstrual cycle, increase during pregnancy, and fall postpartum, and decline gradually, following high fluctuations, during the transition to menopause. After childbirth, parous women have shorter menstrual cycles and lower levels of estradiol than nulliparous women.

4. Potential links between pregnancy, menopause, and brain aging

Immune processes related to reproductive history could potentially link to individual variation in menopause-related inflammation, leading to more or less favorable brain aging trajectories. To the best of our knowledge, no studies have thus far examined the long-term implications of pregnancy-related immune adaptation on menopausal inflammation and subsequent brain aging. In this section, we discuss possible links between neuroimmune and endocrine mech-

anisms in pregnancy and menopause, and whether these transition periods may have an integrated effect on women's brain aging trajectories.

Two mechanisms through which pregnancy-related immune adaptations could modulate women's brain aging are the pervasive elevation of Treg cells [215], and the potential transfer of immunocompetent fetal cells during pregnancy. Both processes may confer a protective effect on menopausal inflammatory processes later in life [39, 40]. While the transition to menopause triggers a Th1 phenotype involving increased risk for autoimmune activity and neuronal injury, pregnancy favors a Th2 environment, which antagonizes the emergence of Th1 cells, contributing to the observed improvement in autoimmune MS and RA symptoms during pregnancy [179]. It is possible that a more favorable immune environment during pregnancy may have long-lasting effects, potentially shaping the emerging immune phenotype during menopause, and subsequently influencing brain-aging trajectories.

Pregnancy and menopause are characterized by contrasting changes in estrogens. However, while E2 levels rise up to 300-fold throughout pregnancy [216], they fall 100–1000 fold postpartum [217], and studies suggest that parous women have shorter menstrual cycles and lower levels of E2 than nulliparous women [218, 219]. *In vitro* work shows that exposure to a low concentration of E2 promoted neuronal survival and intracellular calcium homeostasis, whereas exposure to a high concentration was ineffective and resulted in increased cellular vulnerability to neurodegenerative insults [220]. Similarly, low-dose estrogen replacements show anti-inflammatory properties, whereas higher dosages show increases in inflammatory markers such as CRP [221]. Hence, down-regulated lifetime estrogen exposure following pregnancy [218, 219] could possibly contribute to favorable brain aging trajectories later in life [79]. In line with this, conjugated equine estrogen has been associated with greater atrophy [222] and higher rates of ventricular expansion [223] in menopausal women. However, other neuroimaging studies suggest a protective effect of HRT on gray matter [224], white matter, and ventricle size [154], as well as risk for AD [75]. Differences in content, dosage, and administration may contribute to inconclusive findings across observational studies and randomized trials [225, 226], and neuroprotective effects of estrogen could potentially depend on 'optimal' exposure, which could vary between individuals. For instance, some evidence points to genotype-specific influence of estrogen exposure on brain aging: increased E2 levels

induced by HRT have been associated with reduced risk of developing AD in apolipoprotein E type 4 (APOE e4) non-carriers, but not in carriers [227, 228], and higher menopausal levels of E2 have been linked to more evident brain aging in APOE e4 carriers, and less evident brain aging in non-carriers [229].

E2-driven anti-inflammatory effects on microglia activation has also been shown to be dose-dependent [190]. Haim and colleagues reported that microglia density and number was significantly reduced in multiple brain regions in pregnant and postpartum female rats relative to virgin rats [50], and Ritzel and colleagues found that compared to nulliparous mice, parous mice had less reactive microglia [230]. Pregnancy-related alterations in microglia density, number, and activity could contribute to reduced low-grade neuroinflammation later in life, potentially augmenting the capacity for neuroplastic compensation in response to perimenopausal inflammation processes. E2 is a potent regulator of neuroplasticity in the female brain [59], and it has been suggested that neuroplasticity may play a vital part in understanding the borders between normal aging and early stages of AD [231]. Several of the neural symptoms observed in AD are also found in normal brain aging, including accumulation of amyloid protein and brain atrophy [231, 232, 233, 234], and the levels of neuropathology that can be tolerated without neurological symptoms and cognitive decline varies substantially between individuals [167]. Interestingly, research indicates that intensity and duration of perimenopausal symptoms may represent warning signs for an increased risk of adverse health consequences later in life, particularly neurodegenerative diseases such as AD [37]. Targeting the links between estrogen and immune-related neuroplasticity in pregnancy and menopause represents an unexplored avenue for studying individual differences in women's brain aging trajectories.

5. Conclusion

As summarized in this paper, evidence suggests that pregnancy and menopause involve complex and dynamic immune regulations that may play a critical part in brain-aging trajectories through multiple pathways. Longitudinal in-depth studies on how the immunology of these major transitional periods interact and influence brain aging are warranted for a more complete understanding of neural aging processes, as well as the sex-differences in AD prevalence.

With life expectancy exceeding 80 years in Western countries, women spend a considerable part of their lifetime post menopause, making such lines of research of vital importance to public health.

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Highlights

- Women are at higher risk for autoimmune conditions and Alzheimer's disease.
- Estrogen regulates immune function and neuroplasticity.
- Pregnancy and menopause involve considerable changes in estrogen and immune function.
- Previous pregnancies may influence menopausal inflammation processes.
- Pregnancies may affect brain aging by fostering 'optimal' lifetime estrogen exposure.