Frontiers in Neuroendocrinology 58 (2020) 100850

Contents lists available at ScienceDirect

Frontiers in Neuroendocrinology

journal homepage: www.elsevier.com/locate/yfrne

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

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ARTICLE INFO

Keywords:
Women's brain aging
Immunology
Estrogen
Pregnancy
Menopause

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 immunoendocrine transition phases may play a critical part in women's brain aging trajectories.

1. Introduction

The prevalence of Alzheimer's disease (AD) is higher in women compared to men in most regions of the world (Winblad et al., 2016; Nichols et al., 2019), particularly in older age (Miech et al., 2002; Roberts et al., 2014, Fratiglioni et al., 1997). AD pathogenesis involves inflammatory processes (Wyss-Coray and Rogers, 2012) and autoimmune activity (Fymat, 2018; D'Andrea, 2005; Sardi et al., 2011), and several types of autoimmune diseases have been linked to increased risk for AD (Wotton and Goldacre, 2017). Women are in general more frequently affected by autoimmune diseases than men (Whitacre, 2001; Ngo et al., 2014), 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 (Natri et al., 2019). Some autoimmune diseases have considerable impact on brain structure (Cui and Liu, 2017; Wang et al., 2016; Herranz et al., 2016; Argyropoulou et al., 2006; Mohamed and Nassef, 2010; Sardanelli et al., 2005; Gamal et al., 2019), and may accelerate neural aging processes (Høgestøl et al., 2019; Kaufmann et al., 2019; Pini et al., 2016; Perry, 2010).

Despite the known sex differences in prevalence, as well as symptoms, severity, and treatment responses (Golden and Voskuhl, 2017; Mazure and Swendsen, 2016), there has been limited focus on how sex-specific immunology affects brain aging (Ferretti et al., 2018; Golden and Voskuhl, 2017). Recent studies have shown that pregnancy-related hormonal fluctuations influence neural plasticity and brain structure in animals (Galea et al., 2018; Duarte-Guterman et al., 2019; Barha et al., 2015; Galea et al., 2014; Barha and Galea, 2017) and humans (Taylor et al., 2019; Hoekzema et al., 2017; Barth et al., 2016; Luders et al., 2020), and that immunoendocrine processes related to menopause can have significant effects on brain health (Brinton et al., 2015). During pregnancy and menopause, the female immune system undergoes substantial changes (Mor et al., 2011; Mishra and Brinton, 2018), and evidence suggests that the immune regulations that occur during these major transitional phases may influence women's brain aging trajectories later in life (Fox et al., 2018; Mosconi et al., 2017; Ding et al., 2013). 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 (Luppi, 2003), and adapts a state of low-level inflammation characterized by a fine-tuned balance between anti-inflammatory and pro-inflammatory cytokines (Hillerer et al., 2014). 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

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https://doi.org/10.1016/j.yfrne.2020.100850
Received 3 February 2020; Received in revised form 23 March 2020; Accepted 20 May 2020
Available online 03 June 2020

tolerance and growth; and a final pro-inflammatory stage that initiates parturition (Mor et al., 2011, 2017). 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 (Mor et al., 2017). 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 (Barha and Galea, 2017; Fox et al., 2018; Hillerer et al., 2014; Eid et al., 2019; Boddy et al., 2015). In rodents, brain adaptations across pregnancy and postpartum include changes in volume, dendritic morphology, and cell proliferation (Hillerer et al., 2014; Kinsley et al., 2006), as well as altered neurogenesis in the hippocampus (Eid et al., 2019; Rolls et al., 2008). 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 (Eid et al., 2019). 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 (Haim et al., 2017), 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 (Haim et al., 2017), and distinct changes in IL-6 and IL-1β expression have been observed in the hippocampus and medial prefrontal cortex during pregnancy and postpartum (Sherer et al., 2017).

In humans, reduction in total brain volume has been observed during pregnancy, with reversion occurring within six months of parturition (Oatridge et al., 2002). 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 (Hoekzema et al., 2017). The gray matter changes overlapped with brain regions showing activation in response to the women's infants 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 (Kim et al., 2018). 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 (Luders et al., 2020). Alterations in brain structure may thus depend on region and time since delivery (Luders et al., 2020; Duarte-Guterman et al., 2019; Hoekzema et al., 2017; Kim et al., 2018; Kim et al., 2010), and while some maternal brain changes revert postpartum, others may extend beyond this phase (Duarte-Guterman et al., 2019; Hoekzema et al., 2017; Hillerer et al., 2014; Orchard et al., 2019) and influence neurobiological aging trajectories later in life (Pawluski et al., 2016).

2.2. Endocrine-modulated immune adaptations

The brain plasticity that occurs during and after pregnancy is linked to endocrinological modulations (Galea et al., 2014; Kinsley and Lambert, 2008). Changes in hormones such as progesterone, estrogen, prolactin, oxytocin, and cortisol are known to regulate brain plasticity (Galea et al., 2014; Simerly, 2002; Barha and Galea, 2010; Barha and Liu-Ambrose, 2018; Catenaccio et al., 2016; Moreau et al., 2013), and can influence brain structure through regulation of neuronal morphology (Simerly, 2002). 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 (Thomas and Potter, 2013). 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 (Schumacher et al., 2014). For instance, increased levels of progesterone foster the differentiation of CD4 + T cells into T helper type 2 (Th2) cells, which release anti-inflammatory cytokines including IL-4, IL-5, and IL-10 (Szekeres-Bartho et al., 1996). E2 also mediates CD4 + T cell activation and IL-10 secretion, via its control of immunosuppressive regulatory B cells (Muzzio et al., 2014). As such, both progesterone and E2 play an important part in creating an anti-inflammatory immune environment to promote fetal growth (Robinson and Klein, 2012; Raghupathy, 1997). 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 (Robinson and Klein, 2012). The recently proposed *'pregnancy-compensation hypothesis'* (Natri et al., 2019) 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 (Natri et al., 2019). 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 (Faas et al., 2000). 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 (Smith and Studd, 1992; Langer-Gould et al., 2010). However, reports on immune cell modulation throughout the menstrual cycle are limited (see Oertelt-Prigione, 2012 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 (MacLennan et al., 2006; Gibbs and Gabor, 2003) and to lower the risk for AD (Fox et al., 2013), but a recent population-based study found no evidence of an effect of endogenous E2 exposure on incident dementia (Prince et al., 2018). Endogenous sex-hormone exposure can be estimated based on factors such as length of reproductive span (time from menarche to menopause) (Prince et al., 2018) and parity, including age at first birth (Smith et al., 1999) and duration of breastfeeding (Fox et al., 2013). 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 (Fox et al., 2013; Smith et al., 1999). 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 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 (Fox et al., 2018). 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

(Moulton, 2018). 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 (de Lange et al., 2019; Orchard et al., 2019). However, parity has also been linked to Alzheimer's-like brain pathology such as neurofibrillary tangle and neuritic plaque (Beeri et al., 2009; Chan et al., 2012), as well as increased risk of AD (Beeri et al., 2009; Colucci et al., 2006), with a higher risk in women with five or more completed pregnancies (Jang et al., 2018). A recent study also found a J-shaped relationship between parity and mortality with longevity peaking at 3–4 births (Zeng et al., 2016), 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 (Liegeois et al., 1981; Barha and Galea, 2017; Boddy et al., 2015; Bianchi et al., 2001). Microchimerism stems from the bi-directional transfer of cells across the placental barrier during pregnancy (Ye et al., 2010), and involves biological interactions between fetal and maternal cells long after delivery (Bianchi et al., 1996). Fetal chimeric cells are initially undifferentiated and can mature into various cell types in the maternal body (Khosrotehrani et al., 2004; Nelson, 2012), including functional T lymphocytes such as T helper cells (CD4+) and T killer cells (e.g. CD8+) that respond to infection (Khosrotehrani et al., 2008; Evans et al., 1999), as well as glial cells and neurons (Zeng et al., 2010; Tan et al., 2005), and pregnancy-related adaptations in blood brain barrier (BBB) permeability may provide the opportunity for microchimeristic cells to establish in the brain (Chan et al., 2012; Zeng et al., 2010; Schreurs et al., 2012).

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) (Nelson et al., 1998; Scaletti et al., 2002), 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 (Nelson et al., 1998; Scaletti et al., 2002). While some types of inflammation can promote cancer formation, allogeneic inflammation can also be therapeutically used to treat certain cancer types (Ritter and Greten, 2019), which could explain the protective effect of microchimerism on breast cancer documented by several studies (Kamper-Jørgensen et al., 2012; Gadi and Nelson, 2007; Cirello et al., 2010). However, persistent fetal microchimerism is also common in healthy women (Bianchi et al., 1996; Evans et al., 1999), and while some studies suggest that parity involves an increased risk for autoimmune disease (Nelson et al., 1998; Scaletti et al., 2002; Yeung and Dendrou, 2019; Jørgensen et al., 2012), other studies report no evidence for such relationship (Walsh et al., 2005; Pedersen et al., 2006; Rogers et al., 2012; Cooper et al., 2002; Costenbader et al., 2007; Selva-O'Callaghan et al., 2003; Gannagé et al., 2002; Mosca et al., 2003; Murata et al., 1999; Koopmans et al., 2008). 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 (Yehuda et al., 2017). Another study found that in women with MS, a higher proportion were nulliparous at disease onset (Runmarker and Andersen, 1995). There are also studies suggesting that parous women have a *decreased* risk of developing autoimmune disease compared to nulliparous women (Natri et al., 2019), and that the risk further decreases with multiparity (Ulff-Møller et al., 2009; Borchers et al., 2010). While fetal cells could be a potential target of inflammatory activity, emerging evidence indicate that these cells are involved in tissue repair processes (Borchers et al., 2010; Nelson, 2012; Mahmood and O'Donoghue, 2014; Nassar et al., 2012), and lower prevalence and concentration of fetal cells has been found in the brains of women with AD relative to healthy controls (Chan et al., 2012).

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 (Hamilton, 1964; Trivers, 1974). 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 (Boddy et al., 2015; Kinder et al., 2017; Haig, 1993). Conflict over resources has been proposed as a possible explanation for several pregnancy-related conditions such as preeclampsia and gestational diabetes (Haig, 1993, 2014), as well as recurrent miscarriage (Gammill et al., 2014). When the mother-offspring negotiation involves maternally sub-optimal resource allocation, countermeasures including immune targeting of fetal cells in the brain may be initiated (Boddy et al., 2015). 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 (Wisner et al., 2013), has been associated with increased levels of pro-inflammatory cytokines (Kendall-Tackett, 2007), as well as multiparity and shorter intervals between births (Gürel and Gürel, 2000). 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 (Bränn et al., 2017). 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 (Schmaal et al., 2017; Allan et al., 2016; Al Hazzouri et al., 2018). Fetal microchimerism may thus provide a link between pregnancy-related immunology, maternal mental health, and neural aging processes through common mechanisms (Boddy et al., 2015; Consortium et al., 2014; Miller et al., 2016; Andreassen et al., 2015). While the implications of pregnancy-related immunology on brain aging are far from fully understood (Fugazzola et al., 2011; Chan and Nelson, 2013), 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 (Mishra and Brinton, 2018). *Immunosenescence*, a term coined to describe the deterioration of human immunity with aging, comprises both increased inflammation and diminished protective immunity (Goetzl et al., 2010). 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 (Brinton et al., 2015)). 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 (Davis et al., 2015). Preceding the last menstrual period, women undergo perimenopause, which lasts 4 years on average (Harlow et al., 2012) and involves gradual, but highly fluctuating withdrawal of E2 (Burger et al., 2002). 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 (Ağaçayak et al., 2016), and to increase the risk for developing obesity, AD, and autoimmune disorders (Doran et al., 2002). For instance, the incidence of RA increases with menopause (Doran et al., 2002), and MS-related symptoms worsen after menopause (Tutuncu et al., 2013). 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 (Davis et al., 2015; Brinton et al., 2015). The majority of women (80%) will experience such symptoms during perimenopause (Brinton et al., 2015), and altered immunoregulation represents a prominent mechanism underlying this constellation of effects also known as *menopausal syndrome* (Avis et al., 2005).

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 (Brinton et al., 2015). The transition to menopause is characterized by neural changes such as decline in brain glucose metabolism (Ding et al., 2013), reduction in gray and white matter volume in brain regions vulnerable to AD (Fjell et al., 2009; Goto et al., 2011; Storsve et al., 2014; Mosconi et al., 2017), increased amyloid-beta deposition (Mosconi et al., 2018), and a wide array of changes in neurological function (Brinton et al., 2015). 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 (Klosinski et al., 2015). 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 (Thurston et al., 2016). White matter hyperintensities has been shown to be more common among women relative to men, particularly in both deep and periventricular regions (Sachdev et al., 2009). Such sex-differences may not be significant before the age of 50 (Wen et al., 2009), 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 (Ha et al., 2007). For instance, high E2 levels during women's menstrual cycle have been associated with increased hippocampal white matter integrity (Barth et al., 2016), and long-term usage of unopposed E2 has been linked to greater white matter volumes relative to non-users (Ha et al., 2007). Use of OCs may also modulate white matter microstructure during reproductive years (De Bondt et al., 2013), but despite their widespread use (Christin-Maitre, 2013), only a few studies have systematically investigated the effect of OC use on brain structure (see Pletzer and Kerschbaum, 2014 for a review), and reports on the long-term effects of OCs on the female brain are largely missing (Pletzer and Kerschbaum, 2014).

Estrogen is a master regulator of metabolic function (Rettberg et al., 2014), and the menopausal decline in E2 coincides with a bioenergetic deficit in the brain (Ding et al., 2013). 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 (Brinton et al., 2015; Nilsen et al., 2007; Zhao et al., 2012). 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 pathways (Arevalo et al., 2012; Brinton, 2008). 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 (Brinton et al., 2015). Furthermore, new estrogen receptor slice variants may emerge (Wang et al., 2012), leading to reduced binding affinity to E2. Alterations in estrogen receptor degradation (Zhang et al., 2011) as well as epigenetic reconfigurations (Fortress and Frick, 2014) have also been reported. While the brain may be able to adapt to perimenopausal changes in estrogen receptor networks (Scheller et al., 2018), these processes may also give rise to neurological symptoms, such as cognitive dysfunction (Brinton et al., 2015), particularly in women with lower capacity for neuroplastic adaptation (Voss et al., 2017).

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 (Moulton, 2018). 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 (Pfeilschifter et al., 2002). E2 has been shown to impact T cell activation, proliferation, and pathogenic potential (Pernis, 2007; Kassi and Moutsatsou, 2010). 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+ (Berger, 2000). 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 (Romagnani, 2000), and T helper type 2 (Th2), which produce IL-4, IL-5, IL-9, IL-10, and IL-13 (Romagnani, 2000). Th1-type cytokines have been associated with pro-inflammatory action linked to perpetuating autoimmune responses (Berger, 2000), 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 (Berger, 2000). During reproductive years, women have higher CD4 + counts than men (Pernis, 2007). With menopause, the numbers of CD4 + T as well as B2 cell involved in antibody production, decline, leading to diminished immune adaptation (Kamada et al., 2001). Another vital category of CD4 + cell are Treg cells. E2 enhances Treg numbers and function (Nie et al., 2015), 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 (Kobayashi et al., 2019). 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 (Cioffi et al., 2002; Giuliani et al., 2001; Yasui et al., 2007; Goetzl et al., 2010) perturbs the Th1/Th2 balance. Menopause may thus promote a Th1-dominant environment, which entails an increased susceptibility to pro-inflammatory and autoimmune activity (Pernis, 2007; Whitacre et al., 1999). 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 (Kamada et al., 2000). 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 (Porter et al., 2001). 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 (Meier et al., 2018), and may increase the risk for specific autoimmune disease such as MS (Williams, 2017). 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 (Xie et al., 2013; Suenaga et al., 2015; Villa et al., 2016). 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 (Vegeto et al., 2008), that exacerbate the primary insult (Giulian et al., 1995), and may foster the development of neurodegenerative diseases such as AD (Kalaria, 1999). For instance, pro-inflammatory marker IL-1β is expressed by activated microglia, and may promote the production and metabolism of amyloid precursor protein, augmenting amyloid deposition and plaque formation (Sardi et al., 2011). Estrogen receptors are present in microglia, and E2 seems to exert anti-inflammatory effects on microglia activation in a dose-dependent manner (Bruce-Keller et al., 2000). One *in vitro* study showed that while high concentrations (1 μM) 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 (Bruce-Keller et al., 2000). 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 (Sárvári et al., 2012), 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 (Maggi et al., 2004; Pozzi et al., 2006; Vegeto et al., 2008). 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 (Bake and Sohrabji, 2004; Burek et al., 2010). The peripheral transfer of inflammatory cytokines and pathogens into the brain due to breaches in the BBB can potently affect neuronal health, and has been reviewed as a potential cause for AD (Sohrabji, 2006).

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) (Sammaritano, 2012). Low levels of E1 have been associated with greater all-cause mortality (Mansur et al., 2012), as well as reduced bone mineral density in postmenopausal women (Suzuki et al., 1995). 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 (Gubbels Bupp and Jorgensen, 2018) and progesterone (Hughes, 2012) 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 (Sammaritano, 2012). Reduced androgen levels have been reported for Th1-mediated autoimmune diseases such as RA and MS in both male and female patients (Cutolo et al., 2002), particularly during active phases of the disease (Tomassini et al., 2005). This is in line with research showing that testosterone has the ability to enhance Th2 cytokine production and inhibit Th1 differentiation (Kissick et al., 2014). However, effects of androgens differ between the sexes. Uniquely to women, androgens are capable of directly converting peripheral T cells into Treg cells (Gubbels Bupp and Jorgensen, 2018), 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 (Yasui et al., 2012). Hence, similar to the dose-dependent effects of E2 on the immune system (Bruce-Keller et al., 2000), 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 (Østensen et al., 1983; Shah et al., 2019). 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 (Garay et al., 2011). 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 (Athreya et al., 1993; Sabharwal et al., 1992). Elevated FSH may contribute to the genesis of postmenopausal osteoporosis by directly stimulating TNF-α production from bone marrow granulocytes and macrophages (Iqbal et al., 2006). One study found that the number of B cells and CD4 + T cells correlated positively with LH and negatively with FSH serum levels (Giglio et al., 1994). 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 (Giglio et al., 1994). 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-1β in postmenopausal RA patients, contradicting any beneficial effects of high FSH levels (Kåss et al., 2010). However, no significant associations were found between hormonal or cytokine fluctuations and changes in disease activity (Kåss et al., 2010), 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 (Desai and Brinton, 2019). 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

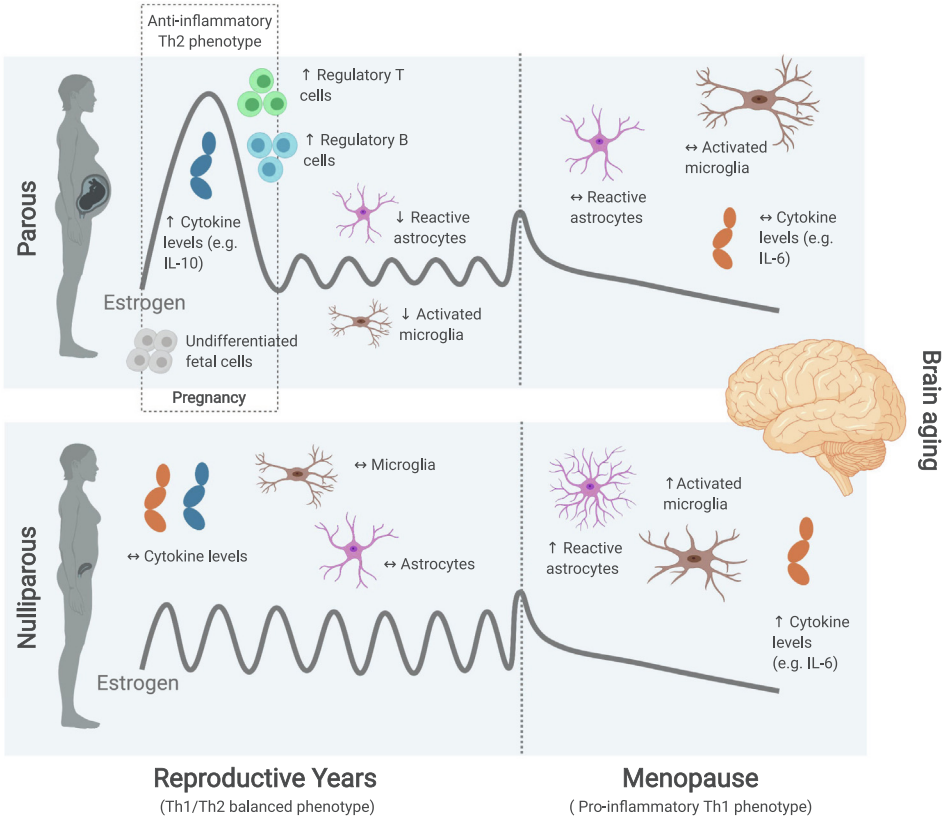

Fig. 1. Conceptual framework for potential effects of parity on menopausal inflammatory processes and subsequent brain aging. In healthy women, pro- (Th1) and anti-inflammatory (Th2) responses are balanced during reproductive years. While pregnancy fosters a Th2-phenotype (cytokines in dark blue), menopause 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. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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.

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 mechanisms in pregnancy and menopause, and whether these transition periods may have an integrated effect on women's brain aging trajectories (see Fig. 1).

Two mechanisms through which pregnancy-related immune adaptations could modulate women's brain aging are the pervasive elevation of Treg cells (Kieffer et al., 2017), and the potential transfer of immunocompetent fetal cells during pregnancy. Both processes may confer a protective effect on menopausal inflammatory processes later in life (Mishra and Brinton, 2018; Fox et al., 2018). 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 (Whitacre et al., 1999). 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 (Schock et al., 2016), they fall 100–1000 fold postpartum (Nott et al., 1976), and studies suggest that parous women have shorter menstrual cycles and lower levels of E2 than nulliparous women (Bernstein et al., 1985; Dorgan et al., 1995). *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 (Chen et al., 2006). Similarly, low-dose estrogen replacements show anti-inflammatory properties, whereas higher dosages show increases in inflammatory markers such as CRP (Prestwood et al., 2004). Hence, down-regulated lifetime estrogen exposure following pregnancy (Bernstein et al., 1985; Dorgan et al., 1995) could possibly contribute to favorable brain aging trajectories later in life (de Lange et al., 2019). In line with this, conjugated equine estrogen has been associated with greater atrophy (Resnick et al., 2009) and higher rates of ventricular expansion (Kantarci et al., 2016) in menopausal women. However, other neuroimaging studies suggest a protective effect of HRT on gray matter (Erickson et al., 2005), white matter, and ventricle size (Ha et al., 2007), as well as risk for AD (Fox et al., 2013). Differences in content, dosage, and administration may contribute to inconclusive findings across observational studies and randomized trials (Vandenbroucke, 2009; Col and Pauker, 2003), 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 (Yaffe et al., 2000; Manly et al., 2000), 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 (de Lange et al., 2020).

E2-driven anti-inflammatory effects on microglia activation has also been shown to be dose-dependent (Bruce-Keller et al., 2000). 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 (Haim et al., 2017), and Ritzel and colleagues found that compared to nulliparous mice, parous mice had less reactive microglia (Ritzel et al., 2017). 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 (Barha and Galea, 2010), and it has been suggested that neuroplasticity may play a vital part in understanding the borders between normal aging and early stages of AD (Fjell et al., 2014). Several of the neural symptoms observed in AD are also found in normal brain aging, including accumulation of amyloid protein and brain atrophy (Fjell et al., 2009, 2014; Driscoll et al., 2009; Morris et al., 2010), and the levels of neuropathology that can be tolerated without neurological symptoms and cognitive decline varies substantially between individuals (Voss et al., 2017). 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 (Brinton et al., 2015). 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 though 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.

Acknowledgements

This work was funded by the Research Council of Norway (286838; AM.G.dL).

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