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Pregnancy, Postpartum and Parity: Resilience and Vulnerability in Brain Health and Disease

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Abstract

Risk and resilience in brain health and disease can be influenced by a variety of factors. While there is a growing appreciation to consider sex as one of these factors, far less attention has been paid to sex-specific variables that may differentially impact females such as pregnancy and reproductive history. In this review, we focus on nervous system disorders which show a female bias and for which there is data from basic research and clinical studies pointing to modification in disease risk and progression during pregnancy, postpartum and/or as a result of parity: multiple sclerosis (MS), depression, stroke, and Alzheimer's disease (AD). In doing so, we join others (Shors, 2016; Galea et al., 2018) in aiming to illustrate the importance of looking beyond sex in neuroscience research.

Keywords

allogregnanolone; Alzheimer's disease; postpartum depression; estrogen; fetal microchimerism; immune; maternal; multiple sclerosis; progesterone; prolactin; stroke

1. Introduction

Females have long been overlooked in neuroscience and other areas of biomedical research, but in recent years, the appreciation to consider sex as a biological variable has grown, a shift driven in part by the policy changes enacted by the NIH (Miller et al., 2017; Clayton, 2018; Shansky, 2019). While the greater focus on sex differences represents a major step forward, it is also important to take into account how sex-specific variables may affect women's brain health and disease, both in the short term and over the long term across the female lifespan (Duarte-Guterman et al., 2019). Pregnancy and motherhood are among the uniquely female experiences that warrant further attention in preclinical and clinical studies which tend to use virgin animals or not consider reproductive status (Shors, 2016; Galea et al., 2018). It could be argued that studying pregnant, postpartum and/or parous females with one or more reproductive experiences may better reflect the female population since most

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women (>80%) have undergone pregnancy and had offspring at least once (Martinez et al., 2012).

Pregnancy and the postpartum period are characterized by extensive physiological changes. These include drastic hormonal fluctuations that are vital for the maintenance of pregnancy, many of which are unparalleled by any other neuroendocrine events (e.g., menstruation, puberty, menopause) in a healthy female's lifetime (Brett & Baxendale, 2001; Brunton & Russell, 2010). The hormonal events of human pregnancy can be largely attributed to the placenta (Napso et al., 2018) which contributes to the 20-fold rise in progesterone as well as the basal secretion of glucocorticoids at 2–3X above non-pregnant levels. Estrogens rise even more with estradiol (E2) levels increasing up to 300X by the end of pregnancy and estriol (E3), which is nearly undetectable outside of pregnancy, soaring 1000-fold (Brett & Baxendale, 2001). Shortly after delivery, levels of these steroid hormones plummet with the expulsion of the placenta, although glucocorticoid levels remain raised relative to non-pregnant levels. The placenta is also the source of numerous hormones, such as human chorionic gonadotropin (hCG), that are unique to pregnancy. Additional hormones, although primarily produced by sources other than the placenta, also fluctuate during these periods. For example, the pituitary hormone prolactin is elevated during pregnancy as well as postpartum to support milk production (Larsen & Grattan, 2012; Marano & Ben-Jonathan, 2014) while oxytocin from the hypothalamus increases at parturition to stimulate uterine contractions and remains high postpartum as a result of nursing (Gimpl & Fahrenholz et al., 2001). Similar hormonal changes occur in other mammals including rodents albeit with some differences in pattern and timing (Duarte-Guterman et al., 2019).

A multitude of dramatic changes are also evident in cardiovascular, hematological, pulmonary, metabolic, immune and neurobiological systems during pregnancy (Hillerer et al., 2014; Sanghavi & Rutherford, 2014; Leuner & Sabihi, 2016; Soma-Pillay et al., 2016; Napso et al., 2018; Barba-Müller et al., 2019). Many of these are mediated by hormones and collectively function to ensure a successful pregnancy and fetal growth and development as well as promote caregiving behaviors after delivery. While some aspects of maternal physiology recover following pregnancy, others can be long-lasting. For example, persistent changes in circulating hormone levels and hormone receptor expression resulting from reproductive experience have been reported in women and rodents (Bernstein et al., 1985; Dorgan et al., 1995; Musey et al., 1987; Bridges & Byrnes, 2006; Pawluski et al., 2009; Barrett et al., 2014; Bridges, 2016). Parity has also been associated with a differential peripheral immune profile during aging (Barrat et al., 1997; Eid et al., 2019a). Enduring modifications in the brain and behavior following motherhood have been shown as well (Love et al., 2005; Lemaire et al., 2006; Pawluski et al., 2006; Pawluksi and Galea, 2007; Kinsley et al., 2010; Macbeth & Luine, 2010; Barha et al., 2015; Hoekzema et al., 2017; Duarte-Guterman et al., 2019; Eid et al., 2019a).

The hormonal and other physiological changes that females experience as a result of pregnancy can have important implications for health and disease. For example, in both rodents and humans, susceptibility to infection is greater during late pregnancy which is also a time when the severity of infectious diseases is increased and the risk of maternal mortality is heightened (Spencer et al., 2008a; Robinson & Klein, 2012; Sherer et al., 2018).

Pregnancy may also influence women's health well past the reproductive event. Consistent with this possibility are studies showing that parity can positively or negatively modulate later risk for a wide range of conditions such as periodontal disease (Morelli et al., 2018), osteoporotic hip fracture (Wang et al., 2016), cardiovascular disease (Lv et al., 2015), type 2 diabetes (Li et al., 2016), and various cancers (Troisi et al., 2018), to name a few. Here we focus on multiple sclerosis (MS), depression, stroke, and Alzheimer's disease (AD) as examples of central nervous system (CNS) disorders which show a female bias and for which there is data from human work and animal models pointing to modification in disease risk and progression during pregnancy, postpartum, and/or as a result of parity. We also discuss the mechanisms by which these effects might arise including hormonal and immune mediators. Ultimately, we aim to show that a comprehensive understanding of brain health and disease in females requires greater consideration of experiences such as pregnancy, parturition and lactation.

2. Multiple Sclerosis

2.1 Sex differences in MS

MS is a chronic disease that is characterized by aberrant immune targeting of the myelin sheaths surrounding axons in the brain and spinal cord causing demyelinating lesions that can lead to neuroaxonal damage and ultimately neurodegeneration as evidenced by brain tissue loss and atrophy. Clinically, episodes of the disease typically start out as intermittent, and in some cases will seem to enter a temporary remission, but as the disease progresses it can worsen and cause irreversible neurological impairment and disability (Houtchens, 2013). Like other autoimmune diseases, MS disproportionately affects women and does so at three times the rate that it affects men (Koch-Henriksen & Sørensen, 2010; Voskuhl & Gold, 2012). Women also often experience more frequent relapses, tend to develop more inflammatory lesions, and usually present an earlier onset of the disease compared to men with MS (Pozzilli et al., 2003; Confavreux & Vukusic, 2006; Kalincik et al., 2013). The sex difference is thought to arise because females have a more robust immune system than males (Nalbandian & Kovats, 2005; Natri et al., 2019) and the female preponderance in MS suggests a role for hormones (Avila et al., 2018).

2.2 MS during pregnancy and postpartum

For women with MS, the disease can take hold during formative reproductive years with diagnosis typically occurring between 20 and 40 years of age (Houtchens, 2013). Pregnancy was long thought to have a negative effect on disease progression and consequently women with MS were often discouraged from having children (Houtchens, 2013; McCombe, 2018). Even though medical management of MS during pregnancy remains challenging given the potential risk of medication exposure to the fetus, it is now understood that women with MS aren't at increased risk for pregnancy-related complications (Giesser, 2002; Voskuhl & Momtazee, 2017). In fact, pregnancy is considered beneficial for MS symptoms as MS typically undergoes remission during mid to late pregnancy (Confavreux et al., 1998; Finkelsztejn et al., 2011). Likewise, in animal models of MS, such as experimental allergic encephalomyelitis (EAE), significant symptomatic improvements are seen during pregnancy across a range of species (Langer-Gould et al., 2002; Haddady et al., 2010). In contrast to

pregnancy, however, symptom relapse often occurs in women at accelerated rates after delivery during the first 3–6 months postpartum (Confavreux et al., 1998; Vukusic et al., 2004; Finklesztejin et al., 2011).

2.3 Immune-alterations in pregnancy and MS pathophysiology

Early in pregnancy, the immune system is forced to adopt an immunosuppressive state to shield the developing fetus from maternal immune attack (Sherer et al., 2018). This immune state is largely characterized by a phenotypic shift from a pro-inflammatory Th1-profile to an anti-inflammatory Th2-profile (Marzi et al., 1996; Ysrraelit & Correale, 2019). Other immune modifications characteristic of this time include increased numbers of regulatory T cells (T_{Regs}) (Steinborn et al., 2012), elevated expression of anti-inflammatory cytokines, such as interleukin-10 (IL-10), and lowered production of pro-inflammatory cytokines such as Tumor Necrosis Factor-alpha (TNFα) (Marzi et al., 1996; Elenkov et al., 2001). In addition, levels of the chemokine receptor, CXCR3, an important mediator involved in leukocyte recruitment and immune cell activation, is also reduced during pregnancy (Shuster, 2008). How this immune suppression is achieved during pregnancy is still not completely clear, but estrogens, via the estrogen receptor alpha (ERα), are among the factors known to play a major role (Robison & Klein, 2012; Airas, 2015; Ysrraelit & Correale, 2019). The rise in glucocorticoids during pregnancy also contributes to shaping the maternal immune system through the suppression of pro-inflammatory cytokine production and inflammatory gene transcription (Schweingruber et al., 2011).

MS, like many other autoimmune diseases, is dominated by a Th1, pro-inflammatory state. As such, the hormonally-driven shift to an anti-inflammatory Th2 immune state during pregnancy is regarded as a key factor underlying reductions in MS symptoms during this time (Patas et al., 2013). With hormone withdrawal following delivery, the immunosuppressive state is lost and as a consequence, MS disease activity rebounds postpartum (Ysrraelit & Correale, 2019). More recently, a role for fetal microchimerism has been suggested in the immune-related postpartum exacerbation of MS symptoms. In microchimerism, fetal cells gain access to the mother’s circulatory system and thereafter reside in maternal organs, even for decades after pregnancy (Bianchi et al., 1996). It has been proposed that when maternal tolerance to the fetus (and, therefore, also fetal cells) is lifted postpartum, an abundance of fetal cells may lead to an intense maternal immune response, possibly increasing MS symptoms. While fetal cells have been found more frequently in blood/tissue samples from women with some autoimmune conditions (Boddy et al., 2016), their contribution to MS has not been tested and thus remains speculative at this point.

2.4 Remyelination and MS remission in pregnancy

Numerous studies also suggest that along with immunosuppression, other processes may be involved in remission during pregnancy including remyelination of the CNS (Avila et al., 2018). Remyelination in healthy individuals is typically achieved through the generation of new, myelinating oligodendrocytes (Blakemore & Keirstead, 1999; Polito & Reynolds, 2005). While patients with MS are still capable of remyelination, the process is grossly inadequate (Franklin & French-Constant, 2008). However, during pregnancy, increased

proliferation of oligodendrocyte progenitor cells (OPCs) and generation of mature oligodendrocytes, along with higher numbers of myelinated axons, have been shown to occur in the maternal CNS of rodents (Gregg et al., 2007; Haddady et al., 2010; Kalakh & Mouihate, 2019). Remarkably, pregnant mice and rats also exhibit an enhanced ability to remyelinate white matter lesions following demyelinating insult (Gregg et al., 2007; Kalakh & Mouihate, 2019). Pregnancy-related hormones have been implicated in remyelination (see 2.5). This process may, at least in part, explain remission in pregnancy and the accompanying decrease in the number and size of active white matter lesions (van Walderveen et al., 1994).

In addition to oligodendrocytes, microglia, the brain's resident innate immune cells, may also aid in remyelinating efforts. Although not examined within the context of pregnancy, microglia have been shown to play an essential role in various aspects of the remyelination process such as clearing myelin debris (Lampron et al., 2015) and releasing mediators (i.e., TNFα, IGF-1, FGF-2) which are instrumental in inducing OPC differentiation (Kuhlmann et al. 2008). Thus, while microglia are traditionally regarded as detrimental in MS and EAE (Heppner et al., 2005), they can also be beneficial. Microglial alterations have been reported in pregnant and postpartum rats (Posillico & Schwarz, 2016; Haim et al. 2016) but the extent to which these cells contribute to remission and relapse during these times is unknown.

2.5 Pregnancy-related hormones and MS

Prolactin—An extensive literature has documented that prolactin has immune-stimulating properties and thus, it has been classically considered detrimental to MS and in EAE (Dijkstra et al., 1994; De Bellis et al., 2005; Costanza & Pedotti, 2016). Attenuating the pro-inflammatory effect of prolactin with concomitant administration of the immunomodulator interferon-β (IFN-β), however, has been shown to improve the clinical signs and histological scores of EAE (Johnson et al., 2009). Additional work highlights important remyelinating properties of prolactin and has thus further encouraged a reinterpretation of the involvement of this hormone in MS. Indeed, prolactin was found to be necessary for the pregnancy-induced increase in OPC proliferation within the mouse CNS (Gregg et al., 2007). Moreover, prolactin treatment was able to mimic the regenerative effects of pregnancy and promote white matter regeneration and remyelination in virgin females (Gregg et al., 2007). These data raise the possibility that a similar prolactin-mediated regeneration process may occur in humans and contribute to the remission of MS during late pregnancy (Gregg, 2009).

In contrast to pregnancy, the risk for relapse increases postpartum, as noted above. Although still a matter of debate (Hutchinson, 2013; Langer-Gould & Hellwig, 2013; Vukusic & Confavreux, 2013), some evidence suggests that women with MS who exclusively breastfeed are less likely to experience a postpartum relapse compared to women who do not (Langer-Gould et al., 2009; Pakpoor et al., 2012; Hellwig et al., 2015 but see Airas et al., 2010; Portaccio et al., 2011). It could be argued that such data are biased as women with less severe MS may be able to breastfeed while those facing a more severe disease state may be forced to forego breastfeeding for the continuation of disease-modifying drug regiments (Airas et al., 2010; Yssraelit & Correlae, 2019). Alternatively, because breastfeeding maintains high prolactin levels, these data could suggest that prolactin may too protect

against relapse postpartum although the extent to which this may be due to reduced inflammation and/or remyelination is unknown.

Estrogens—As discussed, elevated estrogen levels during pregnancy have anti-inflammatory effects (Ysrraelit & Correale, 2019). In non-pregnant animals, exogenous estrogens can decrease the severity of EAE by depressing Th1 activity via an ERα dependent mechanism (Jansson et al., 1994; Kim et al., 1999; Polanczyk et al., 2003; Spence et al., 2013; Laffont et al., 2015). Interestingly, E3 (the main estrogen of pregnancy) was shown to be more effective than E2 in EAE. Indeed, pre-treatment with E3 (at doses similar to physiological levels seen in murine pregnancy) before disease onset postponed disease onset for longer than administration of E2, which also required five times the amount to reach the same effect as E3 (Jansson et al., 1994). Furthermore, compared to controls, E3 treated EAE-mice showed a reduction in disease severity and less pathology (Kim et al., 1999). Synthetic ER ligands also have a role in remyelinating the CNS (Avila et al., 2018). Agonists of estrogen receptor beta (ERβ) result in increased functional remyelination and protection of existing axons in EAE models (Crawford et al., 2010). In addition, treatment with ERβ agonists has been shown to increase the number of mature oligodendrocytes (Kim et al., 2018) and to have several other neuroprotective effects (Itoh et al., 2017). Clinical trials have aimed to simulate the benefits of pregnancy with several promising effects of E3 reported to date including reduced relapse rates, improved cognitive functioning, and attenuated cortical atrophy (Sicotte et al., 2002; Soldan et al., 2003; Voskuhl et al., 2016; Makenzie-Graham et al., 2018).

Progesterone—Progesterone also seems to confer protective benefits as evidenced in studies employing EAE models (Yssraelit & Correlae, 2019). For instance, pre-administration of progesterone before disease onset has been associated with reduced neurological damage, enhanced axonal density, and decreased axonal damage in female mice (Hoffmann et al., 2001). Moreover, progesterone administration after disease onset in EAE was effective in obviating neurological damage and cultivating regeneration (Yu et al., 2010; Liu et al., 2010; Yates et al., 2010). These effects may be attributable in part to progesterone's anti-inflammatory properties (Yates et al., 2010; Labombarda et al., 2011). In addition, progesterone is capable of enhancing myelin repair through the proliferation and maturation of oligodendrocytes (Labombarda et al., 2011; Ramien et al., 2016). Interestingly, pretreating ovarectomized EAE animals with progesterone alone resulted in amplified neuroinflammation and worsened symptoms which suggests that progesterone works in tandem with other gonadal factors to induce protection (Hughes, 2012).

Allopregnanolone, a derivative of progesterone, has also been implicated in MS. Like progesterone, allopregnanolone levels rise across pregnancy and drop abruptly in the postpartum (Magure, 2019). Dysregulation in allopregnanolone biosynthesis pathways has been reported in brain tissue from MS patients as well as in CNS tissue derived from MS animal models (Noorbakhsh et al., 2011). Allopregnanolone bestows numerous neuroprotective benefits in the context of MS such as minimizing axonal damage and promoting myelin gene expression in oligodendrocytes (Noorbakhsh et al., 2014). A

potential role of allopregnanolone in enhancing OPC proliferation following a demyelination insult during pregnancy was also recently demonstrated in rats (Kalakh & Mouihate, 2019).

Taken together, these data suggest that higher levels of progesterone or allopregnanolone during pregnancy may enhance the ability of the CNS to repair demyelinated axons as well as preserve axonal integrity. However, a clinical trial employing high doses of progestin and estradiol immediately following delivery was not successful in reducing relapse-rate during the postpartum and thus was terminated early (Vukusic et al., 2012; Durand-Dubief et al., 2014). Future trials could be designed to assess whether progesterone treatment improves remyelination or other outcome measures more aligned with known effects of progesterone rather than assessment of its effect on relapse (Voskuhl & Momtazee, 2017).

2.6 Role of parity in MS risk and progression

A number of epidemiological studies have found no association between number of pregnancies and subsequent MS risk (Weinshenker et al., 1989; Thorogood et al., 1998; Alonso et al., 2005). In contrast, other work suggests that parity may reduce MS risk with increased numbers of pregnancies being associated with lower risk of developing the first demyelinating event (Runmarker et al., 1995; Ponsonby et al., 2012; Magyari et al., 2013). To date, nothing is known about the biological factors that may mediate the link between multiparity and MS risk.

Since MS is a chronic disease that can render a patient disabled over time, it is important to consider the extent to which one or more pregnancies may influence the trajectory of long-term MS outcomes. One metric to quantify long-term outcomes is disability progression, most often assessed with the Expanded Disability Status Scale (EDSS) which provides a measure of ambulatory and other neurological impairments. The role of parity on the development of future MS disability is another matter of continued debate as studies examining this issue have yielded conflicting results (D'Hooghe & De Keyser, 2014; Hutchinson, 2014, McCombe & Callaway, 2014). For example, several retrospective and prospective longitudinal studies have found no effect of pregnancy on MS disability (Weinshenker et al., 1989; Roullet et al., 1993; Confavreux et al., 1998; Vukusic et al., 2004; D'Amico et al., 2016). In contrast, a recent prospective study reported that pregnant women with MS tended to have worse disability outcomes after delivery (Lai et al., 2018), although the follow-up period was short (i.e., one-year after delivery). Yet other long-term studies have produced results which suggest a beneficial effect of parity. For example, Verdru et al., (1994) showed that wheelchair dependence occurred after 18.6 years in those women with MS who experienced at least one pregnancy after onset versus 12.5 years for non-parous women. Similarly, it has been shown that women with one or more children have less disability and/or reach a given disability after a longer period of time (Runmarker & Andersen, 1995; D'Hooghe et al. 2010; Masrea et al., 2015). In other work, pregnancy was found to be 4.5X more effective than first-line disease modifying therapies in preventing long-term disability accrual. Interestingly, anytime spent pregnant, including induced or spontaneous abortions, was beneficial in minimizing future disability from MS (Jokubaitis et al., 2016). It should be acknowledged that most of these studies are prone to selection bias as young women with more severe disease onset are less likely to become pregnant. In contrast,

women with MS who are able to become pregnant may reflect a disease course that is less severe. Thus, the results of these studies may be skewed toward interpretations that reflect a lessened disease course.

There has been little attempt to understand how changes that occur during pregnancy might mechanistically engender long-term protective changes for mothers with MS. If parity does beneficially influence long-term MS outcomes, then lasting changes on immune function (Eid et al., 2019a) or CNS mechanisms including remyelination would be expected. One way these could arise is through epigenetic effects. A recent gene-wide association study of differentially expressed genes in parous versus non-parous women with MS identified over 500 genes that changed with parity (Mehta et al., 2019). Many of these genes were pertinent to axonal guidance, developmental biology, and cell-to-cell communication pathways and were significantly upregulated in parous women with MS as compared with nulliparous women with MS (Mehta et al., 2019). This suggests that parity may alter the epigenome to enhance the repair of damaged axons in MS.

3. Depression

3.1 Sex differences in depression

Major depression is an affective disorder characterized by symptoms including sad mood, anhedonia, restlessness and/or agitation, sleep disturbances, and impaired concentration, among others. Major depression affects 300 million people worldwide (WHO, 2017) but is twice as prevalent in women as men (Kessler, 2003). In addition to incidence, various clinical manifestations of depression also vary by sex. Compared to men, women with depression experience higher symptom severity and are more likely to present with atypical symptoms such as hypersomnia, weight gain, and excessive fatigue as well as somatic complaints (Halbreich & Kahn, 2007; Marcus et al., 2008; Schuch et al., 2014). Sex differences in comorbidity are also seen in depression such that women show higher rates of anxiety whereas men show more substance use disorders (Marcus et al., 2008, Schuch et al., 2014). The sex differences in depression points to a role for hormones in the underlying pathophysiological mechanisms (Eid et al., 2019b; Rainville & Hodes, 2019; Rubinow & Schmidt, 2019).

3.2 Depression during the peripartum period

The peripartum period is a time of elevated susceptibility to mood disorders with an estimated 15–20% of women developing depression during this time (O'Hara et al., 1990; Vesga-Lopez et al., 2008). While the DSM-V recognizes peripartum depression as major depression with onset during pregnancy or within the first four weeks postpartum (American Psychological Association, 2013), this definition has been challenged by many clinicians, researchers, and major health organizations (WHO, CDC) who consider postpartum depression to occur within the first 12 months after birth (DiFlorio et al., 2013). Further, the DSM-V definition is considered problematic because it disregards timing of depression onset during pregnancy vs. postpartum which likely represents different subtypes with different underlying mechanisms (Altemus et al., 2012; Putnam et al, 2017). Some have also argued that peripartum depression should be a unique syndrome distinct from major

depression as it presents differently (e.g., greater comorbid anxiety) than depression in women outside of the peripartum period (Fox et al., 2018a) and because of its timing which coincides with unprecedented hormonal change.

Postpartum depression is detrimental for maternal well-being and is the leading cause of maternal mortality resulting from suicide (Lindahl et al., 2005; Chesney et al, 2014). Moreover, postpartum depression is often associated with impaired mother-infant interactions which can have a long-lasting, negative impact on offspring development (Grace et al., 2003; Field, 2010). Thus, despite ongoing controversies, postpartum depression is considered to be a major public health concern due to its prevalence and the risk it poses to mothers and their children (Wisner et al., 2006; Meaney, 2018).

3.3 Pregnancy-related physiological changes and postpartum depression

As with other neuropsychiatric disorders, the etiology of depression during the peripartum period is likely multifactorial. While psychological, social, genetic, and environmental factors have all been implicated in maternal depression (reviewed by Brummelte & Galea, 2010; Yim et al., 2015; Meltzer-Brody et al., 2018a; Elwood et al., 2019; Payne & Maguire, 2019), here we will briefly consider some of the main pregnancy-related hormonal and immune factors which have been studied. Where discrepancies are reported, it is important to consider that there is often significant methodological heterogeneity across studies which could impact results, such as timepoint during pregnancy/postpartum in which women were studied, the demographics of the sample population, the severity of depression and various others.

Hormones—Given the timing of symptom onset, hormones have long been thought to contribute to postpartum depression but this has proven difficult demonstrate (Brummelte & Galea, 2010; Schiller et al., 2015). In the majority of studies, there are no consistent changes in estrogen or progesterone levels associated with postpartum depression (reviewed by Yim et al., 2015; Payne & Maguire, 2019). Yet, a role for these hormones in postpartum depression cannot be ruled out given a landmark study by Bloch et al. (2000) which found that estrogen and progesterone withdrawal increased depression in some women, particularly those with a prior history of postpartum depression. Thus, absolute levels of estrogen and progesterone may not differ in women with maternal depression but rather, the brains of women who develop postpartum depression may be differentially sensitive to fluctuations in these hormones. Several studies also suggest that estrogen treatment reduces risk for developing postpartum depression and decreases depression symptoms during the postpartum period (Sichel et al., 1995; Gregoire et al., 1996) although studies on progesterone are more mixed (Buckwalter et al., 1999; Lawrie et al., 2000; Dennis et al., 2008). Further evidence for a role of estrogen and progesterone comes from animal experiments showing that estradiol and progesterone withdrawal can provoke depression-like behavior postpartum (Galea et al., 2001; Stoffel & Craft, 2004; Suda et al., 2008; Green et al., 2009).

Alterations in progesterone metabolites, including allopregnanolone, have also been suggested to play a role in postpartum depression (Maguire, 2019; McEvoy et al., 2018).

Like progesterone, levels of allopregnanolone were not found to significantly differ in women with postpartum depression (Epperson et al., 2006; Deligiannidis et al., 2013). However, conflicting results have been reported (reviewed by McEvoy et al., 2018). For example, Osborne et al. (2017) found that low allopregnanolone levels during pregnancy predicted subsequent postpartum depression while Deligiannidis et al. (2019) showed higher peripartum plasma allopregnanolone concentrations in women who developed postpartum depression. Although differences in allopregnanolone levels have not been consistently associated with postpartum depression, some have proposed that postpartum depression be the result of abnormalities in the ability of allopregnanolone to modulate GABA receptors in the brain. In support of this, an elegant study by Maguire and Mody (2008) showed that knockout mice who lacked the ability to regulate the $GABA_A$ subtype of the GABA receptor during peripartum period developed depressive and anxiety-like behaviors in the postpartum. In a subsequent study, a novel synthetic neuroactive steroid (SGE-516) was also effective in alleviating depression-like behaviors in this mouse model of postpartum depression (Melón et al., 2018a). These animal findings have translational relevance to humans as the drug brexanolone, a synthetic formulation of allopregnanolone, was recently approved by the FDA to treat postpartum depression after successful clinical trials (Meltzer-Brody et al., 2018b; Wisner et al., 2019).

Oxytocin regulates many functions of relevance to postpartum depression including emotion, stress, affiliation, and maternal care (Post & Leuner, 2019). Therefore, it is perhaps not surprising that oxytocin has been implicated in postpartum depression. Oxytocin has also received attention in postpartum depression because of its role in nursing and breastfeeding difficulties often seen in depressed mothers (Steube et al., 2013). While a number studies suggest that low levels of oxytocin in pregnancy or postpartum may be a risk factor for postpartum depression (Skrundz et al., 2011; Apter-Levy et al., 2013; Stuebe et al., 2013, Eapen et al., 2014; Cox et al., 2015; Jobst et al., 2016) there are conflicting findings as well (Garfield et al., 2015; Zelkowitz et al., 2014; Massey et al., 2016). Furthermore, the limited number of studies which have examined oxytocin administration in postpartum women indicate that it may worsen mood and increase risk of postpartum depression and may or may not be beneficial in alleviating maternal care deficits often seen in depressed mothers (Kim et al., 2014; Mah 2016; Moura et al., 2016; Mah et al., 2017; Kroll-Desrosiers et al., 2017). Like oxytocin, prolactin also has a well-known role in maternal care and lactation (Larsen & Grattan, 2012) but fewer studies have examined the role of prolactin in postpartum depression. Nonetheless, available evidence points to a link between low prolactin, postpartum depression, and early cessation or absence of breastfeeding (Abou-Saleh et al., 1998; Groer and Morgan, 2007; Stuebe et al., 2012).

In addition to reproductive and lactogenic hormones, cortisol and other hormones (ACTH, CRH) of the hypothalamic-pituitary-adrenal (HPA) axis have been proposed to be involved in postpartum depression. This is in part because of the multiple changes that occur in the HPA axis during pregnancy and postpartum but also because stress is one of the greatest risk factors for postpartum depression (Yim et al., 2015; Brummelte & Galea, 2010; Payne & Maguire, 2019). While the HPA axis has been implicated in depression at other times in life (Pariante & Lightman, 2008), the link between perinatal changes in HPA axis hormones and postpartum depression is less clear (Okano & Nomura, 1992; Corwin et al., 2005; Groer &

Morgan, 2007; Yim et al., 2009; Meltzer-Body et al., 2011; de Rezende et al., 2016). Studies that have found a relationship actually report *lower* cortisol levels in women with postpartum depression (Seth et al., 2016; Dickens & Pawluski, 2018; Szpunar & Parry, 2018). Moreover, other work employing reactivity tests (e.g., dexamethasone suppression or stressors) in depressed mothers points to decreased responsiveness of the HPA axis (Bloch et al., 2003; Nierop et al., 2006; Jolley et al., 2007). Notably, rodent models have also been used to understand the contribution of the HPA axis to postpartum depression and these support a role for glucocorticoids and HPA axis dysfunction in inducing depressive-like behaviors in postpartum females (Brummelte & Galea, 2010; Melón et al., 2018b). Thus, there is some indication that HPA dysregulation occurs in postpartum depression, but more work is needed (Garcia-Leal et al., 2017; Dickens & Pawluski, 2018).

Immune factors—Late pregnancy and the postpartum period are characterized by a pro-inflammatory state (see 2.3) and heightened inflammation has been associated with depression outside of the postpartum period (Rainville & Hodes, 2019). Because of these parallels, immune mechanisms have been hypothesized to contribute to the development of peripartum depression (Corwin & Pajer, 2008; Anderson & Maes, 2013; Osborne & Monk, 2013; Leff-Gelman et al., 2016). Several lines of evidence support this possibility. For example, peripheral immune cells were shown to have different gene expression signatures in women with postpartum depression than those without (Segman et al., 2010; Pan et al., 2018). In addition, several studies assessing circulating pro-inflammatory cytokines in blood or urine samples found an association between postpartum depression and increased levels of IL-6 (Maes et al., 2000; Boufidou et al., 2009; Christian et al., 2009; Cassidy-Bushrow et al., 2012; Simpson et al., 2016) as well as higher levels of levels of IL-β in association with depression scores during the postpartum period (Corwin et al., 2008; Cassidy-Bushrow et al., 2012). Although such findings suggest an exaggerated inflammatory response with maternal depression, others have found no link between postpartum depression and these pro-inflammatory cytokines (Blackmore et al., 2014; Skalkidou et al. 2009; Corwin et al., 2015). Moreover, one study reported lower levels of inflammatory markers (TNF-α) for the first days postpartum among women that later developed depression (Corwin et al., 2015). Further adding to the complexity, a recent wide-scale exploratory examination of inflammatory gene expression in blood during late pregnancy found a host of immune-related genes that were downregulated in women who later developed depressive symptoms eight weeks postpartum, irrespective of their pro- or anti-inflammatory properties (Bränn et al., 2017). Thus, at this stage, studies have been somewhat contradictory. One potential caveat is that peripheral immune changes may not necessarily reflect what is happening in the brain and therefore may not be a good marker (Setiawan et al., 2015). Only one study to date has looked at central immune changes in CSF samples from women undergoing epidural anesthesia and found an association between elevated IL-6 and depressed mood postpartum (Boufidou et al. 2009). There is also recent evidence from animal models showing central immune dysregulation in postpartum females exhibiting depressive-like behavior (Posillico & Schwarz, 2016; Leuner et al., 2019). Given the limited number of studies, additional work assessing neuroimmune disruption as a contributor to postpartum depression is needed.

Critically, although we have discussed the various hormonal and immune factors separately, they do not operate in isolation but in complex, interconnected ways. For instance, a study by Bloch et al. (2005) demonstrated an exaggerated cortisol response and increased depression symptoms upon withdrawal of estrogen and progesterone in women with a history of postpartum depression suggesting hormonal crosstalk. As another example, $GABA_A$ receptor deficient postpartum mice have been shown to exhibit increased HPA axis responsiveness which points to an interplay among allopregnanolone, GABA receptors, and HPA axis function in the pathophysiology of postpartum depression (Maguire & Mody, 2008). Various endocrine-immune interactions have also been proposed (Corwin & Pajer, 2008). These and other relationships (Brummelte & Galea, 2010; Payne & Maguire, 2019) have yet to be fully understood in the context of postpartum depression but it is critical we do so in order to gain better insights into the causes of, and potential treatments, for this condition.

4. Stroke

4.1 Sex differences in stroke

Stroke affects nearly 17 million individuals every year and accounts for approximately six million deaths globally (Benjamin et al., 2017). There are two main types of stroke, ischemic and hemorrhagic. About 85% of strokes are ischemic which occurs when there is obstruction of a blood vessel supplying the brain. The remaining 15% of strokes are hemorrhagic and result when one or more blood vessels rupture causing blood to leak into the brain. Although less common, hemorrhagic stroke is more likely to result in death. Among individuals that survive a stroke, many experience permanent physical and neurological disability including sensory and motor impairment as well as mood disorders such as depression (Carod-Artal, 2012; Cai et al., 2019). Another major debilitating consequence of stroke is cognitive dysfunction or post-stroke dementia which affects almost one third of survivors shortly after stroke (Leys et al., 2005; Mok et al., 2017). Those individuals who survive a stroke without acute onset cognitive decline are nonetheless at much greater risk of developing dementia at a later stage (Ivan et al., 2004; Mijajlović et al., 2017; Mok et al., 2017).

Stroke is a sexually dimorphic disease (Girijala et al., 2017). Although men have a higher incidence of stroke throughout most of the lifespan, women have higher stroke prevalence overall because of the increase in stroke risk with aging, particularly after menopause, and a longer average lifespan in females (Appelros et al., 2010; Roy-O'Reilly & McCullough, 2018; Robison et al., 2019). In addition, stroke severity is greater in women who often suffer more intense, debilitating strokes than men and as a result have poorer post stroke outcomes including a higher mortality risk (Niewada et al., 2005; Appelros et al., 2009; Choleris et al., 2018).

Sex differences in stroke pathology are also evident in animal models and map on well to what has been reported in humans (Roy-O'Reilly & McCullough, 2018). Neonate and young-adult male animals are typically more susceptible to stroke pathology while younger female animals typically show resiliency as evidenced by decreased infarct size and less tissue damage in response to an equivalent insult (Banerjee et al., 2013; Herson et al., 2013). *In vitro* studies using oxygen glucose deprivation as a model of deoxygenated conditions

during an ischemic stroke have revealed that male-derived neurons, astrocytes, and endothelial cells all suffer greater damage than female-derived cells (Sharma et al., 2011; Fairbanks et al., 2012). Furthermore, there are sex differences in the post-ischemic inflammatory response such that microglia from male animals display heightened ischemia-induced activation as compared to female microglia and thus underscoring sex-differences in stroke pathology (Bodhankar et al., 2015; Dotson et al., 2015; Rahimian et al., 2019). During middle age or following ovariectomy, however, female animals tend to demonstrate exacerbated stroke pathology in a manner similar to what is observed in humans following menopause (Kim et al., 2019).

4.2 Pregnancy-associated stroke

For females, a variety of sex-specific factors, including pregnancy, have been shown to influence stroke risk (Demel et al., 2018; Gannon et al., 2018; Roy-O'Reilly & McCullough, 2018). Indeed, the peripartum period represents a window of susceptibility during which the risk of enduring a stroke is acutely increased, especially for those with pre-existing cardiovascular problems, blood vessel abnormalities and coagulation disorders, or that develop hypertension or preeclampsia-eclampsia during pregnancy (Jaigobin & Silver, 2000; Sanders et al., 2018). A recent meta-analysis estimated that stroke affects 30 pregnancies out of 100,000 with most taking place in the third trimester or early postpartum, within the first 12 weeks (Swartz et al., 2017). While the incidence of pregnancy-related stroke may seem low, stroke poses a serious risk to the mother – 15% of pregnant women who experience a stroke die as a result making it the 8th leading cause of pregnancy-associated deaths in the United States (Kochanek et al., 2014). The women that survive can go on to experience residual fatigue, loss of mobility or speech, and cognitive impairments (Lanska & Kryscio, 2000). In addition, maternal stroke in pregnancy can affect fetal and neonatal health and well-being (Sanders et al., 2018). Although a direct comparison of stroke outcomes in pregnant versus non-pregnant women hasn't been done, a study in rats found that neuronal injury following global cerebral ischemia was enhanced in pregnancy (Spencer et al., 2008b).

4.3 Pregnancy-related physiological changes and stroke risk

Strokes that happen during the peripartum period are evenly divided between both types. A variety of pregnancy-related physiological changes have been suggested to enhance vulnerability to both ischemic and hemorrhagic stroke and to potentially impact stroke outcomes (Kittner et al., 1996; Treadwell et al., 2008).

Hemodynamic and Cardiovascular Changes—Vast hemodynamic changes take place during pregnancy to meet the increased circulatory needs of the uterus, placenta, developing fetus, and the demands of delivery (Sells & Feske, 2017; Sanders et al., 2018; Camargo et al., 2019). One of the initial changes is an increase in blood volume, which is as much as 50% greater than pre-pregnancy values by delivery. There are also substantial increases in cardiac output and heart rate which are elevated as much as 30–50% during pregnancy and even further during labor and birth. In addition, early pregnancy is accompanied by a drop in systemic vascular resistance. With this, there is a drop in blood pressure until mid-pregnancy which can promote venous stasis or slow blood return from the

lower extremities. These various changes can persist for weeks after birth and may contribute to greater stroke incidence by increasing the risk of clot formation or by straining vessel walls making them more susceptible to rupture.

Pregnancy also causes remodeling of the heart and all blood vessels resulting in increased vascular distensability during early pregnancy (Mackey et al., 1992). By late pregnancy, however, the walls of systemic arteries show a reduction in collagen and elastin content and a loss of distensibility. It has been suggested that the hemodynamic changes of pregnancy, when combined with structural changes of blood vessels, may result in a state in which more vulnerable vascular walls experience greater hemodynamic stress, possibly contributing to the risk of hemorrhagic stroke (Sells & Feske, 2017).

Changes in the Coagulation System—Changes in the coagulation system take place during pregnancy to produce a state of hypercoagulation, likely an adaptive mechanism to reduce the risk of hemorrhage during and after delivery (Struble et al., 2015). However, the hypercoagulable state, which persists for at least six weeks postpartum, also makes it more likely for women to form and retain clots that lead to stroke. Increased hypercolaguability in pregnancy is due to elevations in clotting factors VIII, IX, X, fibrinogen and von Willebrand factor along with decreases in factors that inhibit clot formation such as antithrombin and protein S (Sanders et al., 2018; Carmgo et al., 2019). Fibrinolysis, factors involved in the breakdown of clots, also decrease which makes it more likely that clots will circulate throughout the body (Sanders et al., 2018). Together, these changes alter the balance within the coagulation system in favor of clotting, predisposing pregnant and postpartum woman to venous thrombosis. The potential for pathological clotting is further exacerbated by venous stasis and other factors such as caesarean birth or injuries during delivery that may synergize with hypercoagulability to increase risk of pregnancy-related stroke (Carmago et al., 2019).

Hormonal Changes—The hormones of pregnancy may also predispose peripartum women to higher risk of stroke risk by regulating one or more of the mechanisms above. For example, elevated levels of estrogen affect blood clotting by upregulating several coagulating factors while simultaneously downregulating inhibitors of coagulation. Thus, the pregnancy-related elevation in estrogen may increase the likelihood of experiencing a blood clot leading to stroke (Howie, 1979). Notably, however Spencer et al. (2008b) found that enhanced neuronal damage in pregnant female rats following stroke was independent of changes in estrogen. Further, exogenous estrogen and other pregnancy-related hormones such as progesterone have been shown in some cases to be beneficial for mitigating stroke damage and some of the underlying pathological processes although such hormonal effects are modified by numerous variables such as route of administration, type of ligand used, experimental model of stroke, age, and timing of treatment (Azcoita et al., 1998; Ginson et al., 2009; Suzuki et al., 2009; Andrabi et al., 2017; Guennoun et al., 2019; Rahimian et al., 2019; Sohrabji et al., 2019). Taken together, these data highlight the complex relationship between hormones and stroke in females.

Although the risk of stroke remains elevated postpartum, evidence from animal models suggest nursing may be protective. Work using intracerebral injections of kainic acid, which results in an excitotoxic insult much like ischemic stroke, has shown that lactation offers

neuroprotection against excitotoxity (Cabrera et al., 2009). Prolactin was specifically shown to mediate this effect as hippocampal neurons treated with prolactin before a glutamate-induced excitotoxicity demonstrated increased cell viability. Furthermore, the neuroprotective effect was lost when prolactin receptor expression was diminished further suggesting that prolactin mediates neuroprotection in response to excitotoxic insult through prolactin receptor signaling (Vergara-Castañeda et al., 2016). A recent study also found that nursing protected postpartum mice from injury after stroke, an effect attributed to anti-inflammatory effects of oxytocin (Stary et al., 2019) which is consistent with previous evidence for a neuroprotective role of oxytocin in ischemia outside of pregnancy (Karelina et al., 2011; Kaneko et al., 2016; Etehadi Moghadam et al., 2018)

4.4 Reproductive experience: stroke risk and outcome

The association between parity and risk of stroke remains to be clarified. A number of studies have reported a link between greater number of pregnancies and stroke risk (Qureshi et al., 1997; Zhang et al., 2009; Jung et al., 2010; Zhang et al., 2015). This may be related to findings showing that increasing parity is also associated with obesity, a major risk factor for stroke (Harris et al., 1997; Zoet et al. 2019). Conversely, several studies have reported a protective effect of parity on stroke risk (Gaist et al 2004; Yang et al., 2009; Yao et al., 2018) or no consistent relationship (Jacobsen et al., 2011). The inconsistencies may be related to emerging research reporting an association between breastfeeding history and decreased risk of stroke later in life. Using data collected from the Women's Health Initiative Observational Study, Jacobson et al. (2018) found that postmenopausal women with a history of breastfeeding had an approximately 20% lower risk of stroke — an effect that remained even after controlling for various confounding variables such as age, smoking history and body mass index.

Available evidence in rodent models also suggests that pregnancy and reproductive experience may have differential effects on stroke outcome. In contrast to the negative impact of pregnancy on ischemia outcome in rats (Spencer et al., 2008b), recent results from a stroke model in mice suggest that reproductive history may lead to better outcomes. Specifically, Ritzel et al. (2017) found several acute and long-term protective effects of parity after stroke with multiparous mice exhibiting smaller infarct sizes, reduced numbers of microglia and astrocytes near the infarct, decreased levels of pro-inflammatory cytokines (e.g., IL-6) and chemokines (e.g., CCL-2) as well as increased concentrations of growth factors (e.g., bFGF, VEGF) when compared to nulliparous controls. Further, multiparous mice demonstrated greater post-stroke angiogenesis which correlated with improved performance on sensorimotor and cognitive tasks. Importantly, parity-associated neuroprotection occurred despite greater sedentary behavior, weight gain, and other indictors of metabovascular risk (e.g., upregulated triglyceride and cholesterol levels, suppressed immune activity, and increased muscle fatigue). Other work has similarly demonstrated greater recovery in multiparous female rats after excitotoxic insult as compared to virgin females even though both groups suffered a similar degree of initial damage (Franssen et al., 2012). Together, these data indicate that parity may confer some degree of protection against stroke-related pathology in rodents. The underlying mechanism is unknown but some evidence points to a role for fetal microchimerism. Studies on animals and humans have

found that fetal microchimeric cells are recruited to sites of injury in the body to aid in recovery processes (Wang et al., 2004; Khosrotehrani et al., 2007; Kara et al., 2012; Nassar et al., 2012; Mahmood & O'Donoghue, 2014). This was shown to occur in brains of multiparous female mice following stroke — fetal cells migrated to the areas of brain tissue injury where they adopted endothelial morphology (Ritzel et al., 2017).

5. Alzheimer's Disease

5.1 Sex Differences in AD

In the U.S alone, 5.5 million people over the age of 65 have AD. Among them, women are disproportionally afflicted with nearly 2/3 of the cases (Snyder et al., 2016; Alzheimer's Association, 2018). Moreover, by the age of 45, one in five women are at a risk of developing AD in the future as compared to a life time risk of one in ten for men (Nebel et al., 2018). Women are not only more susceptible to AD, but are also more likely than men to progress into clinical dementia (Barnes et al., 2005). Female sex as a risk factor for AD is also supported by studies using transgenic mouse models of AD which too show that females are more vulnerable to AD neuropathology (Vest & Pike, 2013).

Various reasons have been proposed for the greater vulnerability of females to AD. Notably, on average, women live longer than men; therefore, it is more likely that men are to die of other causes, such as cardiovascular events, before the AD dementia is fully realized (Chêne et al., 2015). Consequently, collected sex-related data may suffer from an intrinsic survival bias—those men that do live into older age are likely healthier, and therefore, are less likely to succumb to dementias related to AD pathology. Others argue that the basis for the discrepancy is largely biological with evidence highlighting the depletion of estrogens during menopause as a risk factor partially accounting for the different outcomes (Paganini-Hill & Henderson, 1994; Tang et al., 1996; Nebel et al., 2018). Indeed, a longer reproductive span (i.e., earlier menarche and later menopause), and consequently greater lifetime estrogen exposure, has been associated with a lower incidence of dementia (Fox et al., 2013a). Taken together, these studies underscore the interplay between estrogen and AD and suggest that sex-specific variables like pregnancy, which drastically affect levels of estrogen and other hormones, could affect AD.

5.2 Parity and AD

Multiple groups have suggested that having children may increase the likelihood of developing AD and experiencing symptom onset at an earlier age (Geerlings et al., 2001; Ptok et al., 2002; Sobow & Kloszewska, 2004; Colucci et al., 2006; Jang et al., 2018). Of these studies, one found parity to a better predictor of future AD development above and beyond smoking status, reproductive years, and age at menopause (Sobow & Kloszewska, 2004). Furthermore, a recent retrospective analysis found that women with five or more completed pregnancies had an approximately two-fold increase in AD risk compared to nulliparous women and women with four or less completed pregnancies (Jang et al., 2018). These findings remained even after controlling for demographical information, hypertension, hormone replacement therapy, reproductive period, and age at menopause. In addition to risk, amount of parity has been positively associated with greater AD neuropathology (Beeri

et al., 2009). One possible explanation for the link between parity and AD is fetal microchimerism. However, when comparing women with and without AD, women with AD were unexpectedly shown to have a lower prevalence of microchimerism in the brain and lower concentrations in regions most affected by AD (Chan et al., 2012). Given the modest number of subjects tested and the incomplete pregnancy histories, replication of these results is needed.

Not all studies examining the relationship between parity and AD show a detrimental effect. In rats, multiparity has been shown to mitigate age-related cognitive decline and brain aging as indicated by reduced amyloid precursor protein (APP), a central player in AD (Gatewood et al., 2005). In humans, Fox et al. (2013a; 2018b) found that a higher number of cumulative months spent pregnant had protective effects against AD risk. Likewise, a recent epidemiological investigation reported that women with three or more children had a 12% lower risk of dementia later in life compared to mothers with only one child (Gilsanz, 2018). The reason for the inconsistencies across studies require further investigation but could be due to differential accounting for such factors such as age at first pregnancy, miscarriages, and breastfeeding (Fox et al., 2013a; 2013b). Genetic factors might also play a role as suggested by work showing that the effect of parity on AD onset may be influenced by apolipoprotein E (APOE) genotype. Specifically, parity is associated with lower age of AD onset in women carrying the e*3/e*3 genotype while e*4 carriers did not show this effect (Corbo et al., 2007). Genotype has also been shown to interact with parity in a mouse model of AD (APP23) with parity having a detrimental effect on cognitive function and neuropathology in APP23, but not wild type, mice (Cui et al., 2014).

5.3 Parity, AD and pregnancy-related hormones

Various pregnancy-related hormones affect pathological hallmarks of AD such as amyloid-beta plaques (Aβ) and neurofibrillary tangles (NFT) both of which can perturb local cellular function thereby contributing to diffuse disruptions across the brain and cognitive decline (Wenk, 2003).

Estrogens—As noted above, estrogen deprivation has been implicated as a risk factor for AD (Paganini-Hill & Henderson, 1994; Tang et al., 1996; Nebel et al., 2018). Despite the high levels of estrogen during pregnancy, pregnancy appears to reduce lifetime estrogen exposure relative to nulliparity. Circulating estrogen levels are ~20% lower in parous women compared to nulliparous women (Bernstein et al., 1985), a difference which persists through menopause (Chubak et al., 2004). Because estrogens are neuroprotective, parity could be associated with AD through a longer-term reduction in estrogens. The neuroprotective effects of estrogens are numerous. For instance, estrogens can obviate the synthesis of Aβ peptides by altering the processing pathway of amyloid precursor protein (Xu et al., 2006). In addition, estrogens protect and promote neuronal health through multiple pathways including the regulation of apoptotic factors, which become activated under pathological conditions such as Aβ accumulation (Garcia-Segura et al., 1998; Pike, 1999; Nilsen & Diaz Brinton, 2003; Koski et al., 2004); the restoration of calcium homeostasis under Aβ-induced excitotoxic conditions (Goodman et al.,1996); and the recruitment of microglia in Aβ plaque clearance (Li et al., 2000; Yue et al. 2005; Xu et al., 2006). Furthermore, estrogens are

capable of combatting inflammation (Uchoa et al., 2016), a hallmark of AD, through the scavenging of free radicals (Sugioka et al., 1987; Subbiah et al., 1993) complemented by the inhibition of microglial activation (Vegeto et al., 2001). Lastly, other enzymes involved in Aβ metabolism, such as neprilysin and insulin-degrading enzymes are also upregulated by estrogens (Liang et al., 2010; Zhao et al., 2011). In conjunction with the effects on Aβ pathology, estrogens also exerts direct and indirect effects that contribute to the amelioration of NFT that form as a result of the hyperphosphorylation of tau—a protein involved in microtubule formation. Directly, estrogens can inhibit GSK3-β, a kinase involved in the hyperphosphorylation of tau, which consequently minimizes the potential to form NFT. Indirectly, estrogens can activate other intracellular proteins, such as Akt, that act as a brake on GSK3-β activity which in turn also circumvents the aggregation of NFT (Muñoz-Mayorga et al., 2018). The influence of parity on these various neuroprotective effects of estrogens are unknown.

In addition to estrogen levels, parity could alter risk for AD by impacting the brain's long-term sensitivity to estrogens via effects on ER expression or functioning. While a number of rodent and human studies have explored the influence of aging and AD on ERα and ERβ in the female brain (Savaskan et al., 2001; Ishunina et al., 2007; Foster, 2012), parity hasn't been examined as a factor. In the only study to our knowledge to do so, reproductively experienced middle-age female rats were found to have higher numbers of ERα positive cells in the striatum when compared to age-matched, nulliparous controls (Byrnes et al., 2009).

In women, the use of hormonal replacement therapies (HRT) following menopause has been demonstrated in some studies to be a potentially efficacious preventative measure against AD pathology although there are inconsistencies in the literature. These have generally been attributed to variations across studies in timing, dosage, and type of estrogen used (Depypere et al., 2016; Nebel et al., 2018) but it is likely that reproductive history, which is often not included in the analyses, may also play a role. Studies in rats support this possibility and show that HRT therapy cam have differential cellular and behavioral effects in middle-age rats with reproductive experience compared to those without (Barha & Galea, 2011; Galea et al., 2018).

Progesterone—Although less studied than estrogens, progesterone has also been associated with neuroprotection. For example, progesterone reduces neuronal vulnerability to glutamate and Aβ toxicity (Goodman et al., 1996). In addition, ovarectomized female rats administered progesterone show upregulated mRNA expression of several enzymes involved in Aβ clearance, and lowered Aβ in the brain following treatment with an estrogen-progesterone cocktail (Jayaraman et al., 2012). In contrast, other work has shown that progesterone may actually attenuate the ameliorative effects of estrogen on Aβ (Carroll et al., 2007). Notably, progesterone treatment alone has been shown to have no effect on Aβ accumulation (Carroll et al., 2007; Jayaraman et al., 2012). In regards to tau pathology, both cyclic and continuous administration of progesterone have yielded significantly less hyperphosphorylated-tau (p-tau) immunoreactive neurons in a transgenic model of AD (Carroll et al., 2010). Moreover, OVX female transgenic-AD mice treated with progesterone and estrogen demonstrated significantly less p-tau in the hippocampus — an effect that

could be mediated by the regulation of GSK3-β by progesterone (Guerra-Araiza et al., 2007; Muñoz-Mayorga et al., 2018).

Prolactin—Fox et al. (2013b) found that women who reported greater durations of breastfeeding also experienced a reduced risk of AD later in life. Given that prolactin is a hormone that plays a central role in lactation, it likely has some involvement in mediating this association. In support of this possibility, prolactin is able to indirectly inhibit GSK3-β (Domínguez-Cáceres et al., 2004) which suggests it may play a neuroprotective role against hyperphosphorylated tau (Steinmetz et al., 2015).

hCG—hCG is another pregnancy related hormone that has been linked to AD (Barron et al., 2010). hCG activity can have a negative effect on cognition and can accelerate AD pathology (Berry et al., 2008; Barron et al., 2010), through the upregulation of amyloidogenic processing (Saberi et al., 2013) and accumulation of Aβ (Berry et al., 2008; Barron et al., 2010). Considering that this hormone only reaches detectable concentrations during pregnancy and having more children (i.e., more exposure to hCG) has been associated with greater risk for AD (Sobow & Kloszewska, 2004; Beeri et al., 2009; Jang et al., 2018), the role of hCG in AD warrants further investigation.

5.4 Parity, AD and immune factors

Some studies suggest that there is a protective effect of parity on AD risk (Fox et al., 2013a; 2018b) possibility due to the shift from a Th1 dominant state towards a Th2 immunosuppressive state during pregnancy (Fox et al., 2018b). This immunosuppressive state is associated with an upregulation of T_{Regs}, which dramatically rise during the first trimester and continue to gradually increase for at least a year postpartum (Heikkinen et al., 2004; Somerset et al., 2004). Like other neurodegenerative disorders, AD pathology is characterized by a dysregulated immune system. As such, enduring elevated levels of T_{Regs} may supply mothers with protective immunosuppression during critical periods when AD pathology, and ensuing inflammation, might flourish otherwise. Results from Fox et al. (2018b) do suggest that T_{Regs} may be accounting for protection against AD more so than estrogen. Specifically, they found not only a positive correlation between total months pregnant and lower risk of AD, even when controlling for reproductive span, but that the cumulative number of first trimesters reduced the risk of AD while the cumulative number of third trimesters did not significantly reduce risk of AD. The drastic upregulation of T_{Regs} during the first trimester suggests that this may be the mechanism by which AD protection is conferred, and since third trimester, when estrogen levels peak, had no bearing on risk reduction, estrogen exposure during pregnancy may not account for AD risk reduction. However, when interpreting the results, it is important to consider that hormones and the immune system are not independent operators, but are rather integrated systems that engage in extensive cross-talk. For example, estrogen meditates the induction and generation of regulatory T-cells (Tai et al., 2008) as well as reduces the activation of effector T cells (Polanczyk et al., 2006). Progesterone also contributes to the protective immune environment during pregnancy by promoting T-helper cells that produce Th2-type cytokines (Piccinni et al., 1995; Arck et al., 2007). Thus, there is likely a complex interaction between immune and hormonal factors in regulating the effects of parity on AD.

6. Parity, Lifespan and Telomeres

By modulating disease risk and resilience, parity may ultimately affect mortality. Some evidence suggests higher parity is associated with shortened lifespan (Penn and Smith, 2007; Sun et al., 2015) and that telomere attrition may play a role. Telomeres are repetitive nucleotide sequences located at the ends of chromosomes that protect chromosomes from degradation, fusion and recombination (Blackburn, 1991). Over time, with each cell division, telomere length decreases due to incomplete end replication; although, telomere shortening may be also influenced by a variety of endogenous and environmental factors. Telomere length can be used as an index of cellular aging with longer telomeres being correlated with longevity (Barrett et al., 2013) and shorter telomeres being associated with accelerated aging, a variety of chronic diseases (e.g., cancer, Alzheimer's) and mortality (Cawthon et al., 2003; Sanders & Newman, 2013). Consistent with the shorter life expectancy as a result of parity, having at least one child has been associated with shortened telomeres (Kresovich et al., 2018; Pollack et al., 2018). Strikingly, one study estimated the difference in telomere length between parous and non-parous women to be equivalent to 11 years of cellular aging — an effect observed to be larger than the effect smoking or obesity had on telomere length (Pollack et al., 2018). Conversely, longer telomere lengths have been observed in women who had their last child at a later age (Fagan et al., 2017) which has been linked to greater longevity (Perls et al., 1997; McArdle et al., 2006; Sun et al., 2015) and a resistance to dementia later in life (Gilsanz et al., 2018). Interestingly, longer telomeres have also been associated with greater breastfeeding duration (Kresovich et al., 2018) as well as greater endogenous estrogens which is typically associated with lower parity (Lin et al., 2011).

7. Conclusion

Risk and resilience in CNS health and disease can be influenced by a variety of factors. While there is a growing appreciation to consider sex one of these factors, far less attention has been paid to sex-specific variables that may differentially impact females such as pregnancy and reproductive history. As noted by Ritzel et al. (2017), data from the CDC estimates that 85% of women in the United States have given birth by age 40. Given that child-bearing women represent such a significant proportion of the female population, a better understanding of whether pregnancy, motherhood and parity influence brain health and disease is needed, and if they do, how such effects arise. Ultimately, a greater of consideration of these and other female-specific variables may lead to more-informed treatments for women suffering from a variety of CNS disorders.

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Highlights

- The physiological changes of pregnancy/motherhood can affect brain health and disease
- Multiple sclerosis, depression, stroke and Alzheimer's are among those impacted
- A full understanding of the female brain requires consideration of female-specific experiences