Beyond Sex Differences: Short and Long-Term Implications of Motherhood on Women's Health

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Highlights

Physiological changes during pregnancy influence many aspects of maternal health

Steroid and peptide hormones are elevated dramatically during gestation

Reduced grey matter is detected in multiple regions after motherhood

Physiological changes with motherhood are detected years after giving birth

Sex differences exist in development, physiology, behaviour, disease prevalence, manifestation, and outcome. It is vitally important to consider sex differences in research towards a better understanding of precision medicine for both men and women. However, for substantial progress in women's health we need to acknowledge that female physiology is different from males and uniquely female experiences such as pregnancy and motherhood can affect the physiology of females. Pregnancy is associated with dramatic changes in physiology (cardiac, pulmonary, immune, and metabolic) and endocrinology (steroids and peptide hormones, many of which are unique to pregnancy). Thus, it is not surprising that there can be repercussions both in the short and in the long-term for the health of the female. Here, we discuss research demonstrating that pregnancy and the postpartum period are associated with changes in neuroplasticity and cognition, and a greater risk of developing certain mental health disorders with some of these effects having lifelong consequences. As a potential implication, we also discuss how drug treatments may work differently in parous women. Finally, we argue that, in addition to sex differences, the physiological challenges unique to women need to be taken into consideration for a better understanding of women's physiology and disease.

Pregnancy and the postpartum are times of dramatic changes in a woman's lifetime. Many physiological processes are inundated during pregnancy to allow for fetal growth and are orchestrated by the newly created endocrine gland, the placenta. During gestation, cardiac, and pulmonary systems are increased in capacity, immune tolerance is upregulated, and steroid hormone levels skyrocket [1]. In terms of hormones, in pregnant women, the placenta releases progesterone at least 20 times normal levels, and glucocorticoids around twice the normal levels [2]. In addition, estrogens show arguably the more dramatic increases during pregnancy, with 17β-estradiol rising up to 200 times normal levels by week 20 and 300 times by week 30 of pregnancy [2]. The placenta secretes a variety of bioactive hormones and enzymes at levels that are generally not seen outside of pregnancy and/or hormones not detectable except during pregnancy such as placental lactogen and human chorionic gonadotropin [2,3]. Estriol, one of the estrogens, is secreted at much higher levels during pregnancy than at any other time point in a woman's lifespan [4]. These hormones are needed to ensure successful gestation; however, the long-term consequences of exposure to these hormones to the host mother have not been frequently addressed in the literature. This is an important consideration as maternal physiology is altered for decades after giving birth in the mother. These changes in physiology likely affect drug efficacy, and disease susceptibility, outcome, and manifestation, and yet reproductive experience is not often considered in women's health research. In this opinion piece, we argue that reproductive experience is a critical determinant of female physiology that has been grossly overlooked in the health and wellbeing of women and can serve to drive discovery for women's health.

The typical duration of a full-term pregnancy is approximately 38-40 weeks highlighting that the sustained high in hormone levels are not short in duration and is the time of maximal exposure to many of these hormones during a woman's lifetime. Thus, it is of little surprise that due to the presence of hormones, such as estrogens and progesterone, at sustained high levels for weeks, as well as changes to the renal, cardiac, immune, metabolic, and pulmonary systems, that there may be some lifelong repercussions for the mother. While, research in this area is scarce, data indicate that levels of estradiol are lower across the menstrual cycle after resumption of cycling, which typically occurs 180 days after parturition [5], This has lead researchers to indicate that cumulative estrogen exposure is lower if women are parous (e.g., see [6]). However, this may prove difficult to ascertain, as excessive estrogens during pregnancy may offset the lower levels of estrogens seen after pregnancy. Nonetheless, previous parity is an important consideration for the influence of hormone exposure on brain and body health. Many of these changes can have long lasting impacts on the brain, body, and disease risk as we report below. We urge the community to acknowledge, record, and report parity as a demographic variable when utilizing women in their studies.

While we are focussing on hormones, many other systems are also besieged during pregnancy and likely contribute to influencing long-term female physiology long after giving birth. For example, pulmonary function, cardiac output, salt/mineral balance, insulin sensitivity, and immune function are all strained during pregnancy [7]. Indeed, pregnancy is often cited as a woman's first cardiac stress test given the demands on the cardiac system that needs to increase output and efficiency by 50% [8]. Even more telling, in case of complications during pregnancy or low birth weight in babies, there is a greater risk of heart disease or metabolic syndrome in women later in life [9,10]. Both multiparity and earlier age of first pregnancy is associated with obesity in postmenopausal women [11]. Excessive weight gain during pregnancy is also associated with obesity in later life but the mechanisms are unclear. It is possible that pregnancy and motherhood interact and/or exacerbate pre-existing conditions in women later in life.

Indeed, pregnancy complications, such as pre-eclampsia, are associated with early mortality [12]. However, intriguingly, mortality rates for childless women that had undergone in vitro fertilization were higher than women that had biological children, although pregnancy and obstetric complications were not addressed in this study [13]. Another study found that while parous women were more likely to die from coronary heart disease, be overweight, present with diabetes or hypertension, mortality was decreased with increasing parity, though again, complications during pregnancy or parturition were not studied [14]. Nonetheless, the number of physiological demands during pregnancy, many mediated by placental hormones, and the dramatic maternal adaptation necessary during pregnancy are associated with long-term impacts on maternal health, that likely depend on a number of parameters such as maternal age, parity, and pregnancy complications.

After giving birth, women show increased and decreased susceptibility to a variety of diseases. In the short term, postpartum depression is seen in approximately 15% of women, while 80% of women will experience the postpartum blues [15]. It should be noted that approximately 40% of the 15% of women that experience postpartum depression will be experiencing depression for the first time in their lives [15]. Intriguingly, postpartum blues are considered a normal consequence of giving birth and is thought to be mediated, at least in part, by the rapid change in levels of steroid and peptide hormones with the expulsion of the placenta [16]. In addition, obsessive-compulsive disorder is more likely to present after giving birth, and postpartum psychosis occurs in approximately one percent of parous women [17,18]. Much of the focus has been devoted to the increased susceptibility to these mental health disorders during and after pregnancy, and less work has centred on any long-term consequences of reproductive experience. Nevertheless, oncology research has examined long-term effects on a variety of cancers, with previous parity related to either increased or reduced susceptibility to a variety of cancers, that can last a couple of decades (ovarian) or a lifetime (breast, endometrial) [19,20]. Reproductive history is associated with shorter leukocyte telomere length indicating an accelerated cellular aging [21]. Indeed, telomere attrition has been associated with a variety of chronic diseases, such as cancer, inflammation, type 2 diabetes, and Alzheimer's disease (see below) [22]. Clearly, reproductive experience influences the prevalence of a number of disorders and is an important consideration in women's health.

After pregnancy, new mothers must elicit a host of new maternal behaviours in order to ensure the care and survival of her offspring. In rodents, the initiation of maternal behaviours is due to the hormones during pregnancy and the fluctuations at parturition [23–25], and there is some evidence that the estradiol to progesterone ratio and oxytocin are important in establishing maternal attachment in humans [26–28]. This induction of maternal behaviours suggests that an extraordinary amount of plasticity, related to learning, needs to occur in the early postpartum. Indeed, there are reports of increased grey matter in the amygdala, hypothalamus, and prefrontal cortex [29] and an increase in whole brain volume [30], after the decrease during pregnancy, 3-6 months postpartum. Furthermore, prefrontal cortical thickness in both hemispheres is increased with increasing postpartum months. In addition, prefrontal cortical thickness was positively associated with self-reported parental self-efficacy in first time mothers between 1-7 months postpartum [31]. Intriguingly, evidence also exists to the contrary, in that reduced grey matter and neuroplasticity are seen in a number of regions in the brain, including the hippocampus (a region associated with memory), in both humans and rodents [30,32–34]. These reductions in grey matter are positively related to maternal attachment [32]. Many of the changes in grey matter reduction are evident at least two years after first birth [32] but it is not clear if subsequent pregnancies may have a greater, lesser, or longer lasting impact on the brain. Intriguingly,

work in rats suggests that primiparity versus biparity is associated with differing outcomes on neurogenesis levels in the hippocampus [34]. Primiparous but not biparous rats exhibit reduced survival of new neurons in the dentate gyrus of the hippocampus across the postpartum [34]. This reduction in survival of new neurons in primiparous rats is due to pregnancy and not exposure to pups. Nulliparous rats exposed to pups for 21 days (foster moms) show an increase in the survival of new neurons, while pregnancy alone (removal of the pups within 24 h of birth) reduced the survival of new neurons across the postpartum to similar levels of primiparous rats [34]. In other regions of the hippocampus (CA3 and CA1), dendritic complexity is reduced in primiparous but not biparous rats at weaning, suggesting that the dentate gyrus is not the only area within the hippocampus that shows a disparity in outcome between primiparous and biparous rats [35]. Other studies have shown that new cells are also reduced in the dorsal raphe nucleus during the postpartum [36] but increased in other areas (nucleus accumbens and bed nucleus of the stria terminalis [37] or the olfactory bulb [38] in rodents. Thus, collectively a number of studies indicate that neuroplasticity is reduced in the hippocampus and the dorsal raphe [32], but increased in the nucleus accumbens, bed nucleus of the stria terminalis, and prefrontal cortex, with some changes evident as long as two years after giving birth [31,32,34,36]. Intriguingly, both reductions and increases in many of these areas are positively associated with parenting.

Although there are numerous changes seen in neuroplasticity in the short term in both rodents and humans, fewer studies have examined whether there are changes to neuroplasticity in the long-term with previous reproductive experience. Middle-aged multiparous rats have higher levels of hippocampal neurogenesis [39], increased BDNF levels [40], synaptophysin [41], and reduced amyloid precursor protein [42] than nulliparous rats. Furthermore, the hippocampus responds differently to estrogens with previous reproductive experience in rodents [43]. While estrogens do not significantly influence neurogenesis in middle-aged nulliparous rats, surprisingly, estrogens increase neurogenesis in middle-aged multiparous rats, showing a similar response as young adult nulliparous female rats [43,44]. One possible explanation for these findings is that, perhaps with the lower estradiol levels across the estrous cycle after reproductive experience [45] the hippocampus maintains its ability to show plasticity in response to estrogens in middle age. Primiparous middle-aged rats show increased neurogenesis in the hippocampus compared to nulliparous rats [46], while both parous groups show reduced neurogenesis in response to Premarin, conjugated equine estrogens. However, Premarin facilitated early learning and reversal learning in nulliparous rats, but impaired performance in primiparous middle aged rats [46]. These findings have profound implications for hormone treatment in postmenopausal women as the effects may be very different in parous versus non-parous women in later life, an effect that has not been investigated to our knowledge.

As there are changes in neuroplasticity, what does the evidence indicate about changes in cognition seen during pregnancy and in the short- and long-term postpartum? Anecdotally women report baby brain particularly later in the pregnancy, but laboratory measures of memory do not indicate any measurable memory deficits in women [47]. However, cognitive deficits associated with verbal memory are seen in the third trimester of pregnancy [48] with the deficits increasing with parity [49]. Furthermore, deficits in working memory and spatial memory are seen in women that are pregnant with girls but not boys [50]. An impairment in hippocampus-dependent learning during late pregnancy and the early postpartum is also seen in rodents [33,51]. Intriguingly, these motherhood-associated deficits in cognition reverse in the late postpartum, as parous rats exhibit better cognition after weaning compared to non-parous rats [52,53]. While there are only a few studies, executive function may be

facilitated with previous parity and age of first pregnancy, with better performance at 4-6 months postpartum in women that were older during their first pregnancy [54]. More concerning, parity may negatively affect cognition in later life, dementia risk, and pathology associated with Alzheimer's disease in later life [55–59]. However, the results in humans with respect to parity influences on cognitive function and dementia risk have been mixed. This may be due to a number of factors such as the age of first parity [60], breastfeeding duration [61], sex of children [50], and genotype [62,63]. Nevertheless, these studies cumulatively suggest that the amount of parity, as well as sex of child, age of first birth, play a role in short- and long-term influences on cognition and neuroplasticity.

One important implication of the altered physiology in parous women is that drug treatments may work differently, possibly due to the differences in hormone levels and changes in pharmacokinetics during gestation and beyond [64]. Although there is surprisingly very little work in this area, there are some studies indicating changes in cytochrome P450 enzymes occur during pregnancy [65–68] and possibly in the postpartum [69], which affect metabolism of drugs including antidepressants. One mechanism of action behind the efficacy of selective serotonin reuptake inhibitors (SSRIs) in females has been the ability of SSRIs to work more effectively with liable, and/or increased levels of estradiol [70]. Thus, it may not be surprising given that estradiol levels are decreased during the postpartum that selective serotonin reuptake inhibitors (SSRIs) may not be as efficacious during the postpartum. Certainly, studies in our laboratory have accumulated to suggest that efficacy of SSRIs such as fluoxetine and paroxetine are blunted during the late postpartum [71–73]. We have found that in a rodent model of postpartum depression, fluoxetine does not restore reduced levels of neurogenesis or increased levels of passive coping in the forced swim test at the end of the postpartum period (postpartum day 24, after 22 days of continual exposure to SSRI). Curiously however, we do see that fluoxetine can reverse maternal care deficits assessed in the early postpartum [71–73], suggesting that SSRIs may be effective in the early postpartum, but not in the late postpartum. Furthermore, Lonstein and colleagues [36,74,75] have noted changes in serotonin signalling during pregnancy and the postpartum, and these alterations likely influence the efficacy of SSRIs. More recently, we have found that exercise can be used in the postpartum as a viable option to increase neurogenesis and reduce immobility in the forced swim test with or without the addition of an SSRI [72]. It is not clear what may be interfering with the ability of SSRIs to increase neurogenesis across the postpartum but it may be related to the hormonal milieu and changes to serotonin signalling during the postpartum period. Collectively these studies suggest that the postpartum period is a period of decreased efficaciousness to SSRIs. Whether or not pharmacokinetics differ with reproductive experience in the long-term remains to be determined but should be an important consideration when investigating the effectiveness of therapies in women.

Lastly, many of the long-term physiological changes may be moderated or mediated by fetal microchimerism. During pregnancy, there is bidirectional flow of fluids from mother to fetus via the circulation to the placenta [76]. In the process, there is some transfer of fetal tissue to the circulatory system of the mother and these cells remain in the woman's system for life [77]. While there are few studies in this fascinating area, higher levels of XY cells were negatively correlated with neuropathology related to Alzheimer's disease [78] and a decrease in mortality [79] in women. The possibility of fetal microchimerism influencing female health is intriguing but puzzling and may be related to the immune system. The immune system undergoes complex changes during pregnancy with immune tolerance and sensitivity in an orchestrated system that has not been fully elucidated [80]. It is possible that the HY antigen on male cells can re-program or stimulate the maternal immune system with long-term

repercussions. Although it seems incredible that this tiny number of cells can have a dramatic impact, some research points to long-lasting effects on maternal cognition based on fetal sex [50].

In conclusion, pregnancy and the birth of baby are accompanied by a host of physiological and psychological changes that occur in mother (and to a lesser extent the father). That there are lifelong alterations in the physiology of the mother should not be surprising with the advent of pregnancy. However, the idea that previous reproductive experience should be used as a moderator/variable to consider in women's health has not received much attention. While, there is much focus on how biological sex alters disease trajectory and outcome, we argue that it also important to study the physiological challenges unique to women towards a better understanding of the influence of factors on women's health. In the area of animal research, a number of studies on aging have used retired breeders but given that multiparous rodents show differences in the effects of estrogens, levels of BDNF, and cognition as they age, this could be an important consideration when examining aging in female animal models. When considering reproductive experience, amount, age of first pregnancy, biological sex of children, and pregnancy complications are likely to play modifying roles. Clearly, while parity is a modifiable factor, it is not likely that women will chose or not chose to have children based on long-term health consequences but nonetheless it is important to acknowledge and understand that parity has life-long implications in the treatment of women and may need to be considered in treatment strategies as women age.

Figure 1. Physiological changes seen during pregnancy, and in the short and long term after birth. Pregnancy is associated with dramatic physiological and hormone changes, many driven by the placenta. During pregnancy and postpartum, there is a reduction in grey matter in numerous areas such the superior temporal sulcus, medial and inferior frontal cortex, the fusiform areas and the hippocampus, changes that are seen even 2 years later but also increases in cortical thickness in the prefrontal cortex and grey matter increases in the amygdala. Cognitive difficulties are noted in late pregnancy and the early postpartum. In the short term, within the first few months after giving birth, parous women have an increased susceptibility to a variety of mental health disorders including postpartum depression, obsessive-compulsive disorder, and postpartum psychosis. Even many years after giving birth in middle-aged and older women, while studies are few, studies have found increased risk of developing obesity, and metabolic disorders in women that had complications during pregnancy such as preeclampsia and there is a suggestion that Alzheimer's disease may be related to parity. Figure created by Medical Illustrator, Vicky Earle, BSc AAM MET.

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Short and Long Term Implications of Pregnancy

Pregnancy

Maternal Physiological Changes
↑ cardiac capacity
↓ pulmonary capacity
↑ immune tolerance
↑ insulin sensitivity
↑ steroid hormones
↓ grey matter

Placental Hormones
↑ progesterone
↑ glucocorticoids
↑ 17β estradiol

! A human being will never experience these levels of hormones except during pregnancy

Short Term Changes

Maternal Changes
↑ postpartum depression
↑ postpartum psychosis
↑ OCD
↓ grey matter

Long Term Changes

Maternal Changes
↑ obesity
↑ Alzheimer's disease
↑ metabolic system