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Clinical Immunology

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REVIEW

Effects of pregnancy and breastfeeding on the multiple sclerosis disease course ☆

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Received 8 December 2012; accepted with revision 17 January 2013

Available online 27 January 2013

KEYWORDS

Breastfeeding;
Pregnancy;
Multiple sclerosis

Abstract Multiple sclerosis (MS) commonly affects young women of childbearing age. Thus, the challenges of the disease are often faced simultaneously with the challenges of early adult life and family planning. This has led to great interest in the effects of pregnancy and breastfeeding on MS. It is now well known that the risk of MS relapse declines during pregnancy but increases in the first 3–4 months postpartum. However, important gaps in knowledge remain and are the focus of this review. What factors predict postpartum relapses? Are there modifiable factors, such as breastfeeding, particularly exclusive breastfeeding, that could reduce the risk of postpartum relapses? Does pregnancy or breastfeeding have any long-term effects on MS disease course? What immunological mechanisms underlie the effects of pregnancy and breastfeeding? Answering these questions will improve our ability to care for women with MS and may provide a greater understanding of the pathophysiology of the disease.

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☆ Disclosures: Brandon E Beaber reports no disclosures. Annette Langer-Gould is a site-investigator for multicenter clinical trials funded by Biogen Idec and Hoffman-La Roche.

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1. Introduction

Pregnancy is a complex state of transient immunological tolerance to the fetus. It is therefore not surprising that pregnancy modulates the course of many autoimmune and infectious diseases. However, the direction and magnitude of the effects of pregnancy on these diseases can vary in counterintuitive ways and must be determined from careful, rigorous clinical studies.

1.1. Pregnancy, the postpartum period and MS relapses

In the early part of the 20th century it was believed that pregnancies could be harmful to women with MS by causing severe postpartum exacerbations or increasing the risk of long disability [1]. Starting in 1959, numerous studies that questioned this belief have been conducted, and no convincing evidence of a harmful effect has been uncovered [2–7]. It is now well-understood that the risk of relapse significantly declines during pregnancy, particularly during the third trimester, only to increase three-fold in the first 3–4 months postpartum compared with pre-pregnancy. This 70% reduction in disease activity during the third trimester was definitively established through a relatively large multicenter prospective study of 227 pregnant women with MS followed prospectively through the remainder of pregnancy and one year postpartum [7]. Even though this study was conducted before the era of DMTs, the magnitudes of reduction in relapse rate during pregnancy and increase in the postpartum period have remained remarkably stable in subsequent prospective and retrospective cohort studies conducted during the treatment era [8–10].

1.2. Pregnancy, neuromyelitis optica and radiologically isolated syndrome

That giving birth may have pro-inflammatory effects on autoimmune CNS demyelinating diseases is also supported by recent reports of the effects of pregnancy on neuromyelitis optica (NMO) and radiologically isolated syndrome (RIS). In women with NMO, two small studies [11,12] with remarkably similar results have shown that NMO symptom onset is more likely to occur during the postpartum year than during pregnancy and that the risk of relapse increases in the first 3 to 6 months postpartum. In women with RIS—the asymptomatic precursor of MS—preliminary evidence suggests that pregnancy may accelerate time to MS symptom onset [13]. All three of these descriptive studies are limited by retrospective design and small numbers of pregnant women ($n=40$ [11],

20 [12], and 7 [13]) and thus await confirmation in larger, hypothesis-driven studies. Nevertheless, these findings are consistent with the much more extensive literature in MS and beget the question of why the risk of relapse is elevated in the immediate postpartum period.

2. Postpartum MS relapse risk factors

Studies explicitly designed to identify risk factors of postpartum MS relapses have not been performed therefore little is known about how the risk of postpartum relapses could be diminished. One study found that a higher relapse frequency prior to pregnancy and relapses during pregnancy were strongly associated with an increased risk of postpartum relapses [7], but these two factors correctly predicted only 12.7% of women who had postpartum MS relapses [14]. Thus, most of the risk remains unexplained. It is also interesting to note that pre-pregnancy relapse frequency may no longer be a strong predictor of postpartum relapses now that many women are on MS treatments that suppress relapses prior to pregnancy. This issue remains to be resolved in contemporary cohorts.

3. Modifiable risk factors of postpartum MS relapses

Modifiable factors like breastfeeding, particularly the biologically distinct state of exclusive breastfeeding, resuming MS treatments, hypovitaminosis D, diet, smoking, alcohol and stress have not been adequately studied despite the obvious clinical importance of these questions (Table 1).

3.1. Breastfeeding

A recent meta-analysis found that women who breastfed were almost half as likely to have a postpartum MS relapse compared to women who did not breastfeed [15]. As acknowledged by the authors, this meta-analysis is limited by significant heterogeneity in how studies defined and measured the exposure (breastfeeding) and outcomes (relapses) and whether pregnancy disease severity was taken into account. Therefore, this meta-analysis does not exclude the potential for confounding by disease severity nor does it address the biologically distinct state of breastfeeding.

Previous studies of breastfeeding and postpartum relapses have found either no association [5,7,9] or a protective effect [8,16,17]. The studies that found no effect [5,7,9] defined breastfeeding crudely and failed to distinguish exclusive breastfeeding (which is a biologically distinct state) from non-exclusive breastfeeding [18]. In studies that measured

Table 1 Summary of knowledge and gaps.

Current understanding

1. *Pregnancy is not harmful to women with MS*
Risk of relapse decreases during pregnancy by ~70%
Risk of relapse increases 3-fold in the first 3–4 months postpartum
No significant impact on long-term disability
2. *Breastfeeding is not harmful to women with MS*
Even in the era of immunomodulatory treatments
3. *Pre-pregnancy disease severity increases the risk of postpartum MS relapse*
But this correctly predicts only 12.7% of women who have postpartum relapses

Gaps in knowledge

1. *Effect of modifiable risk factors of postpartum relapses are unclear*
Exclusive breastfeeding
Hypovitaminosis D
Diet, tobacco, alcohol
Stress and sleep deprivation
MS immunomodulatory treatments
2. *The immunological underpinnings of pregnancy-related changes in MS disease activity are unknown*
Could shed light on mechanisms of relapse in pregnant and non-pregnant MS patients
3. *Is there a lasting benefit of pregnancy or breastfeeding on the MS disease course?*
Either through immunomodulation or neuroprotection

breastfeeding more precisely [8,17], a protective effect was found among those women who breastfed exclusively.

Biological studies in healthy women have shown that exclusive breastfeeding is hormonally distinct whereas supplemental feeding and not breastfeeding at all have similar hormonal effects (Fig. 1). Exclusive breastfeeding results in high prolactin levels, low and non-pulsatile luteinizing hormone (LH) levels and ovarian suppression (lack of ovulation and post-menopausal levels of estradiol and progesterone) [19,20]. High frequency and intense sucking maintain high prolactin levels, low LH levels and lactational amenorrhea. Once regular supplemental infant feedings are introduced, the frequency and total duration of sucking episodes decline, prolactin levels drop, ovarian activity resumes, and menses returns, typically within 2 months [18]. The biological effect is similar to complete weaning. In addition, immunological studies in healthy women have shown that tumor necrosis factor (TNF)-alpha production—a pro-inflammatory cytokine important in MS—fluctuates with the menstrual cycle [12]. This suggests that behaviors that result in earlier return of menses—like combining breastfeeding with early supplemental feeding or not breastfeeding at all—could have a pro-inflammatory effect whereas behaviors that result in amenorrhea like exclusive breastfeeding could have an anti-inflammatory effect.

In our small yet rigorous prospective pilot study we found that breastfeeding supplemented with formula and not breastfeeding at all (i.e. non-exclusive breastfeeding) conferred a similar and significant increase in the risk of postpartum relapses compared with exclusive breastfeeding

[8]. We also found that prolonged lactational amenorrhea was associated with a four-fold decreased risk of postpartum relapses and with a decrease in TNF-alpha producing CD4 cells demonstrating a distinct immunological effect induced by the behavior of exclusive breastfeeding [21]. Our findings have been confirmed in a larger prospective cohort (n=72) through our collaboration with the German MS Pregnancy Registry [22]. Among women who breastfeed exclusively, relapses returned shortly after supplemental infant feedings began with remarkably similar timing as women who introduced formula feedings shortly after delivery [23]. If these findings can be reproduced, it would provide a key piece of evidence that would greatly strengthen a causal relationship between exclusive breastfeeding and a reduced risk of postpartum MS relapses. Taken together, these findings suggest that it is plausible that exclusive breastfeeding could lead to decreased disease activity in MS. In addition, findings from these studies suggest that the most likely reason other studies [5,7,9] found no effect of breastfeeding on postpartum relapses is that they obscured the beneficial effects of exclusive breastfeeding by combining those who exclusively breastfed with those who supplemented breastfeeding with formula. In our studies, the latter group had the same risk of relapse as women who do not breastfeed at all.

The exclusive breastfeeding hypothesis is extremely attractive because it is available to women worldwide regardless of financial status thus offering a potentially high-impact strategy to reduce the risk of postpartum MS relapses and improve the health of their offspring. Breast milk provides the infant with antibodies and other factors that aid the healthy development of their immune system. Breastfeeding also reduces the risk of childhood illnesses including infections, asthma, leukemia and autoimmune diabetes as well as obesity during adolescence and adulthood [24]. However, uncertainty remains as to whether our findings are due to confounding by indication, with women who are not as sick prior to pregnancy being more likely to breastfeed exclusively and less likely to have postpartum MS relapses. In addition, sampling error remains a possibility as it does with findings from any single study. While our clinical results have been confirmed in the German MS Pregnancy Registry, an important limitation of this study is that it consists of a biased sample as most women are recruited through direct-to-patient drug company advertisements [22,23].

3.2. MS treatments

Pregnant women with MS, regardless of whether they breastfeed or not, should at some point resume immunomodulatory treatments (IMAs) and need to decide when they will do this. While some experts advocate foregoing nursing all together in order to resume treatment with IMAs, particularly in women with more severe disease [9], whether resuming IMAs sooner rather than later reduces the risk of postpartum relapses has not been studied. We hypothesize that for IMAs to effectively reduce the risk of postpartum MS relapses they need to be resumed quickly after delivery since these medications have a delayed onset of action [25–27] and most postpartum relapses occur in the first 4 months postpartum [7,8]. In our pilot study, women who resumed IMAs appeared

to have a higher risk of postpartum relapses than women who breastfed exclusively (unpublished data). However, this study was too small to address whether very early resumption of IMAs reduces the risk of postpartum relapses, particularly among women who do not want to breastfeed.

3.3. Hypovitaminosis D

Lactation increases the risk of hypovitaminosis D [28,29] which is a well-described risk factor for MS in whites [30] and has been linked to a worse prognosis [31,32]. Hypovitaminosis D has been associated with a higher risk of MS relapses in children [32] and with more brain MRI gadolinium-enhancing plaques in adults [33]. The vitamin D-MS relapse hypothesis is attractive because vitamin D deficiency is common [34] in pregnant and lactating women, thus offering a potentially high-impact strategy to reduce postpartum MS relapses. In our pilot study we found that hypovitaminosis D was associated with exclusive breastfeeding but was not associated with an increased risk of postpartum relapses [35]. However our study was limited by the inability to account for other factors that lower 25(OH)D levels like less sun exposure, darker skin tone and low dietary intake.

3.4. Epidural anesthesia

The few studies that have addressed the use of epidural anesthesia [7,35,36] did not find any association with postpartum MS relapses. However, the comparator groups (no anesthesia, local infiltration, general anesthesia) and doses of anesthetics were not clearly defined. Thus a small beneficial or harmful effect of epidural anesthesia cannot be excluded.

3.5. Smoking, alcohol, diet, stress and sleep deprivation

There are no published studies examining the effect of tobacco smoke, alcohol consumption, diet, stress and sleep deprivation on the risk of postpartum MS relapses. Tobacco smoke and alcohol consumption may prove difficult to study because most women abstain or significantly reduce their use during pregnancy and breastfeeding. Self-perceived stress and sleep deprivation may also prove difficult to study as these are common complaints during late pregnancy and the postpartum period.

4. Long term effects of pregnancy and breastfeeding on MS disease course

Whether pregnancy or breastfeeding has a lasting effect on MS disease activity and long term disability has not been carefully studied. Studies of pregnancy and long term MS-related disability found either no association [37–39] or a protective effect [36,40–42]. However, a major challenge of these studies is that they could not exclude the possibility that women with more severe disease chose not to get pregnant. In addition, some studies also did not distinguish whether pregnancies occurred before or after MS onset. It is important to note that no studies have found a harmful effect of pregnancy, so women with MS can be reassured

that child-bearing will not increase their risk of long-term disability. Future studies of pregnant women with MS should include non-pregnant women with MS and carefully measure postpartum behaviors to determine whether these factors influence disease course.

No studies have examined the long-term effect of breastfeeding, particularly exclusive breastfeeding. A longer duration of breastfeeding has been shown to reduce the risk of developing metabolic syndrome up to 20 years later in both women with and without gestational diabetes [43]. Thus, the possibility that prolonged breastfeeding may have a lasting beneficial effect in MS analogous to women with gestational diabetes is worthy of further study.

5. Immunological underpinnings of postpartum MS relapses

The immunology of pregnancy is very complex and has evolutionary origins in preserving the viability of an antigenically foreign fetus. However, why women with MS and other autoimmune diseases like rheumatoid arthritis (RA) and Hashimoto's thyroiditis flare in the postpartum period is not well understood. There are many hypotheses that fall in and out of vogue to explain this phenomenon. However, the amount of evidence from studies conducted in women with autoimmune diseases pales in comparison to the number of review articles and opinion pieces written on this subject.

Popular hypotheses to explain pregnancy-related amelioration of MS include suppression of the principal pro-inflammatory T cells in MS and RA (CD4+ cells that produce IFN γ , TNF or IL2; T-helper-1 or Th1 cells) through augmentation of their mutual inhibitors—CD4 cells that produce IL10 or IL4 [44]; enhancement of regulatory T cells [45], diminished Th17 cells [46], impairment of antigen presenting cells by estrogen or pregnancy specific glycoproteins [47]; a direct neuroprotective effect of estrogen [48] or progesterone [49]; intralesional suppression inflammation by

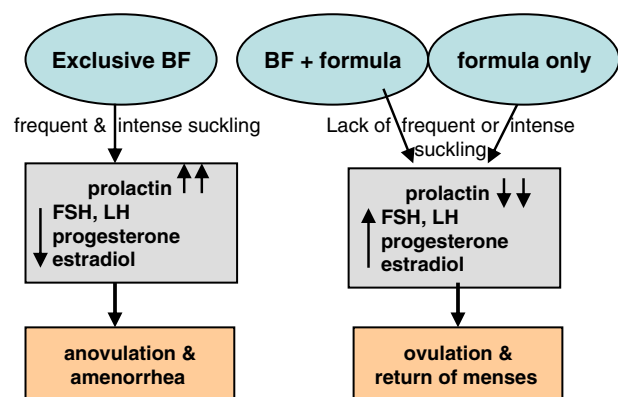


Figure 1 Distinct hormonal effect of exclusive and non-exclusive breastfeeding. This figure shows that breastfeeding (BF) supplemented with formula feeding induces the same hormonal effects as not breastfeeding at all, with both behaviors resulting a drop in prolactin, rise in follicle-stimulating hormone (FSH) and LH, with return of ovulation and menses. In contrast, exclusive breastfeeding results in high prolactin levels, anovulation and lactational amenorrhea.

a pregnancy-related serum protein or glycoprotein [50] or exosomes [51] and/or fetal cell microchimerism. However, support for most of these hypotheses comes primarily from animal studies and to a lesser extent, studies of healthy pregnant women [52–55].

Few studies have examined changes in cytokines or immunological cell types during pregnancy and the postpartum period in women with MS [21,56–60]. Most of these studies have significant methodological limitations most importantly that all but one [21] failed to examine the relationship of immunological changes to postpartum relapses or other factors [56–60]. In addition, most of these studies did not identify which T cell subset was producing the cytokines of interest. Thus it is unclear if the immunological changes they observed are best explained by pregnancy, MS, MS disease activity or other factors such as lactational amenorrhea [56–60].

In our pilot study we found that IFN γ -producing CD4 $^{+}$ cells declined in all women with MS during pregnancy [21]. But after parturition, this cell type diverged among the women with MS who had postpartum relapses and those who did not. These lymphocytes continued to decline in the group of women who went on to have relapses and increased or remained stable in the group of women who were relapse-free in the postpartum year. Among the women with MS who breastfed, prolonged lactational amenorrhea was associated with a rise in IFN γ -producing CD4 $^{+}$ cells. However, we found no significant, measurable changes in CD4 $^{+}$ IL2, IL4 or IL-10 producing subsets in relationship with either pregnancy or MS relapses. Thus, why the IFN γ -producing CD4 $^{+}$ cells fluctuate with pregnancy, lactational amenorrhea, and MS relapse remains unknown.

We interpreted these findings to mean that the pathophysiological process leading to postpartum relapses is likely initiated during pregnancy in all women with MS but that factors associated with parturition (such as exclusive breastfeeding) are able to successfully interrupt this process. This idea that pregnancy may actually be initiating relapses could explain why Achiron et al. [35] found that prophylactic treatment with intravenous immunoglobulin to prevent postpartum relapses was significantly effective if started during pregnancy but only marginally effective if started shortly after delivery. It may also explain why resuming beta-interferons or glatiramer acetate even as soon as 2 weeks after delivery does not significantly reduce the risk of postpartum MS relapses [35].

Nevertheless, our study demonstrates that for future studies aimed at unraveling the relationship between changes in the immune system, pregnancy, the postpartum period and MS or MS disease activity, it will be critical to examine potential confounders like menstrual status and breastfeeding and to distinguish between the T cell subsets producing the cytokine. Parturition is one of the only clear risk factors for MS relapses, so careful studies of immunological changes in pregnant and postpartum women with MS are likely to shed light on the pathophysiology of MS relapses and could potentially lead to new drug targets.

6. Summary

Over the last thirty years enough evidence has been gathered to be able to reassure women with MS who desire a family that

pregnancy and breastfeeding are not harmful. However, significant gaps in knowledge remain, particularly about modifiable risk factors of postpartum relapses that limit our ability to counsel women and develop strategies to decrease the risk of postpartum relapses. The most pressing issue that needs to be resolved is the trade-off between resuming MS treatments in lieu of breastfeeding. This issue should be approached both through epidemiological studies of postpartum relapses and studies aimed at establishing the safety of MS treatments during lactation and/or pregnancy.

Even more significant gaps in knowledge exist in our understanding of the long and short-term biological effects of pregnancy and breastfeeding on MS disease course. Advances in metabolic diseases raise the intriguing possibility that pregnancy, particularly followed by prolonged breastfeeding, may have lasting immunomodulatory and/or neuroprotective benefits. Careful immunological studies of pregnant and postpartum women with MS also present a biologically rich opportunity to improve our understanding of MS relapse pathophysiology. Improving our understanding of the transient and potentially lasting immunomodulatory and/or neuroprotective effects of pregnancy and breastfeeding is likely to shed light on MS pathophysiology in general and aids in optimizing treatment strategies.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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