Sex and gender issues in multiple sclerosis

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Abstract: Multiple sclerosis (MS) is universally found to be more prevalent in women than men. This has led to extensive studies of differences in the immune system or nervous system between women and men, which might be caused by the effects of gonadal hormones, genetic differences, and different environmental exposures and modern lifestyle in men and women. We review the effects of sex and gender from a genetic, immunological and clinical point of view. We discuss the effects of sex on the clinical expression of MS and responses to therapy, as well as issues concerning pregnancy.

Keywords: Multiple sclerosis, sex, female, pregnancy, genes, immunology

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Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) that is prevalent in the northern hemisphere (0.5–1.5 per 100,000) [Simpson *et al.* 2011]. The disease usually causes relapsing–remitting attacks of inflammation, demyelination and axonal damage, leading to various degrees and spectra of neurological symptoms and disability. An increased gradient of MS is observed in northern compared with southern regions of the northern hemisphere, postulated to be due to genetic, environmental, cultural and behavioural differences. MS is now universally found to be more prevalent in women than men [Ahlgren *et al.* 2011; Compston and Coles, 2002], a phenomenon shared with several other autoimmune diseases. This has led to extensive studies of differences in the immune system or nervous system between women and men, which might be caused by the effects of gonadal hormones, genetic differences, as well as different environmental exposures and modern lifestyle in men and women [Greer and McCombe, 2011]. The effects of sex on the clinical expression of MS and response to therapy will have implications for follow up and treatment of patients with MS. Thus, the effects of sex in MS need to be taken into consideration [Jobin *et al.* 2010].

The MS prevalence ratio of women to men has increased markedly during the last decades (2.3–3.5:1), which indicates a true increase in MS among women but not men [Ahlgren *et al.* 2011; Compston and Coles, 2002; Orton *et al.* 2010; Wallin *et al.* 2012]. This rapid increase probably reflects unidentified changes in the environment or nutrition. Interestingly, the predominance in women varies with latitude [Kampman *et al.* 2013; Trojano *et al.* 2012]. The effect of sex on clinical features of MS is not as clear as the effect on MS prevalence; however, there is evidence that women generally have an earlier onset of disease, they have a slightly lower prevalence of primary progressive disease course and show in general less progression of disability than men [Bergamaschi, 2007].

Genes and environment affect susceptibility of women and men to multiple sclerosis

The cause of MS is not known but all evidence points to an interaction between environmental and genetic factors in the development of the disease. There is an increasing body of evidence showing that some specific environmental factors are implicated in the development of MS. Epstein–Barr virus (EBV), low levels of vitamin D and smoking are best documented as associated with a modest increased risk of MS [Ascherio and Munger, 2010; Tselis, 2011]. MS susceptibility is also reported to be associated with month of birth, indicating that seasonal environmental agents like maternal ultraviolet exposure or viral infections during the foetal period may impact the risk of MS development later in life [Saastamoinen *et al.* 2011; Staples *et al.* 2010]. A relative increase in smoking in women has been proposed to partly explain the increasing MS incidence seen in women [Celius and Smestad, 2009; Koch-Henriksen and Sorensen, 2010a]. Women and men might also have different responses to other environmental factors, like sun exposure and vitamin D supplements [Kragt *et al.*

2009]. Recently, increased dietary salt intake is also postulated to be an environmental risk factor for the development of autoimmune diseases through the induction of pathogenic T-helper 17 cells [Kleinewietfeld *et al.* 2013]. However, there is no direct evidence that differences in the gene–environment interplay explain the difference in MS prevalence between women and men, but possible mechanisms of such effects will be discussed later in this review.

A genetic contribution to the susceptibility of development of MS is well documented [reviewed in Gourraud *et al.* 2012]. First, this was observed in family studies, showing a family recurrence rate of MS of approximately 15% [Compston and Coles, 2002], as well as an increased risk of MS in first-degree relatives [Ebers *et al.* 1995; Nielsen *et al.* 2005], decreasing with genetic distance [Robertson *et al.* 1996]. Twin studies show higher concordance rates for monozygotic (24–25%) than dizygotic twins (3–5%) [Hansen *et al.* 2005; Willer *et al.* 2003]. Studies of adopted children who develop MS illustrate genetic and not environmental causes for aggregation of MS in families [Dyment *et al.* 2006; Ebers *et al.* 1995]. Thus, genetic explanations for the differences observed between women and men with MS have been searched for in series of genetic studies; however, they have been difficult to identify.

The major histocompatibility (MHC) region, discovered to be associated with MS in the 1970s, confers the most important and best documented risk factor for MS, suggested to account for 20–60% of genetic susceptibility [Oksenberg *et al.* 2008]. Jersild and colleagues showed an association to human leukocyte antigen (HLA)-A serotypes [Jersild *et al.* 1972], later defined to be due to linkage disequilibrium with the DR2 haplotype, which contains the tightly linked HLA-DRB1*1501 and HLA-DQB1*0602 alleles [Olerup and Hillert, 1991; Olsson *et al.* 1976]. Allelic heterogeneity of the HLA-DRB1 locus is clearly shown [Sawcer *et al.* 2011], and additional independent risk loci within the HLA class I region have also been confirmed [Harbo *et al.* 2004; Link *et al.* 2012; Sawcer *et al.* 2011]. However, no clear differences between women and men concerning the HLA association in MS have been identified.

When genome-wide association studies (GWAS) were made technically and economically feasible, evidence for MS association was for the first time shown for non-MHC loci, that is, single nucleotide polymorphisms (SNPs) in the *IL7Ra* and *ILR2a* genes [International Multiple Sclerosis Genetics Consortium, 2007]. In 2011 the International MS Genetics Consortium (IMSGC) published in collaboration with Wellcome Trust Case Control Consortium 2 (WTCCC2) a very large MS GWAS, including approximately 10,000 MS cases and 20,000 healthy controls, collected by multinational research groups [Sawcer *et al.* 2011]. This study increased the list of MS-associated loci to 52 and identified lists of additional others as interesting candidate genes. As predicted, all the non-HLA MS risk variants show modest odds ratios (<1.3). The new list of MS loci also consisted of genetic variants mainly located in or near genes involved in immunological pathways, in particular pathways of importance to T-cell differentiation. Since then, additional MS studies have expanded this list [Patsopoulos *et al.* 2011], and large international collaborative studies are still ongoing [reviewed in Harbo *et al.* 2011]. None of these studies of non-HLA genes have convincingly shown genetic differences between women and men concerning MS susceptibility.

Genetic association to multiple sclerosis subphenotypes

Genetic differences in clinical subgroup of patients with MS, including sex, have been sought for many years. However, many of these studies are hampered by the modest sample sizes that are created when cohorts are divided into subgroups and by incomplete registration of clinical variables across research databases. Most convincingly, an association between the HLA-DRB1*1501 allele and early age at onset of MS have been shown in recently published large MS GWAS [Sawcer *et al.* 2011], showing that each copy of the minor allele decreased the age at onset by 10.6 months. No other locus showed genome wide significance with age at onset in this well powered screen. No robust evidence was found for genetic association with sex, clinical course (including MS subtype), disease severity or month of birth for HLA or non-HLA markers. However, this study did not include data on more detailed clinical phenotypes and was also hampered by challenges caused by differences between the multinational cohorts, concerning clinical assessment and genetic differences between populations.

The association of HLA-DRB1*1501 with age at onset confirmed in the IMSGC GWAS [Sawcer

et al. 2011] has also been reported in other, smaller studies, some of which also indicated that this effect was most pronounced in women [Celius *et al.* 2000; Masterman *et al.* 2000]. Furthermore, there are reports showing an excess maternal-side transmission of MS when the transmission is through an unaffected parent [Herrera *et al.* 2008]. Some studies report increased disability progression in HLA-DRB1*1501-positive patients with MS, but others point to HLA-DRB1*01 and HLA-DRB1*04 alleles [Romero-Pinel *et al.* 2011]. Both carriage of HLA-DRB1*15 and the presence of oligoclonal bands in the cerebrospinal fluid have been reported to hasten disease progression [Imrell *et al.* 2009]. HLA-DRB1*1501 has been shown to increase disease severity in MS by facilitating the development of more T2 foci evaluated by brain magnetic resonance imaging (MRI) examination, as well as a decline in brain volume and an impact on cognitive performance [Okuda *et al.* 2009]. HLA B*44 may moderate disease course, preserving brain volume and reducing the burden of T2 hyperintense lesions in subjects with MS [Healy *et al.* 2010]. Variation in drug responses between patients with MS might also be due to genetic differences between individuals [Comabella and Vandenbroeck, 2011]. For instance, glatiramer acetate (GA) has been reported to show better treatment response in HLA-DRB1*15:01 homozygote patients [Gross *et al.* 2011], which may be based on HLA binding properties of this highly variable polypeptide. One may speculate that genetic differences between men and women may affect treatment responses, which remains to be further studied.

In conclusion, using improved technologies we are starting to characterize subphenotypes of MS that show different genetic profiles. So far, none of these subphenotypes have shown significant, replicated genetic differences between women and men. But our methods are constantly improving, with the potential to identify factors of importance to the clinical handling of patients with MS.

Genetic mechanisms for sex differences in multiple sclerosis

What are the mechanisms for how sex causes differences in MS characteristics? Novel techniques and strategies search for answers to these questions, and some novel and promising approaches will be mentioned briefly.

Some of the dimorphism seen might be driven by differences in gene expression of autosomal genes [Kantarci *et al.* 2004a, 2004b]. Epigenetic modification of DNA may be caused by external factors, including hormonal or environmental stimuli that differ between men and women. For instance, men and women might have different responses to environmental factors like sun exposure and vitamin D supplements. In line with this, it has been reported that higher levels of vitamin D may decrease the incidence of MS, mainly in women due to biological differences [Kragt *et al.* 2009], but studies dissecting these issues are warranted.

It has also been postulated that the X chromosome may have a direct role in autoimmunity [Selmi, 2008]. In the animal model of MS experimental autoimmune encephalomyelitis (EAE) it has been shown that the presence of two X chromosomes increases susceptibility to EAE independent of hormones [Smith-Bouvier *et al.* 2008]. Furthermore, X chromosome inactivation in women (the random inactivation of one X chromosome in each cell in embryogenesis) may be skewed, resulting in an overrepresentation of MS susceptibility genes in women. This has not been definitively shown in MS studies, although a possible difference in degree of skewing between patients with a progressive *versus* a relapsing course has been indicated [Knudsen *et al.* 2007]. To date, no MS susceptibility regions are confirmed to be located on the X chromosome. However, candidate genes on the X chromosome, including *TLR7, CD40L* and *FoxP3*, show expression differences that may be due to X dosage effect (escape from X inactivation) or imprinting [Gutierrez-Roelens and Lauwerys, 2008; Sellebjerg *et al.* 2012]. Such effects will not be picked up in association studies studying SNPs as in GWAS. Similarly, there are currently no indications of the impact of Y chromosome genes in MS, although *Hya, Yaa* and *Sry* genes seems to confer relative resistance in young EAE mice [Spach *et al.* 2009].

Imprinting of MS risk or protective genes may have important implications for the parental transmission of MS. In humans some genes are expressed only from the paternal or maternal allele due to methylation and histone modifications. Several hundred imprinted genes in the adult brain have a sex-specific parental allelic bias, and brain expression of imprinted genes is shown to be regulated depending on localization

and time [Gregg *et al.* 2010]. Another explanation for maternal transmission of disease is mitochondrial inheritance which is only possible through the ovum, and some report an association with specific mitochondrial DNA haplotypes and mutations in MS [Ban *et al.* 2008].

In conclusion, the available evidence suggests that clinical phenotype, including sex and disease progression, correlates only modestly with the strongest genetic risk factor in MS, that is, HLA alleles. However, a well powered genetic study of fully characterized MS subphenotypes in MS has not been undertaken, thus many questions remain to be answered.

Effect of sex hormones on multiple sclerosis

Epidemiological data clearly underline the increased susceptibility for women to develop MS compared with men. This may speak for the role of hormones, which is further supported by observations of changes in disease symptomatology with alterations in sex hormone levels during pregnancy. Especially in pregnancy, high levels of progesterone, oestradiol and oestriol are measured. Whereas progesterone and estradiol also occur during various stages of the female menstrual cycle, oestriol is undetectable except during pregnancy [Voskuhl and Palaszynski, 2001a].

On first glance the role of sex hormones in MS seems to be restricted to women. Yet the situation is much more complex. As detailed below, the high hormone levels during pregnancy clearly ameliorate the disease course of MS. Also in the animal model EAE we observe a milder disease course under the influence of estrogens (see below).

The therapeutic potential of estrogens in MS may rely on immunomodulatory and neuroprotective pathways [Gold and Voskuhl, 2009]. Of course, one should consider complex levels of safety of oestrogen treatment in both sexes. In several gynaecological studies, oestriol has been accepted as the safest hormone in women of climacteric age. Dosage may lead to unwanted side effects in men, such as gynaecomestia.

A first pilot trial of 8 mg oral oestriol per day has already been performed in women, with a sophisticated crossover design. Great care was put on assessing baseline inflammation by regular pretrial MRIs. There were several beneficial immunological changes which correlated well with gadolinium-enhanced lesions in MRI [Soldan *et al.* 2003]. There are now two phase II trials ongoing which may shed further light on this important aspect.

Sex differences in the immune system and response to immunotherapy

Interestingly, the observations that women have increased susceptibility for autoimmunity in the nervous system have also been made in the experimental model of EAE, which is induced by immunization with myelin proteins and complete Freund's adjuvant [Gold *et al.* 2006]. Also, the improvement of MS symptoms during pregnancy is reflected in EAE, when SJL mice are used as a susceptible strain. When female and male mice are housed under identical conditions, several groups showed that female mice are much more susceptible [Cua *et al.* 1995]. This even goes into the next level: in the early 1980s, Ben-Nun and colleagues showed that, in principle, sensitized T cells can be isolated from immunized rodents and then be transferred into littermates, a variant called adoptive-transfer EAE (AT-EAE) [Ben-Nun *et al.* 1981]. When Voskuhl and colleagues isolated T lymphocytes from draining lymph nodes of immunized female or male mice, their adoptive transfer caused many more cases and stronger EAE when cells came from female donors [Voskuhl *et al.* 1996]. Thus the immunological processes leading to T-cell priming and induction of the immune response must be much stronger in female mice. Similarly, when the lymph node cells came from just one sex and were injected into female *versus* male recipients, again female mice were much more susceptible to developing AT-EAE. Thus in a similar manner the immunological events occurring during the effector phase [Kawakami *et al.* 2004] must be facilitated in female mice as well. When female mice were exposed to estradiol at supraphysiological dosage, clearly a dosage above naturally occurring hormonal levels during menstrual cycles was needed to maintain the therapeutic effect [Voskuhl and Palaszynski, 2001b].

Theoretically one may postulate that male sex hormones may be protective in autoimmunity. As a first step, orchiectomy can be performed and both active EAE and AT-EAE were much more severe in the castrated mice compared with sham-operated littermates [Bebo *et al.* 1998]. In turn, when testosterone precursors were injected into female mice, no clear effect could be achieved at physiological levels. However, testosterone

replacement treatment of EAE has shown testosterone to be protective [Palaszynski, 2004].

Recently, the role of vitamin D in the pathogenesis of MS has been examined at several levels in relation to sex hormones. Interestingly stored serum samples from patients, who developed MS later on, already exhibited lower levels of vitamin D [Decard *et al.* 2012]. When the role of vitamin D was investigated in EAE, only female mice had a milder disease course upon feeding with a vitamin D enriched diet [Spach and Hayes, 2005]. Yet this protection was abrogated when ovarectomy was performed. This complex interplay was addressed by Correlale and Villa, who transferred these findings to human T cells [Correale and Villa, 2010]. They showed that similar to EAE, vitamin D acts much more strongly on female lymphocytes, and the effect was mediated at the level of vitamin D transporters and vitamin D inactivating enzymes. In turn, higher secretion of interleukin 10 and increased ratio of Foxp3 regulatory T cells were observed. Of note, similar changes could be induced in cell culture of male cells via exposure to 17-ß estradiol. In conclusion, all these studies support the protective role of oestrogen hormones in conjunction with vitamin D, especially on disease course and T-lymphocyte reactivity.

In addition to the above discussed immunological effects of sex hormones, there is increasing evidence that estrogens may impact neuroprotection. Gray matter atrophy is an important correlate to clinical disability in MS and can also be examined in the EAE model. The Voskuhl group treated mice with EAE with either oestrogen receptor (ER)-α ligand or ER-β ligand [MacKenzie-Graham *et al.* 2012]. Importantly MRI and histopathology showed preservation of cerebellar gray matter and Purkinje cells upon treatment with ER-α ligand only. This may open new avenues of research in the future.

The findings reported here may be of special note in view of the increasing incidence of MS in women. Yet we should be aware that the role of hormones may also reflect a double-edged sword, since they seem to increase the susceptibility of women to MS [Branch, 1992; Koch-Henriksen and Sorensen, 2010b]

Pregnancy and multiple sclerosis

For decades, pregnancy was thought to have a negative impact on the evolution of MS and pregnancy was not recommended. However, we now have evidence that there is a decrease in relapse rate during pregnancy, especially during the third trimester (70% decrease compared with the year before pregnancy). A rebound effect can occur after delivery, with increased relapses [Confavreux *et al.* 1998]. A systematic review of 22 papers confirms the reduction of relapses during pregnancy and the increase in relapses in the postpartum period [Finkelsztejn *et al.* 2011]. No increase in disability during pregnancy and 2 years post partum, beyond that expected by natural history studies, has been seen [D'Hooghe *et al.* 2010; Vukusic *et al.* 2004].

Pregnancy tends to suppress the immune system of the mother to prevent rejection of the foetus, which has paternal foreign antigens [Tafuri *et al.* 1995]. Therefore, pregnancy is considered to be an immunomodulatory state [Voskuhl and Gold, 2012]. Pregnancy involves hormonal changes in the levels of oestriol, progesterone, prolactin, α fetoprotein, early pregnancy factor (EPF) and leptin. Low levels of oestrogens and prolactin are associated with a T helper 1 (Th1) deviation responsible for a proinflammatory profile. By contrast, high levels of oestrogens, as seen during pregnancy, are associated with a Th2 deviation. Progesterone promotes Th2 deviation *in vitro* and reduces the severity of EAE [Garay *et al.* 2007]. EPF has also been beneficial in EAE [Zhang *et al.* 2003]. There is an increase in the level of regulatory T-cell (Treg) and Th2 populations and a decrease in Th1 and Th17 T cells [Saito *et al.* 2010]. The increase in Tregs is probably mediated through the effects of estradiol on the immune system [Tai *et al.* 2008].

During pregnancy, microchimerism occurs from the drive of haematopoietic stem cells from the foetus to the maternal circulation or from the maternal to the foetal circulation. Microchimerism has been considered to contribute to autoimmunity. Association between microchimerism and MS was found in a Canadian study of twins who were discordant for MS [McCombe and Greer, 2012; Willer *et al.* 2002]. However, if foetal microchimerism had to be implicated in the development of MS, multiparous women should have a greater risk of MS, which does not seems to occur.

A different question is whether pregnancy can influence whether a person develops MS. The AusImmune study recently showed that, among women, higher parity was associated with a

Table 1. Overview of outcomes of pregnancies with accidental exposure to immunomodulatory drugs. (Adapted from Lu *et al.* [2012].)

	Interferon β	Glatiramer acetate	Natalizumab
Shorter birth length, mean	Yes	Unknown	No
Lower birth weight, mean	Yes	No	No
Birth weight <2500 g	No	Unknown	Unknown
Preterm birth <37 weeks	Yes	No	Unknown
Lower gestational age, mean	No	Unknown	No
Spontaneous abortion	No	No	Unknown
Caesarean delivery	No	Unknown	Unknown
Congenital anomaly	No	No	Unknown

reduced risk of first attack [Ponsonby *et al.* 2012]. In another study, women and men with reproductive history had a lower risk of MS than childless people [Nielsen *et al.* 2011]. Of course, one cannot exclude a selection bias, in that mildly affected patients are more positive towards having children than those with early disability.

The clinical predictors of a postpartum relapse are the number of relapses in the previous year, the number of relapses during pregnancy and disability at pregnancy onset [McCombe and Greer, 2012; Vukusic *et al.* 2004]. One study correlated the postpartum relapses with an increased level of interleukin 8 in the first trimester [Neuteboom *et al.* 2009]. Pregnancy should be planned according to the patient's desire and disease quiescence.

Accidental exposure to multiple sclerosis treatments during pregnancy

Even though contraception needs to be recommended for fertile women with MS during treatment with immunomodulatory drugs, accidental exposure to treatments may happen (for an overview, see Table 1) [Lu *et al.* 2012].

Some early reports suggested that interferon β (IFNβ) exposure (mean exposure time 9 weeks, range 2–38 weeks) was associated with a higher risk of foetal loss (39% in exposed women *versus* 5% in nonexposed women) and to a lower infant weight (3.189 kg *versus* 3.783 kg) [Boskovic *et al.* 2005]. However, the majority of reports on accidental IFNβ treatment exposure during the first weeks of pregnancies (most pregnancies were exposed for less than 45 days) do not show an increase in the number of abortions or neonatal complications [Sandberg-Wollheim *et al.* 2005, 2011]. Due to the relative safety of exposure times of up to 4 weeks, neurologists may decide to continue IFNβ in patients with high disease activity, advising discontinuation as soon as the pregnancy test is positive [Amato *et al.* 2010].

For GA or natalizumab exposure, fewer studies with limited sample sizes are available. In a systematic review, GA was not associated with lower mean birth weight, congenital anomaly, preterm birth or spontaneous abortion [Fragoso *et al.* 2013]. Small studies have reported GA exposure up to the third trimester of pregnancies. No congenital abnormalities related to GA were reported [Lu *et al.* 2012] One study on paternal use of IFNβ or GA during conception found no effect on gestational age or birth weight [Hellwig *et al.* 2010].

A prospective study of 35 pregnancies exposed to one single natalizumab infusion showed 29 normal births and one hexadactly [Hellwig *et al.* 2011a]. Although natalizumab exposure did not appear to be associated with lower mean birth weight, shorter mean birth length or lower mean gestational length, further studies should seek to confirm these findings. Based on animal studies and human case reports, exposure to mitoxantrone is associated with potential harm. A patient with secondary progressive MS who was exposed periconceptionaly to mitoxantrone and delivered a child with Pierre Robin Sequence (glossoptosis, micrognatia and palate clefts) has been reported [Hellwig *et al.* 2011b].

Few data on accidental exposures to fingolimod and teriflunomide have been reported to date, but because of the potential risk of foetal toxicity based on animal studies, use of effective contraception is mandatory. Outcomes of exposed pregnancies are being collected in multinational

registries. Pregnancies exposed to fingolimod (140 as of February 2012) disclosed 34 normal births, 31 abortions, 14 spontaneous abortions and 3 cases of congenital anomalies. The rate of congenital anomalies reported from women in clinical trials was 3.7%, similar to the background rate in the general population (3%). Regarding teriflunomide, a total of 43 outcomes in exposed pregnancies were reported in female patients participating in teriflunomide clinical studies. No structural or functional deficits were reported in newborns with prenatal teriflunomide exposure. Upon learning of the pregnancy, teriflunomide has to be rapidly eliminated by cholestyramine or activated charcoal [Kieseier *et al.* 2012].

Pregnancy in multiple sclerosis with assisted reproduction techniques

Treatments used during assisted reproductive techniques (ARTs) may influence the evolution of MS by modifying the hormonal status of the patient. The use of hormone therapy to induce pregnancy can include gonadotrophin-releasing hormone (GnRH) agonist and GnRH antagonist. Increases in relapse rate have been reported after pregnancies with ART using GnRH agonist and GnRH antagonist [Michel *et al.* 2012]. In a recent paper, 13 French university hospitals retrospectively studied the association between ARTs and the occurrence of MS relapses. A significant increase in the annualized relapse rate was observed during the 3 months following ART compared with the same period just before ART and to a control period 1 year after ART. The increase in relapses was associated with the use of GnRH agonists and with *in vitro* fertilization failure [Michel *et al.* 2012]. In another recent study, 16 patients with MS subjected to 26 ART treatment cycles with GnRH agonists and recombinant follicle-stimulating hormone were evaluated clinically, immunologically and by MRI. ART was associated with a sevenfold increase in risk of MS exacerbation, and a ninefold increase in risk of enhanced disease activity on MRI. ART treatment was associated with a three- to eightfold increase in oestrogen and progesterone levels, however these levels were significantly lower than those observed during normal pregnancy. Sexual hormones are most likely to exert Th2 influence only at high concentrations physiologically associated with pregnancy. Lower concentrations, such as those seen in ART, may promote a proinflammatory environment. ARTs also augmented immune cell migration across the blood–brain barrier [Correale *et al.* 2012]. A controlled study confirming these results is needed.

Pregnancy and neuromyelitis optica

Neuromyelitis optica (NMO) has been considered an antibody-mediated disease in which the astrocyte is the primary target. Typically, antibody-mediated diseases such as systemic lupus erythematous worsen during pregnancy. A small number of studies suggested that pregnancy can increase the relapse rate in patients with NMO [Bourre *et al.* 2012]. Recently, 20 women with NMO accounting for 25 pregnancies were identified. A tendency for an increased relapse rate during the year postpartum (mainly for the second trimester) was seen [Bourre *et al.* 2012]. Epidural analgesia and breastfeeding had no influence on the course of NMO. The Expanded Disability Status Scale score increased from 1.5 (±1.7) before pregnancy to 2.6 (±1.9) in the year after pregnancy. Fifty-four pregnancies have been studied in 40 patients with NMO spectrum disorder (NMOSD) [Kim *et al.* 2012]. The relapse rate before and during pregnancy was similar, however 77% of deliveries were associated with a relapse. Numerous cases of NMOSD onset after pregnancy suggest that delivery adversely affects the course of NMOSD [Kim *et al.* 2012]. Prospective studies are needed.

Planning of birth and postpartum period in multiple sclerosis

Pregnancy or delivery complications are not increased among women with MS [van der Kop *et al.* 2011]. Epidural analgesia is not associated with an increased risk of relapse. Obstetric outcomes were similar to the general population in patients with MS [van der Kop *et al.* 2011]. However, a recent prospective nationwide study performed in Finland showed a higher incidence of instrumental delivery in patients with MS than in women without the disease [Jalkanen *et al.* 2010]. Disability may be associated with a higher risk of instrumental carriage [van der Kop *et al.* 2011]. Malformations and infant death are not increased in women with MS. Although low birth weight was reported in women with clinical evidence of MS, the majority of studies do not confirm this finding [Dahl *et al.* 2005, 2008].

During the postpartum period there is a decrease in pregnancy hormones. During breastfeeding,

there is an increase in prolactin, oxytocin, progesterone and glucocorticoids. Controversies exist regarding the role of lactation. Studies have shown a protective effect in relapse rate, no effect on relapse rate or even an increase in relapse rate [Langer-Gould *et al.* 2009, 2011]. Exclusive breastfeeding was associated with a lower relapse rate compared with no breastfeeding or partial breastfeeding [Langer-Gould *et al.* 2009]. However, mothers with active disease prior to pregnancy are less likely to undertake breastfeeding. A recent meta-analysis compared a total of 869 patients with MS who breastfed *versus* 689 patients with MS who did not. The authors found that women with MS who breastfeed are almost half as likely to experience a postpartum relapse compared with women who do not. While this suggests that breastfeeding has a protective effect on MS clinical activity, there is a strong possibility for confounding factors as women who breastfed were significantly less likely to use disease-modifying drugs before pregnancy, suggesting that the choice to breastfeed may be associated with more benign prepregnancy disease activity, and thus women with more severe MS may be less likely to breastfeed because of disability or in order to restart medication. Importantly, the study highlights the need for a large prospective study to assess the influence of breastfeeding on postpartum relapses in patients with MS to reach a robust conclusion as to whether breastfeeding truly influences disease outcome for patients [Pakpoor *et al.* 2012].

Conclusion

Autoimmune diseases (cell or antibody mediated), including MS, occur more frequently in women. Emerging technologies might provide novel methods with the potential to further dissect the genetic and immunological mechanisms causing the observed differences between women and men with MS. Such studies will require large collaborative efforts, including careful characterization of standardized, detailed clinical characteristics across clinics and nations. As the knowledge grows, molecular methodologies may be implemented in clinical practice and influence the choice of better and individualized follow up and therapies in men and women with MS.

Pregnancy tends to suppress the immune system of the mother to prevent the rejection of the foetus, and treatments used during ARTs may also influence the evolution of MS by modifying the hormonal status of the patient. Discontinuation of disease-modifying treatments before conception is generally recommended. The use of treatments around conception should be considered on an individual basis taking into account the risks associated with drug exposure and the risks of relapses.

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