Published in final edited form as:

Nat Rev Neurol. ; 8(5): 255–263. doi:10.1038/nrneurol.2012.43.

Sex-related Factors in Multiple Sclerosis: Genetic, Hormonal and Environmental Contributions

Rhonda R. Voskuhl, M.D.¹ and Stefan M. Gold, Ph.D.²

¹Department of Neurology, Multiple Sclerosis Program, David Geffen School of Medicine, University of California Los Angeles (UCLA), Los Angeles, CA, USA

²Center for Molecular Neurobiology and Department of Neurology, University Hospital Hamburg-Eppendorf, Hamburg, Germany

Abstract

The pathogenesis of multiple sclerosis (MS) involves complex interactions between genetic susceptibility and environmental triggers. Clinical observations suggest that the study of sex differences may provide important insight into mechanisms of MS pathogenesis and progression. One clinical observation is that MS occurs more frequently in women than in men, indicating an impact of sex-related factors on susceptibility to MS. These factors include hormonal, genetic, and environmental influences, as well as gene x environment interactions and epigenetic mechanisms. Despite a higher incidence and more robust immune responses, females do not have a poorer prognosis, suggesting a biological mechanism of resilience. A second clinical observation is the pregnancy strongly affects disease activity, leading to a reduction in relapse rates in the last trimester but an increase post partum. However, pregnancy has little effects on long-term disability. Unraveling mechanisms underlying these clinical observations at the laboratory bench, with subsequent translation back to the bedside is a unique and potentially fruitful strategy in MS. In this paper, we review the current knowledge in the field and discuss novel therapeutic approaches currently in development that were derived from the study of sex-related factors.

INTRODUCTION

Epidemiological studies spanning decades have shown that females are more likely than males to be affected with multiple sclerosis¹. Another well-established clinical phenomenon

Correspondence: Rhonda Voskuhl, M.D., Professor, UCLA Department of Neurology, Jack H. Skirball Chair for Multiple Sclerosis Research, Director, UCLA Multiple Sclerosis Program, Neuroscience Research Building 1, Room 475D, 635 Charles Young Drive South, Los Angeles, CA 90095, USA, rvoskuhl@ucla.edu, Voice: (310)206-4636, Fax: (310)206-9801.

CONFLICTS

The University of Los Angeles, California (UCLA) holds a use patent for estradiol treatment of multiple sclerosis for which Dr. Voskuhl is an inventor. Dr. Voskuhl provides consulting advice about MS treatments to Adeona Pharmaceuticals with compensation capped at a maximum of \$10,000 per year.

SEARCH STRATEGY

The search strategy involved searching Pub Med with terms “gender or sex”, “multiple sclerosis”, “male”, “female”, “estrogen or testosterone”, “hormones”, “pregnancy”, “sex chromosome”, “environment”, “MRI”, and “immune.” Dates were 1975 to December 2010 published in English. Articles were also identified through searches of the references of articles and authors’ own files. Information on ongoing trials was obtained from www.clinicaltrials.gov. The final set of references was selected based on consideration of a combination of factors including originality and relevance to the topic, journal impact, date of publication with bias toward more recent, recognition of the paper within the field, and critical reading of the paper by the authors.

in MS is a disease modifying effect of pregnancy, where relapse risk is decreased during the third trimester but increased during the post partum period². Together, these two clinical observations indicate that the study of sex-related variables may yield significant insight to better understanding pathological factors involved in MS. Herein, we will review clinical and preclinical data examining the effect of sex-related factors on MS susceptibility as well as on the activity and progression in established disease.

GENDER DIFFERENCES IN MS

Clinical evidence

A female preponderance in MS susceptibility—There is a distinct female preponderance of a variety of autoimmune diseases including MS and systemic lupus erythematosus³. The female to male ratio in MS currently varies by region around 2:1 to 3:1¹. Notably, over the last decades, the sex ratio in MS appears to be increasing (see below). The difference in average age at onset between male and female patients is small but there is evidence that in younger patients (onset before age 20) the gender ratio is greater (3.2:1) than in the MS population as a whole (2:1)⁴.

Unlike pregnancy, which is protective in MS and RA, but not in lupus, the higher incidence of disease in females as compared to males is present across a broad spectrum of autoimmune diseases including both those that are driven principally by cell mediated immune responses (MS, RA) as well as antibody mediated responses (systemic lupus erythematosus). Thus, the factors involved in the increased susceptibility of females to such a wide variety of autoimmune diseases are likely due to a ubiquitous pathway in immune responses.

Some aspects of gender differences in autoimmune diseases can be studied using animal models. For example, in the most widely used animal model of MS, experimental autoimmune encephalomyelitis (EAE), the SJL strain of mice has a female sex bias that parallels that of MS⁵. Similarly, a female preponderance is also seen in other autoimmune disease models including diabetes, thyroiditis, arthritis and lupus³. However, some strains (B10.PL and PL/J) have more susceptibility to EAE in males⁶, and there is no sex bias in the C57BL/6 strain⁷. Thus, there appears to be an interaction between sex specific factors and autosomal genetic background. This is in line with an autosomal gene linkage with MS risk in one gender but not the other⁸.

A role of gender in MS activity?—Within the major subtypes of relapsing remitting (RR) and secondary progressive (SP) MS, early predictors of future disability have included sex, age of onset, and degree of recovery from first episode^{9, 10}. Some early studies indicated higher levels of gadolinium enhancing lesions on brain MRIs in women^{11, 12}. However, larger studies controlling for age of onset and type of MS did not find a sex difference^{13–15}. Having said that, there are clear sex differences in immune responses. Responses in females to various immune challenges are stronger than in males¹⁶. This is also true when comparing autoantigen specific responses in women versus men with MS^{17–19}.

A role of gender in MS progression?—A large study of the natural history of MS, which included RR, SP and primary progressive (PP) types, indicated that the median time between disease onset to reaching a given disability level was shorter in men⁹. A subsequent review of placebo treated subjects in large clinical trials revealed that while there was no apparent gender effect on short term disability related to relapses in RR subjects, there did appear to be more long term disability progression in PP MS²⁰. Further, a recent large natural history study of untreated MS patients found that male gender was associated with a shorter time to, and a younger age for, conversion to SPMS²¹. Also, one study found that gray matter atrophy was greater in men than women with MS¹³. T1 holes on MRI may also be more frequent in male patients¹¹, although that has not been replicated¹³.

In summary, an enigma has arisen. If the incidence of disease is higher and peripheral immune responses are more robust in women, then why would one not see faster progression and more neurodegeneration in women? Progression and neurodegeneration are either faster in men or are, at best, no different between women and men. Consequently, the study of sex related factors in MS needs to take into consideration that these may play different, and possibly opposing, roles in the immune system versus the central nervous system (CNS).

Potential mechanisms of gender difference in MS

Hormones—There are no convincing data that low levels of cycling ovarian hormones in female mice are disease promoting in EAE. Some studies show no effect of ovariectomy²², while others show a slight worsening of clinical EAE in ovariectomized compared to sham operated^{23, 24}, thereby suggesting if anything a slight protective effect of low levels of female hormones. In contrast, there is good evidence showing that physiologic levels of testosterone in are protective since castration of young male mice clearly worsens EAE disease course (reviewed in ²⁵). Several immunomodulatory and possibly neuroprotective mechanisms of testosterone have been described (reviewed in ²⁵). Notably, gonadectomy to remove endogenous testosterone, only increased disease susceptibility in strains characterized by a female sex bias²⁶, thereby suggesting that a protective effect of physiologic testosterone may indeed be responsible, at least in part, for the female sex bias on a given genetic background.

Genetic factors—Sex differences in EAE and MS may also be influenced by a direct genetic effect. Novel mouse models that allow dissection of the effect of sex hormones and chromosomes have provided interesting clues. In these mice, the testis-determining gene *Sry* is “moved” from the Y chromosome to an autosome, thereby separating genetic and hormonal sex. In this model, the XX sex chromosome complement was associated with more severe disease compared to the XY[−] complement in EAE and lupus²⁷. Sex chromosomes were also shown to affect autoantigen specific immune responses^{27, 28}. Also, other studies have suggested that the Y chromosome contains polymorphic genes that may confer protection from EAE^{29, 30}. Taken together, sex chromosome effects on EAE may be due to 1) gene(s) unique to the Y chromosome, 2) a higher dose of X genes which escape X-inactivation, or 3) paternal imprinting of X genes.

Epigenetics, environmental factors and gene-environment interaction—

Transmission of MS risk shows a maternal parent-of-origin effect (e.g.³¹) that is related to MHC³². Parent-of-origin effects are generally considered to reflect genomic imprinting, an epigenetic mechanism of methylation and histone modification to achieve monoallelic gene expression. A parent of origin effect has been described in imprinting of both sex chromosome and autosomal genes³³ and provides evidence that environmental factors can influence imprinting in a sexually dimorphic manner³⁴. However, parent of origin effects may also be caused by a number of other mechanisms. Some animal studies have pointed to the possibility that environmental effects can act on endogenous sex hormone levels which in turn alter the hormone's interaction with MS susceptibility genes³⁵. It has also been demonstrated that within HLA-DRB1*15-positive patients, the female-to-male ratio is higher than in affected individuals with HLA-DRB1*15-negative genotypes, suggesting a role for MHC in the gender gap via gene-environment interaction and epigenetic mechanisms³⁶.

One intriguing observation is that the female to male ratio has increased in the past decades in most locations studied with a few notable exceptions (reviewed in¹). This increase in the female to male ratio is driven by increased incidence in women, not by decreased incidence in men. The reasons for the increased incidence in women remain speculative, however, it has been noted that the time span over which it is occurring should exclude a genetic cause³⁷. Instead, the underlying factors may be environmental or resulting from gene-environment interactions. In order to explain the change in sex ratio, environmental factors proposed would have to interact with factors that are sexually dimorphic or would have to be more commonly encountered in one sex than the other. Several possibilities have been suggested. While the change in sex ratio appears to predate use of oral contraceptives or changes in smoking behavior in women, other factors such as changes in lifestyle, roles in the workforce, dietary habits or alterations in menarche could contribute to the increasing incidence in females³⁷. It should be noted that to date there is little direct evidence for any of these factors. Experimental data suggest that the peroxisome proliferator-activated receptor (PPAR) α , which is involved in gender differences of lipid metabolism, also exerts gender-specific effects in EAE, indicating a potential interaction between sex related factors and diet in autoimmunity³⁸. Recently, it was found that increased parity of women was associated with decreased risk of first demyelinating event³⁹. The authors noted a correlation between the increased incidence of MS in women over the last decades with women waiting longer, and having fewer, children over this same time period. Thus, it is possible that the increasing incidence of MS in women that is driving the observed widening of the gender gap³⁷ is in part due to a loss or delay in the protection conferred by being multiparous³⁹.

Translating Female versus Male Differences in MS: Testosterone in EAE and MS

As mentioned above, removal of endogenous testosterone affects disease only in mouse strains with a sex difference in EAE. However, supplemental testosterone treatment of EAE was shown to be protective in gonadally intact males of a strain with (SJL) and without (C57BL/6) a gender bias²⁶. This suggests that mechanisms of protection from disease conferred by endogenous testosterone and mechanisms underlying exogenous testosterone

treatment may differ. Importantly, a therapeutic effect in EAE can also be seen when using dihydrotestosterone, indicating that androgens are not merely protective via conversion to estrogen²⁶.

A pilot clinical trial of testosterone was conducted in men with RRMS⁴⁰. While no effect was found on active lesions (possibly due to low inflammatory activity at baseline), there was a reduction in the annualized brain atrophy rate on MRI in the treatment period compared to pretreatment. One of several potential mechanisms through which testosterone may be protective is the induction of neurotrophic factors in PBMCs⁴¹. Larger placebo controlled trials of testosterone treatment in men with MS are warranted.

PREGNANCY AND MS

Clinical evidence

Pregnancy and MS relapses—The effects of pregnancy on disease activity of MS and other autoimmune diseases have been known for decades³. Studies in MS demonstrated a decrease of approximately 70% in relapse rates in the third trimester compared to pre-pregnancy levels^{2, 42–45}. These studies have also consistently shown an increase in relapse rate in the first 6 months post partum (see meta analysis⁴⁶). The relapse reduction during pregnancy is remarkable considering the 30–60% reduction in relapses induced by current MS treatments⁴⁷. The clear evidence for an effect of pregnancy on MS disease activity (see Table 1) is a seminal clinical observation to be understood and translated.

Pregnancy and disability—The effect of pregnancy on disability remains unknown. Short term follow up after pregnancy showed no effect on permanent disability^{2, 48}. Some long term follow up studies also showed no effect^{49, 50}. However, other long term studies addressing time to reach a given disability suggested a protective effect of pregnancy on disability with some, but not all, studies having groups matched initially for deficit, disease duration and age^{51–54}. Such observational studies are prone to selection bias since rigorous matching of groups at baseline is not possible. For example, women with more benign disease are potentially more likely to opt to have children. Taken together, currently available data do not provide convincing evidence that there is a significant beneficial effect of pregnancy on long term disability (see Table 1).

Pregnancy and MS incidence—MS onset is rare during the latter half of pregnancy but the risk of developing MS is elevated in the post partum period⁵⁵. Several epidemiological studies found no associations between number of pregnancies and subsequent MS risk^{50, 55–58}. However, one recent study³⁹ demonstrated an approximate 50% reduced risk of a first clinical presentation for a demyelinating event for each birth independent of other well-established risk factors (e.g. HLA, EBV). Importantly, first demyelinating event was the endpoint, not relapses in established MS, thereby removing a selection bias regarding differential likelihood to get pregnant. Moreover, this association was only seen in women with children, not in men with children, indicating that prenatal factors in the mother, not postnatal factors in the family environment, were underlying the parity effect³⁹. Further examination of the effect of parity on MS risk is now warranted (see Table 1).

Protective mechanisms during pregnancy

Pregnancy is not protective in a broad spectrum of autoimmune diseases. Rather, pregnancy is protective in autoimmune disorders principally driven by cell mediated immunity, such as MS, rheumatoid arthritis and psoriasis, but not in other autoimmune disorders such as systemic lupus erythematosus (SLE)⁵⁹. This would suggest that immune alterations during pregnancy are not generally immunosuppressive but rather shift immune responses in a way that is beneficial in cell mediated, but not antibody mediated, diseases. Important insights into the immunopathogenesis of MS relapses may thus be gained by a closer look at current concepts in reproductive immunology (see Box 1).

A shift in immune function?—A few studies in small samples have investigated immune changes during MS pregnancy. A genome-wide transcription analysis provided evidence for a decrease of several inflammation-related transcripts in peripheral blood mononuclear cells (PBMCs) during pregnancy with a corresponding increase post partum⁶⁰. A shift from Th1 to Th2 was shown at both the mRNA and protein level in peripheral blood from MS subjects followed longitudinally during pregnancy^{42, 61–63}. One study found a decline in interferon gamma (IFN γ) producing CD4+ T cells during pregnancy but no increase post partum⁶⁴. Serum interleukin 8 (IL8) has been shown to decrease during MS pregnancy⁶⁵. Two small studies in MS pregnancy showed an increase⁶⁶ or a decrease⁶⁷ in T regulatory cells and no change in Th17 T cells⁶⁷. The larger Finish study showed no effect of MS pregnancy on T regulatory cell percentage, but rather an increase in CD56^{bright} NK cells, during pregnancy with a decrease post partum⁴².

Taken together, there is evidence for shifts in some immune markers during MS pregnancy, however, no marker has been convincingly implicated in causality regarding effects on relapses. To better understand the effect of pregnancy on MS, it is necessary to move beyond cytokine shifts and enumerative changes in cell phenotype and include functional analyses (e.g. regulatory T cells or CD56^{bright} NK cells). Very little evidence is available regarding Th17 cells, and potential contributions by the innate immune system have also not been explored. Importantly, immunological correlates of post partum relapses are still missing. Given recent experimental evidence from an arthritis model⁶⁸, some of the immune shifts during pregnancy may be autoantigen specific, which should be taken into consideration in future studies.

Endocrine mechanisms—The strongest relapse protection is seen during the last trimester². Two estrogens (estradiol and estriol) and progesterone each increase progressively during pregnancy with a peak in the third trimester, then drop within days after birth, making their temporal profile consistent with protection from relapses. Both estriol and estradiol can ameliorate EAE. In contrast, treatment with progesterone had only small effects on EAE when used alone^{69, 70}. On the other hand, one study showed that progesterone treatment was deleterious in EAE in Lewis rats⁷¹. However, progesterone appeared to be additive with estrogen in offering protection when given in combination⁷². This complementary effect of estrogen and progesterone treatment may be due to potentially beneficial effects of progesterone on axonal protection, decreased demyelination or increased remyelination^{73, 74}.

Pregnancy is complex. A role for one hormone is not mutually exclusive of a role for another. For example, 1,25-hydroxyvitamin D is increased during pregnancy. In EAE, diets high in vitamin D reduced disease severity in female but not male mice⁷⁵. Consistent with this, the protective effect of 1,25-dihydroxyvitamin D on EAE has been shown to depend on the presence of estrogen⁷⁶. Intriguingly, one epidemiological study provided indirect evidence that vitamin D intake during pregnancy may not only affect the mother but could also lead to decreased risk for developing MS in the offspring⁷⁷. Cortisol, a potent immunomodulatory steroid, also increases to within high normal range during later pregnancy. Increased 11 β -hydroxysteroid dehydrogenase and higher glucocorticoid receptor (GR) α expression have been described in decidual cells during the second trimester of human pregnancy⁷⁸, which may increase cortisol bioavailability even before the increase in circulating cortisol levels occur in the third trimester. In addition, prolactin is increased during pregnancy and stays elevated during the post partum period in those who are breastfeeding. Interestingly, prolactin is involved in oligodendrocyte precursor proliferation⁷⁹. Pregnancy in mice increases the capacity to remyelinate noninflammatory white matter lesions, an effect that can be mimicked by prolactin⁷⁹. However, prolactin may also be detrimental since it is thought to be immunostimulatory and indeed blocking prolactin by bromocriptine ameliorated EAE⁸⁰. Some small studies in humans suggested that hyperprolactinemia may be associated with MS relapses^{81, 82}. Thus, a given pregnancy factor may have different, even opposing, effects in the immune system versus the CNS, and this needs to be considered when exploring therapeutic potential in MS.

Breast-feeding and MS relapses—Three large and one smaller study showed no effect of breast-feeding on post partum relapse rate in MS^{48, 83–85}. Rather, the best predictor of post partum relapse was pre-pregnancy relapse rate^{2, 48, 85}. One small study suggested that exclusive breastfeeding might be associated with decreased relapse rate as compared to no or partial breastfeeding⁸⁶. Another report using retrospective chart analyses confirmed this finding⁸⁷. However, classification bias, rather than causality, could underlie this finding since those who had a relapse while breastfeeding could have stopped breastfeeding to take disease modifying drugs to manage their MS worsening⁸⁶. Further, it has been shown that mothers with active disease prior to pregnancy were less likely to breast feed^{48, 84}, thereby raising the issue of selection bias. Thus, overall there has been not yet been convincing evidence that breastfeeding causes a significant reduction in MS relapses.

Microchimerism—Some authors have suggested that microchimerism, the exchange of hematopoietic stem cells between mother and fetus during pregnancy, may be involved in autoimmunity⁸⁸. However, the existing data on parity and MS incidence, which show either decreased, or no altered, risk for MS with increasing parity, do not support a major immunopathogenic role for microchimerism in MS. A link between microchimerism and MS should also lead to different risk in women who have children from several partners. However, no evidence for such an association has been found⁸⁹.

Translating Pregnancy Protection: Estrogen Treatment in EAE and MS

EAE in guinea pigs, rats, rabbits and mice improves during pregnancy^{22, 90, 91}, thereby mirroring the effects seen in MS. Studies in EAE to support the therapeutic potential of

estrogens via numerous anti-inflammatory effects in the peripheral immune system including cytokine shifts, downregulation of chemokines in the CNS, modulation of dendritic cell function, increased regulatory T cells, and decreased expression of matrix metalloproteinases (reviewed in ⁹²). Importantly, in EAE, estriol is protective at doses which are physiological with murine pregnancy levels^{23, 69}, while estradiol requires supraphysiological doses to achieve the same effects²³.

Estrogens are lipophilic, can cross the blood brain barrier, and thus have the potential to also directly affect CNS cell populations⁹³. Two main estrogen receptors (ERs), the nuclear receptors ER α and ER β ⁹⁴, are known, but there are also nongenomic membrane effects⁹⁵. The membrane G-protein coupled receptor GPR30 may mediate some therapeutic effects of pregnancy or estrogens in EAE^{96–98}.

The protective effect of estrogen treatment (estradiol and estriol) in EAE was shown to be dependent upon the presence of ER α , not ER β ^{99, 100}, and stimulation of ER α was sufficient for protection in EAE^{101, 102}. Importantly, expression of ER α in the peripheral immune system was dispensable for the therapeutic effect¹⁰³. Thus, increasing attention has been given to the CNS targets of estrogens. Within the CNS, ER α expression in astrocytes, but not in neurons, was required for therapeutic effects of a synthetic ER α ligand in EAE¹⁰⁴. ER β ligand treatment does not have potent effects on the peripheral immune system or on the level of CNS infiltration during EAE,¹⁰⁵ but can qualitatively affect the composition of the CNS infiltrate by reducing dendritic cells therein¹⁰⁶. ER β ligand treatment confers some clinical protection late during EAE and this is associated with reduced demyelination¹⁰⁵, preserved axon numbers^{107, 108} and increased functional remyelination¹⁰⁹. A recent molecular study suggested that ER β signaling in microglia can exert protective effects in CNS inflammation by repressing transcription of inflammatory genes without the binding of ER β to its target DNA sequence¹¹⁰. Of potential therapeutic interest, this mechanism is strongly activated by endogenous non-estrogenic steroids such as 5-androsten-3 β , 17 β -diol (ADIOL). Thus, the recent advances in our understanding of molecular mechanisms involving CNS estrogen receptor signaling in neuroinflammation could lead to more specific targeting of pathological processes, particularly those involving glial cells, using novel ER ligands.

Few studies have investigated the therapeutic or preventative effects of estrogen administration in MS. Four epidemiological studies of oral contraceptive (OC) use^{55–58} did not find evidence for an important role of OC in MS susceptibility. A small pilot study administered estriol at a dose to induce pregnancy levels in serum in nonpregnant female patients with MS¹¹¹. A favorable shift in cytokine profile, decreased release of matrix metalloproteinase-9 by peripheral mononuclear blood cells (PBMCs)^{112, 113} and a reduction in gadolinium enhancing lesions on MRI¹¹¹ was observed. Larger, placebo controlled, clinical trials of estrogens in MS are ongoing. These include a multicenter placebo controlled trial of estriol in combination with glatiramer acetate (ClinicalTrials.gov: NCT00451204) and a trial examining the potential of estradiol and progestin to prevent post partum relapses (NCT00127075)¹¹⁴.

CONCLUSIONS

Being female confers an increase in susceptibility to develop MS, however it does not cause a more aggressive course of disease in females (Table 1). There are lessons to be learned from how, despite a higher incidence and more robust immune responses, females do not have a poorer prognosis in established disease. If processes of biological resilience in females could be identified, for example in protective CNS mechanisms, this knowledge could be used to therapeutically target such mechanisms.

The observed increase in gender ratio suggests gender-specific associations of environmental or gene-environment interactions in MS susceptibility. It is conceivable that some of the underlying factors are of behavioral nature and a better understanding of these associations could potentially be relevant to preventing disease in some patients.

Pregnancy is a state that is clearly protective with regard to inter current relapses, while there is no conclusive evidence that pregnancy affects long term disability (Table 1). Effects on the immune system have been studied, but studies addressing pregnancy effects in the CNS that are not confounded by differences in the immune system are needed (Table 2). Insights into hormonal effects on the immune system versus the CNS are needed to more effectively target therapeutic strategies in an effort to mimic the protective aspects of pregnancy or prevent the detrimental effects of the post partum period.

It summary, the study of sex differences is important for both women and men with MS. Regarding the observation of greater susceptibility in women, the goal of this research is not merely to discern what is making women have increased risk, but also what makes most men have decreased risk. Further, if the cellular and molecular mechanisms mediating protection during late pregnancy were known, this would reveal highly significant targets for which new drugs could be developed for both women and men.

Acknowledgments

This work was supported by grants RO1 NS051591, R21 NS071210 and K24 NS062117 from the NIH (RRV), grants RG3915, RG4033, RG4363 (RRV) from the National Multiple Sclerosis Society (RRV), grant RG268381 from the European Union (SMG) and a grant from the Foundation for Research and Science in Hamburg (SMG). Funding was also provided by the Skirball Foundation, the Hilton Foundation and the Sherak Family Foundation.

Biographies

Rhonda R. Voskuhl, M.D. is a Professor in UCLA's Department of Neurology, Director of the UCLA MS Program, and holds the Jack H. Skirball Endowed Chair in Multiple Sclerosis. She is focused upon understanding the immunopathogenesis and neurodegenerative component of multiple sclerosis. She does basic science research and novel clinical trial design. She has studied the effect of sex hormones and sex chromosomes on both inflammation and neurodegeneration. This has led to novel treatment trials in MS. Overall, she aims to make basic discoveries at the bench and move them to novel therapies at the bedside in the form of clinical trials.

Stefan M. Gold, Ph.D. is a Marie Curie fellow and group leader at the Institute for Neuroimmunology and Clinical Multiple Sclerosis Research (inims), Center for Molecular Neurobiology and the Department of Neurology, University-Hospital Eppendorf, Hamburg, Germany. His research is focused on mechanisms of neuroendocrine immunoregulation in multiple sclerosis. The main interest of his research group is to elucidate the role of glucocorticoids and other steroid hormones in disease activity and neuropsychiatric aspects of MS.

References

1. Koch-Henriksen N, Sorensen PS. The changing demographic pattern of multiple sclerosis epidemiology. *Lancet Neurol.* 2010; 9:520–32. [PubMed: 20398859]
2. Confavreux C, Hutchinson M, Hours MM, Cortinovis-Tourniaire P, Moreau T. Rate of pregnancy-related relapse in multiple sclerosis. Pregnancy in Multiple Sclerosis Group [see comments]. *New England Journal of Medicine.* 1998; 339:285–91. [PubMed: 9682040]
3. Whitacre CC, Reingold SC, O'Looney PA. A gender gap in autoimmunity. *Science.* 1999; 283:1277–8. [PubMed: 10084932]
4. Duquette P, et al. The increased susceptibility of women to multiple sclerosis. *Canadian Journal of Neurological Sciences.* 1992; 19:466–71. [PubMed: 1423044]
5. Voskuhl RR, Pitchekian-Halabi H, MacKenzie-Graham A, McFarland HF, Raine CS. Gender differences in autoimmune demyelination in the mouse: implications for multiple sclerosis. *Annals of Neurology.* 1996; 39:724–33. [PubMed: 8651644]
6. Papenfuss TL, et al. Sex differences in experimental autoimmune encephalomyelitis in multiple murine strains. *J Neuroimmunol.* 2004; 150:59–69. [PubMed: 15081249]
7. Okuda Y, Okuda M, Bernard CC. Gender does not influence the susceptibility of C57BL/6 mice to develop chronic experimental autoimmune encephalomyelitis induced by myelin oligodendrocyte glycoprotein. *Immunol Lett.* 2002; 81:25–9. [PubMed: 11841842]
8. Kantarci OH, et al. IFNG polymorphisms are associated with gender differences in susceptibility to multiple sclerosis. *Genes Immun.* 2005
9. Confavreux C, Vukusic S, Adeleine P. Early clinical predictors and progression of irreversible disability in multiple sclerosis: an amnesic process. *Brain.* 2003; 126:770–82. [PubMed: 12615637]
10. Runmarker B, Andersson C, Odén A, Andersen O. Prediction of outcome in multiple sclerosis based on multivariate models. *Journal of Neurology.* 1994; 241:597–604. [PubMed: 7836963]
11. Pozzilli C, et al. 'Gender gap' in multiple sclerosis: magnetic resonance imaging evidence. *Eur J Neurol.* 2003; 10:95–7. [PubMed: 12535003]
12. Weatherby SJ, et al. A pilot study of the relationship between gadolinium-enhancing lesions, gender effect and polymorphisms of antioxidant enzymes in multiple sclerosis. *J Neurol.* 2000; 247:467–70. [PubMed: 10929279]
13. Antulov R, et al. Gender-related differences in MS: a study of conventional and nonconventional MRI measures. *Mult Scler.* 2009; 15:345–54. [PubMed: 19028830]
14. Barkhof F, et al. Predicting gadolinium enhancement status in MS patients eligible for randomized clinical trials. *Neurology.* 2005; 65:1447–54. [PubMed: 16275834]
15. Stone LA, et al. Blood-brain barrier disruption on contrast-enhanced MRI in patients with mild relapsing-remitting multiple sclerosis: relationship to course, gender, and age. *Neurology.* 1995; 45:1122–6. [PubMed: 7783875]
16. Libert C, Dejager L, Pinheiro I. The X chromosome in immune functions: when a chromosome makes the difference. *Nat Rev Immunol.* 10:594–604. [PubMed: 20651746]
17. Kantarci OH, et al. Interferon gamma allelic variants: sex-biased multiple sclerosis susceptibility and gene expression. *Arch Neurol.* 2008; 65:349–57. [PubMed: 18332247]
18. Moldovan IR, Coteleur AC, Zamor N, Butler RS, Pelfrey CM. Multiple sclerosis patients show sexual dimorphism in cytokine responses to myelin antigens. *J Neuroimmunol.* 2008; 193:161–9. [PubMed: 18022700]

19. Pelfrey CM, Coteleur AC, Lee JC, Rudick RA. Sex differences in cytokine responses to myelin peptides in multiple sclerosis. *J Neuroimmunol.* 2002; 130:211–23. [PubMed: 12225904]
20. Wolinsky JS, Shochat T, Weiss S, Ladkani D. Glatiramer acetate treatment in PPMS: why males appear to respond favorably. *J Neurol Sci.* 2009; 286:92–8. [PubMed: 19426995]
21. Koch M, Kingwell E, Rieckmann P, Tremlett H. The natural history of secondary progressive multiple sclerosis. *J Neurol Neurosurg Psychiatry.* 2010; 81:1039–43. [PubMed: 20639385]
22. Voskuhl RR, Palaszynski K. Sex hormones and experimental autoimmune encephalomyelitis: Implications for multiple sclerosis. *The Neuroscientist.* 2001; 7:258–270. [PubMed: 11499404]
23. Jansson L, Olsson T, Holmdahl R. Estrogen induces a potent suppression of experimental autoimmune encephalomyelitis and collagen-induced arthritis in mice. *Journal of Neuroimmunology.* 1994; 53:203–7. [PubMed: 8071434]
24. Matejuk A, et al. 17beta-estradiol inhibits cytokine, chemokine, and chemokine receptor mRNA expression in the central nervous system of female mice with experimental autoimmune encephalomyelitis. *J Neurosci Res.* 2001; 65:529–42. [PubMed: 11550221]
25. Gold SM, Voskuhl RR. Estrogen and testosterone therapies in multiple sclerosis. *Prog Brain Res.* 2009; 175:239–51. [PubMed: 19660660]
26. Palaszynski KM, Loo KK, Ashouri JF, Liu H, Voskuhl RR. Androgens are protective in experimental autoimmune encephalomyelitis: implications for multiple sclerosis. *J Neuroimmunol.* 2004; 146:144–52. [PubMed: 14698857]
27. Smith-Bouvier DL, et al. A role for sex chromosome complement in the female bias in autoimmune disease. *J Exp Med.* 2008; 205:1099–108. [PubMed: 18443225]
28. Palaszynski KM, et al. A Yin-Yang Effect Between Sex Chromosome Complement and Sex Hormones on the Immune Response. *Endocrinology.* 2005
29. Spach KM, et al. Cutting edge: the Y chromosome controls the age-dependent experimental allergic encephalomyelitis sexual dimorphism in SJL/J mice. *J Immunol.* 2009; 182:1789–93. [PubMed: 19201829]
30. Teuscher C, et al. Evidence that the Y chromosome influences autoimmune disease in male and female mice. *Proc Natl Acad Sci U S A.* 2006; 103:8024–9. [PubMed: 16702550]
31. Ebers GC, et al. Parent-of-origin effect in multiple sclerosis: observations in half-siblings. *Lancet.* 2004; 363:1773–4. [PubMed: 15172777]
32. Chao MJ, et al. Parent-of-origin effects at the major histocompatibility complex in multiple sclerosis. *Hum Mol Genet.* 2010; 19:3679–89. [PubMed: 20634196]
33. Gregg C, Zhang J, Butler JE, Haig D, Dulac C. Sex-specific parent-of-origin allelic expression in the mouse brain. *Science.* 2010; 329:682–5. [PubMed: 20616234]
34. Gabory A, Attig L, Junien C. Sexual dimorphism in environmental epigenetic programming. *Mol Cell Endocrinol.* 2009; 304:8–18. [PubMed: 19433243]
35. Fox HS, Bond BL, Parslow TG. Estrogen regulates the IFN-gamma promoter. *Journal of Immunology.* 1991; 146:4362–7.
36. Chao MJ, et al. MHC transmission: insights into gender bias in MS susceptibility. *Neurology.* 2011; 76:242–6. [PubMed: 21209377]
37. Orton SM, et al. Sex ratio of multiple sclerosis in Canada: a longitudinal study. *Lancet Neurol.* 2006; 5:932–6. [PubMed: 17052660]
38. Dunn SE, et al. Peroxisome proliferator-activated receptor (PPAR){alpha} expression in T cells mediates gender differences in development of T cell-mediated autoimmunity. *J Exp Med.* 2007
39. Ponsonby AL, et al. Offspring number, pregnancy and risk of first clinical demyelinating event: the Ausimmune study. *Neurology.* (in press).
40. Sicotte NL, et al. Testosterone treatment in multiple sclerosis: a pilot study. *Arch Neurol.* 2007; 64:683–8. [PubMed: 17502467]
41. Gold SM, Chalifoux S, Giesser BS, Voskuhl RR. Immune modulation and increased neurotrophic factor production in multiple sclerosis patients treated with testosterone. *J Neuroinflammation.* 2008; 5:32. [PubMed: 18671877]

42. Airas L, et al. Immunoregulatory factors in multiple sclerosis patients during and after pregnancy: relevance of natural killer cells. *Clin Exp Immunol*. 2008; 151:235–43. [PubMed: 18062798]
43. De Las Heras V, De Andres C, Tellez N, Tintore M. Pregnancy in multiple sclerosis patients treated with immunomodulators prior to or during part of the pregnancy: a descriptive study in the Spanish population. *Mult Scler*. 2007; 13:981–4. [PubMed: 17623725]
44. Fernandez Liguori N, et al. Epidemiological characteristics of pregnancy, delivery, and birth outcome in women with multiple sclerosis in Argentina (EMEMAR study). *Mult Scler*. 2009; 15:555–62. [PubMed: 19299437]
45. Finkelsztejn A, et al. The Brazilian database on pregnancy in multiple sclerosis. *Clin Neurol Neurosurg*. 2010
46. Finkelsztejn A, Brooks JB, Paschoal FM Jr, Fragoso YD. What can we really tell women with multiple sclerosis regarding pregnancy? A systematic review and meta-analysis of the literature. *BJOG*. 2011; 118:790–7. [PubMed: 21401856]
47. Vosoughi R, Freedman MS. Therapy of MS. *Clin Neurol Neurosurg*. 2010; 112:365–85. [PubMed: 20362388]
48. Vukusic S, et al. Pregnancy and multiple sclerosis (the PRIMs study): clinical predictors of postpartum relapse. *Brain*. 2004; 127:1353–60. [PubMed: 15130950]
49. Rouillet E, et al. Pregnancy and multiple sclerosis: a longitudinal study of 125 remittent patients. *J Neurol Neurosurg Psychiatry*. 1993; 56:1062–5. [PubMed: 8410003]
50. Weinshenker BG, Hader W, Carriere W, Baskerville J, Ebers GC. The influence of pregnancy on disability from multiple sclerosis: a population-based study in Middlesex County, Ontario. *Neurology*. 1989; 39:1438–40. [PubMed: 2812319]
51. Damek DM, Shuster EA. Pregnancy and multiple sclerosis. *Mayo Clinic Proceedings*. 1997; 72:977–89. [PubMed: 9379704]
52. Runmarker B, Andersen O. Pregnancy is associated with a lower risk of onset and a better prognosis in multiple sclerosis [see comments]. *Brain*. 1995; 118:253–61. [PubMed: 7895009]
53. Verdru P, Theys P, D'Hooghe MB, Carton H. Pregnancy and multiple sclerosis: the influence on long term disability. *Clin Neurol Neurosurg*. 1994; 96:38–41. [PubMed: 8187380]
54. D'Hooghe M B, Nagels G, Uitdehaag BM. Long-term effects of childbirth in MS. *J Neurol Neurosurg Psychiatry*. 2010; 81:38–41. [PubMed: 19939856]
55. Alonso A, et al. Recent Use of Oral Contraceptives and the Risk of Multiple Sclerosis. *Arch Neurol*. 2005; 62:1362–1365. [PubMed: 16157743]
56. Villard-Mackintosh L, Vessey MP. Oral contraceptives and reproductive factors in multiple sclerosis incidence. *Contraception*. 1993; 47:161–8. [PubMed: 8449016]
57. Thorogood M, Hannaford PC. The influence of oral contraceptives on the risk of multiple sclerosis. *Br J Obstet Gynaecol*. 1998; 105:1296–9. [PubMed: 9883921]
58. Hernan MA, Hohol MJ, Olek MJ, Spiegelman D, Ascherio A. Oral contraceptives and the incidence of multiple sclerosis. *Neurology*. 2000; 55:848–54. [PubMed: 10994007]
59. Jungers P, et al. Lupus nephropathy and pregnancy. Report of 104 cases in 36 patients. *Archives of Internal Medicine*. 1982; 142:771–6. [PubMed: 7073417]
60. Gilli F, et al. Learning from nature: pregnancy changes the expression of inflammation-related genes in patients with multiple sclerosis. *PLoS One*. 2010; 5:e8962. [PubMed: 20126412]
61. Al-Shammri S, et al. Th1/Th2 cytokine patterns and clinical profiles during and after pregnancy in women with multiple sclerosis. *J Neurol Sci*. 2004; 222:21–7. [PubMed: 15240191]
62. Gilmore W, et al. Preliminary studies of cytokine secretion patterns associated with pregnancy in MS patients. *J Neurol Sci*. 2004; 224:69–76. [PubMed: 15450773]
63. Lopez C, Comabella M, Tintore M, Sastre-Garriga J, Montalban X. Variations in chemokine receptor and cytokine expression during pregnancy in multiple sclerosis patients. *Mult Scler*. 2006; 12:421–7. [PubMed: 16900755]
64. Langer-Gould A, et al. Interferon-gamma-producing T cells, pregnancy, and postpartum relapses of multiple sclerosis. *Arch Neurol*. 2010; 67:51–7. [PubMed: 20065129]
65. Neuteboom RF, et al. First trimester interleukin 8 levels are associated with postpartum relapse in multiple sclerosis. *Mult Scler*. 2009; 15:1356–8. [PubMed: 19797262]

66. Sanchez-Ramon S, et al. Pregnancy-induced expansion of regulatory T-lymphocytes may mediate protection to multiple sclerosis activity. *Immunol Lett.* 2005; 96:195–201. [PubMed: 15585323]
67. Neuteboom RF, et al. Pregnancy-induced fluctuations in functional T-cell subsets in multiple sclerosis patients. *Mult Scler.* 2010; 16:1073–8. [PubMed: 20610493]
68. Munoz-Suano A, Kallikourdis M, Sarris M, Betz AG, Regulatory T. cells protect from autoimmune arthritis during pregnancy. *J Autoimmun.* 2011
69. Kim S, Liva SM, Dalal MA, Verity MA, Voskuhl RR. Estriol ameliorates autoimmune demyelinating disease: implications for multiple sclerosis. *Neurology.* 1999; 52:1230–8. [PubMed: 10214749]
70. Yates MA, et al. Progesterone treatment reduces disease severity and increases IL-10 in experimental autoimmune encephalomyelitis. *J Neuroimmunol.* 2010; 220:136–9. [PubMed: 20153059]
71. Hoffman GE, Le WW, Murphy AZ, Koski CL. Divergent effects of ovarian steroids on neuronal survival during experimental allergic encephalitis in Lewis rats. *Exp Neurol.* 2001; 171:272–84. [PubMed: 11573979]
72. Garay L, et al. Steroid protection in the experimental autoimmune encephalomyelitis model of multiple sclerosis. *Neuroimmunomodulation.* 2008; 15:76–83. [PubMed: 18667803]
73. Garay L, Deniselle MC, Lima A, Roig P, De Nicola AF. Effects of progesterone in the spinal cord of a mouse model of multiple sclerosis. *J Steroid Biochem Mol Biol.* 2007; 107:228–37. [PubMed: 17692515]
74. Garay L, et al. Protective effects of progesterone administration on axonal pathology in mice with experimental autoimmune encephalomyelitis. *Brain Res.* 2009; 1283:177–85. [PubMed: 19497309]
75. Spach KM, Hayes CE. Vitamin D3 confers protection from autoimmune encephalomyelitis only in female mice. *J Immunol.* 2005; 175:4119–26. [PubMed: 16148162]
76. Nashold FE, Spach KM, Spanier JA, Hayes CE. Estrogen controls vitamin D3-mediated resistance to experimental autoimmune encephalomyelitis by controlling vitamin D3 metabolism and receptor expression. *J Immunol.* 2009; 183:3672–81. [PubMed: 19710457]
77. Mirzaei F, et al. Gestational vitamin D and the risk of multiple sclerosis in offspring. *Ann Neurol.* 2011; 70:30–40. [PubMed: 21786297]
78. Chan J, et al. Glucocorticoid-induced apoptosis in human decidua: a novel role for 11beta-hydroxysteroid dehydrogenase in late gestation. *J Endocrinol.* 2007; 195:7–15. [PubMed: 17911392]
79. Gregg C, et al. White matter plasticity and enhanced remyelination in the maternal CNS. *J Neurosci.* 2007; 27:1812–23. [PubMed: 17314279]
80. Riskind PN, Massacesi L, Doolittle TH, Hauser SL. The role of prolactin in autoimmune demyelination: suppression of experimental allergic encephalomyelitis by bromocriptine. *Ann Neurol.* 1991; 29:542–7. [PubMed: 1859183]
81. Nociti V, et al. Multiple sclerosis attacks triggered by hyperprolactinemia. *J Neurooncol.* 2010; 98:407–9. [PubMed: 19957009]
82. Yamasaki K, et al. Hyperprolactinemia in optico-spinal multiple sclerosis. *Intern Med.* 2000; 39:296–9. [PubMed: 10801143]
83. Nelson LM, Franklin GM, Jones MC. Risk of multiple sclerosis exacerbation during pregnancy and breast-feeding. *Jama.* 1988; 259:3441–3. [PubMed: 3373681]
84. Airas L, Jalkanen A, Alanen A, Pirttila T, Marttila RJ. Breast-feeding, postpartum and prepregnancy disease activity in multiple sclerosis. *Neurology.* 2010; 75:474–6. [PubMed: 20679640]
85. Portaccio E, et al. Breastfeeding is not related to postpartum relapses in multiple sclerosis. *Neurology.* 2011; 77:145–50. [PubMed: 21734184]
86. Langer-Gould A, et al. Exclusive Breastfeeding and the Risk of Postpartum Relapses in Women With Multiple Sclerosis. *Arch Neurol.* 2009
87. Hellwig K, Haghighi A, Agne H, Beste C, Gold R. Protective effect of breastfeeding in postpartum relapse rate of mothers with multiple sclerosis. *Arch Neurol.* 2009; 66:1580–1. author reply 1581. [PubMed: 20008670]

88. Lambert N, Nelson JL. Microchimerism in autoimmune disease: more questions than answers? *Autoimmun Rev.* 2003; 2:133–9. [PubMed: 12848954]
89. Basso O, et al. Multiple sclerosis in women having children by multiple partners. A population-based study in Denmark. *Mult Scler.* 2004; 10:621–5. [PubMed: 15584485]
90. Abramsky O. Pregnancy and multiple sclerosis. *Annals of Neurology.* 1994; 36(Suppl):S38–41. [PubMed: 7517125]
91. Langer-Gould A, Garren H, Slansky A, Ruiz PJ, Steinman L. Late pregnancy suppresses relapses in experimental autoimmune encephalomyelitis: evidence for a suppressive pregnancy-related serum factor. *J Immunol.* 2002; 169:1084–91. [PubMed: 12097417]
92. Kipp M, Beyer C. Impact of sex steroids on neuroinflammatory processes and experimental multiple sclerosis. *Front Neuroendocrinol.* 2009; 30:188–200. [PubMed: 19393685]
93. Wise PM, Dubal DB, Wilson ME, Rau SW, Bottner M. Minireview: neuroprotective effects of estrogen-new insights into mechanisms of action. *Endocrinology.* 2001; 142:969–73. [PubMed: 11181507]
94. Enmark E, Gustafsson JA. Oestrogen receptors – an overview. *J Intern Med.* 1999; 246:133–8. [PubMed: 10447781]
95. Weiss DJ, Gursipide E. Non-genomic effects of estrogens and antiestrogens. *J Steroid Biochem.* 1988; 31:671–6. [PubMed: 2848981]
96. Yates MA, Li Y, Chlebeck PJ, Offner H. GPR30, but not estrogen receptor-alpha, is crucial in the treatment of experimental autoimmune encephalomyelitis by oral ethinyl estradiol. *BMC Immunol.* 2010; 11:20. [PubMed: 20403194]
97. Blasko E, et al. Beneficial role of the GPR30 agonist G-1 in an animal model of multiple sclerosis. *J Neuroimmunol.* 2009; 214:67–77. [PubMed: 19664827]
98. Wang C, et al. Membrane estrogen receptor regulates experimental autoimmune encephalomyelitis through up-regulation of programmed death 1. *J Immunol.* 2009; 182:3294–303. [PubMed: 19234228]
99. Liu HB, et al. Estrogen receptor alpha mediates estrogen's immune protection in autoimmune disease. *J Immunol.* 2003; 171:6936–40. [PubMed: 14662901]
100. Polanczyk M, et al. The protective effect of 17beta-estradiol on experimental autoimmune encephalomyelitis is mediated through estrogen receptor-alpha. *Am J Pathol.* 2003; 163:1599–605. [PubMed: 14507666]
101. Morales LB, et al. Treatment with an estrogen receptor alpha ligand is neuroprotective in experimental autoimmune encephalomyelitis. *J Neurosci.* 2006; 26:6823–33. [PubMed: 16793889]
102. Elloso MM, Phiel K, Henderson RA, Harris HA, Adelman SJ. Suppression of experimental autoimmune encephalomyelitis using estrogen receptor-selective ligands. *J Endocrinol.* 2005; 185:243–52. [PubMed: 15845917]
103. Garidou L, et al. Estrogen receptor alpha signaling in inflammatory leukocytes is dispensable for 17beta-estradiol-mediated inhibition of experimental autoimmune encephalomyelitis. *J Immunol.* 2004; 173:2435–42. [PubMed: 15294957]
104. Spence RD, et al. Neuroprotection mediated through estrogen receptor-alpha in astrocytes. *Proc Natl Acad Sci U S A.* 2011; 108:8867–72. [PubMed: 21555578]
105. Tiwari-Woodruff S, Morales LB, Lee R, Voskuhl RR. Differential neuroprotective and antiinflammatory effects of estrogen receptor (ER){alpha} and ERbeta ligand treatment. *Proc Natl Acad Sci U S A.* 2007; 104:14813–8. [PubMed: 17785421]
106. Du S, Sandoval F, Trinh P, Umeda E, Voskuhl R. Estrogen receptor-beta ligand treatment modulates dendritic cells in the target organ during autoimmune demyelinating disease. *Eur J Immunol.* 2011; 41:140–50. [PubMed: 21182085]
107. Du S, Sandoval F, Trinh P, Voskuhl RR. Additive effects of combination treatment with anti-inflammatory and neuroprotective agents in experimental autoimmune encephalomyelitis. *J Neuroimmunol.* 2010; 219:64–74. [PubMed: 20006910]
108. Tiwari-Woodruff S, Voskuhl RR. Neuroprotective and anti-inflammatory effects of estrogen receptor ligand treatment in mice. *J Neurol Sci.* 2009; 286:81–5. [PubMed: 19442988]

109. Crawford DK, et al. Oestrogen receptor beta ligand: a novel treatment to enhance endogenous functional remyelination. *Brain*. 2010; 133:2999–3016. [PubMed: 20858739]
110. Saijo K, Collier JG, Li AC, Katzenellenbogen JA, Glass CK. An ADIOL-ERbeta-CtBP transrepression pathway negatively regulates microglia-mediated inflammation. *Cell*. 2011; 145:584–95. [PubMed: 21565615]
111. Sicotte NL, et al. Treatment of multiple sclerosis with the pregnancy hormone estriol. *Ann Neurol*. 2002; 52:421–8. [PubMed: 12325070]
112. Soldan SS, Retuerto AI, Sicotte NL, Voskuhl RR. Immune modulation in multiple sclerosis patients treated with the pregnancy hormone estriol. *J Immunol*. 2003; 171:6267–74. [PubMed: 14634144]
113. Gold SM, et al. Estrogen treatment decreases matrix metalloproteinase (MMP)-9 in autoimmune demyelinating disease through estrogen receptor alpha (ERalpha). *Lab Invest*. 2009; 89:1076–83. [PubMed: 19668239]
114. Vukusic S, et al. The Prevention of Post-Partum Relapses with Progestin and Estradiol in Multiple Sclerosis (POPARTMUS) trial: rationale, objectives and state of advancement. *J Neurol Sci*. 2009; 286:114–8. [PubMed: 19758607]
115. Munoz-Suano A, Hamilton AB, Betz AG. Gimme shelter: the immune system during pregnancy. *Immunol Rev*. 2011; 241:20–38. [PubMed: 21488887]
116. Tafuri A, Alferink J, Moller P, Hammerling GJ, Arnold B. T cell awareness of paternal alloantigens during pregnancy. *Science*. 1995; 270:630–3. [PubMed: 7570020]
117. Mor G, Cardenas I. The immune system in pregnancy: a unique complexity. *Am J Reprod Immunol*. 2010; 63:425–33. [PubMed: 20367629]
118. Fallon PG, et al. IL-4 induces characteristic Th2 responses even in the combined absence of IL-5, IL-9, and IL-13. *Immunity*. 2002; 17:7–17. [PubMed: 12150887]
119. Wegmann TG, Lin H, Guilbert L, Mosmann TR. Bidirectional cytokine interactions in the maternal-fetal relationship: is successful pregnancy a TH2 phenomenon? [see comments]. *Immunology Today*. 1993; 14:353–6. [PubMed: 8363725]
120. Chaouat G. The Th1/Th2 paradigm: still important in pregnancy? *Semin Immunopathol*. 2007; 29:95–113. [PubMed: 17626305]
121. Trowsdale J, Betz AG. Mother's little helpers: mechanisms of maternal-fetal tolerance. *Nat Immunol*. 2006; 7:241–6. [PubMed: 16482172]
122. Saito S, Nakashima A, Shima T, Ito M. Th1/Th2/Th17 and regulatory T-cell paradigm in pregnancy. *Am J Reprod Immunol*. 2010; 63:601–10. [PubMed: 20455873]
123. Aluvihare VR, Kallikourdis M, Betz AG. Regulatory T cells mediate maternal tolerance to the fetus. *Nat Immunol*. 2004; 5:266–71. [PubMed: 14758358]
124. Somerset DA, Zheng Y, Kilby MD, Sansom DM, Drayson MT. Normal human pregnancy is associated with an elevation in the immune suppressive CD25+ CD4+ regulatory T-cell subset. *Immunology*. 2004; 112:38–43. [PubMed: 15096182]
125. Santner-Nanan B, et al. Systemic increase in the ratio between Foxp3+ and IL-17-producing CD4+ T cells in healthy pregnancy but not in preeclampsia. *J Immunol*. 2009; 183:7023–30. [PubMed: 19915051]
126. Peters A, Lee Y, Kuchroo VK. The many faces of Th17 cells. *Curr Opin Immunol*. 2011; 23:702–6. [PubMed: 21899997]

KEY POINTS

- The importance of sex related factors in MS pathogenesis and disease activity is supported by the increased risk for women to develop MS and a decrease in relapse rates during pregnancy.
- While MS incidence is higher and immune responses are more robust in females, males may have more progressive disease.
- Sex related factors may exert different, even opposing, effects on the peripheral immune system and the central nervous system.
- Sex specific effects on relapses should be considered separately from sex effects on progression.
- Sex hormones and sex chromosomes can independently contribute to disease.
- The widening in the gender gap in MS are likely due to the interaction of sex specific factors with autosomal genes or environmental/behavioral factors.

BOX 1**Pregnancy and autoimmunity: Insights from reproductive immunology**

During pregnancy, a balance in the immune system has to be achieved to assure survival of the fetus and the mother¹¹⁵. The classical concept of pregnancy as a semi-allograft where paternal alloantigens evade detection by the maternal immune system has been modified. It has been demonstrated that the maternal immune system recognizes paternal antigens but temporarily inhibits the immune response¹¹⁶. Pregnancy is therefore an immunomodulatory state characterized by a complex network of recognition and communication¹¹⁷.

Numerous studies have demonstrated a Th1/Th2 shift during pregnancy, which could contribute to the beneficial effects of pregnancy in cell-mediated autoimmune disorders such as RA and MS. However, animal models suggest that Th2 cytokines are not essential for successful pregnancy¹¹⁸. Thus, the notion that pregnancy represents a Th2 shift¹¹⁹ may be overly simplistic¹²⁰. Mechanisms of immune tolerance during pregnancy have mainly been investigated at the maternal-fetal interface¹²¹. In the context of the beneficial effects of pregnancy on cell-mediated autoimmune diseases, however, the more subtle shifts within systemic immune responses of the mother¹²² might be important. For example, regulatory T cells increase in the maternal circulation early during normal pregnancy in mice¹²³ and humans¹²⁴. In addition, an increase has been described in the ratio between regulatory T cells and Th17 cells¹²⁵, which may play a role in autoimmune inflammation¹²⁶. Recent experimental data suggest that transfer of regulatory T cells from pregnant mice are sufficient to confer protection from autoimmunity in non-pregnant mice⁶⁸. This mechanism may be antigen-specific since regulatory T cells from pregnant mice that had not been exposed to the autoantigen could not confer protection⁶⁸. The cellular and molecular mechanisms of this phenomenon, however, remain to be elucidated.

Table 1
Sex differences and the effect of pregnancy on MS incidence, activity and progression

Gender and pregnancy have been relatively well characterized for their effects on MS incidence and relapse, but evidence does not consistently show sex differences on disability progression. While females are more likely to get MS, their disability progression is not worse than men, thereby suggesting that there may be sex differences in the CNS response to a given immune attack with the female brain being relatively more resilient as compared to males. While late pregnancy decreases, and post partum increases, MS incidence and relapse, there is no major effect of these two time periods on disability. Overall, there are no clear effects of parity on disease, with some evidence suggesting a possible protective role on disease incidence and progression but this needs confirmation.

	Incidence (Onset)	Activity (Relapse)	Progression (Disability)
Sex Difference	F > M	F > M	M > F?
Late Pregnancy	↓	↓	None
Post Partum	↑	↑	None
Parity	None (↓?)	Unknown	None (↓?)

Table 2
Roadmap for future studies of sex-related factors in MS

Given the gender bias in susceptibility as well as the effect of pregnancy on relapse rates, future studies should aim at identifying the underlying etiologic processes including hormonal, genetic, epigenetic and environmental factors so that novel treatments can be developed targeting these factors. Sex specific effects on relapses and the immune system should be considered separately from effects on the central nervous system and progression.

		Immune System	Central Nervous System
Sex Difference	Clinical differences	Do female have more relapses?	Do males have more disability progression?
	Sex Hormones	Is physiologic testosterone anti-inflammatory?	Are physiologic estrogen or progesterone neuroprotective? Is testosterone neurodegenerative?
	Sex	Are X genes pro-inflammatory?	Are X genes neuroprotective?
	Chromosomes	Are Y genes anti-inflammatory?	Are Y genes neurodegenerative?
	Epigenetics	Interactions of sex hormones and sex chromosomes with autosomal genes linked to susceptibility.	Interactions of sex hormones and sex chromosomes with autosomal genes linked to progression.
	Gene-environment interactions	Interactions of sex hormones and sex chromosomes with environmental factors linked to susceptibility.	Interactions of sex hormones and sex chromosomes with environmental factors linked to progression.
Pregnancy	Late pregnancy	Identify pregnancy factor(s) that mediate the decrease in relapses.	Does pregnancy have an effect on disability?
	Post partum	Identify post partum factor(s) that mediate the increase in relapses.	Does the post partum period have an effect on disability?