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Pregnancy, sex and hormonal factors in multiple sclerosis

David H Miller[1], Franz Fazekas[2], Xavier Montalban[3], Stephen C Reingold[4] and Maria Trojano[5]

Abstract

Background: Multiple sclerosis (MS) is influenced by pregnancy, sex and hormonal factors.

Objectives: A comprehensive understanding of the role of pregnancy, sex and hormonal factors can provide insights into disease mechanisms, and new therapeutic developments and can provide improved patient care and treatment.

Methods: Based on an international conference of experts and a comprehensive PubMed search for publications on these areas in MS, we provide a review of what is known about the impact of these factors on disease demographics, etiology, pathophysiology and clinical course and outcomes.

Results and conclusions: Recommendations are provided for counseling and management of people with MS before conception, during pregnancy and after delivery. The use of disease-modifying and symptomatic therapies in pregnancy is problematic and such treatments are normally discontinued. Available knowledge about the impact of treatment on the mother, fetus and newborn is discussed. Recommendations for future research to fill knowledge gaps and clarify inconsistencies in available data are made.

Keywords

Pregnancy, sex, hormones

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Introduction

Sex- and pregnancy-related associations with multiple sclerosis (MS) include a higher and increasing prevalence in females than males and a lower relapse rate during pregnancy. Hormones associated with sex and pregnancy affect experimental models of MS and have therapeutic potential in humans.

Based on proceedings of a European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS)-sponsored international workshop held in March 2013 (see Acknowledgements for attendees list) and a comprehensive literature survey (PubMed search of papers in English, using terms: multiple sclerosis, MS, pregnancy, hormonal factors, treatment and related terms), we present an overview of sex, pregnancy and hormonal factors in MS. We provide etiological and pathophysiological insights from experimental models and clinical studies, and discuss management implications, including pregnancy risk counseling and pharmacological treatment during the reproductive years.

Hormonal effects in experimental models of MS

Animal models of MS demonstrate hormonal effects with potential relevance for pregnancy and development of MS therapies.[1] Estrogens (17β-estradiol-E2- and estriol-E3), progesterone and testosterone may provide anti-inflammatory and neuroprotective effects on induction and effector phases of experimental allergic encephalomyelitis (EAE).[2,3] Anti-inflammatory effects appear mainly mediated by estrogen nuclear receptors alpha (ERα) and beta (ERβ)[4] expressed by regulatory CD4+CD25+ T cells (Treg),[5] regulatory B (Breg) cells[6] and dendritic cells[7] and may be abrogated in the absence of B cells[8] and the co-inhibitory

[1]Queen Square Multiple Sclerosis Centre, Department of Neuroinflammation, Institute of Neurology, University College London, UK.
[2]Department of Neurology, Medical University of Graz, Austria.
[3]Department of Neurology/Neuroimmunology, MS Center of Catalonia (Cemcat), Vall d'Hebron University Hospital and Research Institute, Spain.
[4]Scientific and Clinical Review Associates, USA.
[5]Department of Basic Medical Sciences, Neurosciences and Sense Organs, University of Bari, Italy.

Corresponding author:
David H. Miller, Queen Square Multiple Sclerosis Centre, Department of Neuroinflammation, Institute of Neurology, University College London, London WC1N 3BG, UK.
Email: david.h.miller@ucl.ac.uk

receptor, Programmed Death-1 (PD-1) on CD4+ Foxp3+ Treg cells.[9] E2 protective effects on EAE seem to be mediated by binding to the membrane G-protein-coupled receptor 30 (GPR30).[10] Testosterone may work through androgen receptors[11] or after its conversion to estrogen through ERs, or GPR30. Androgens may induce remyelination in cuprizone-induced central nervous system (CNS) demyelination by acting on neural androgen receptors.[12]

Some neuroprotective effects of estrogens in EAE are mediated by ERα expressed on astrocytes:[13] ERβ ligands can prevent demyelination and stimulate remyelination[14] and ERβ treatment can affect microglia with protective effects in CNS inflammation.[15] Progesterone appears to affect axonal protection[16] and remyelination,[17] and testosterone can restore synaptic transmission deficits in the hippocampus.[18]

Sex-specific prevalence of MS: Temporal prevalence changes

MS is more prevalent in females than males. The female/male ratio has increased in many, but not all, locations[19–23] and may reflect epigenetic factors and gene-environment interactions[24] (including sex differences in expression of and environmental effects on candidate genes on the X or Y chromosome);[3] lifestyle changes (contraception, diet, obesity, smoking, sunlight exposure, vitamin D deficiency);[25] higher age at first childbirth,[26] and fewer life-time pregnancies.[27–29] Better understanding of factors that underlie the differential sex prevalence should illuminate MS susceptibility factors overall.

Preparing for pregnancy

When pregnancy is contemplated, reproductive decision-making questions include: impact of MS on fertility; risk of MS in offspring; risk to the child of a parent's MS medications before and during pregnancy; effect of pregnancy on the course of MS; effect of MS on the ability to provide child care; and associated socioeconomic burden to the family.[30]

MS and fertility

Female and male parenting over five years prior to MS onset has been associated with a reduced risk of MS,[27,31] suggesting that pre-clinical MS may reduce biological fertility or affect reproductive decision making. While MS does not appear to impair fertility in women with MS,[32] the two may occur together. Assisted reproductive techniques using gonadotropin-releasing hormone (GnRH; either agonists or antagonists) and gonadotropins probably increase clinical and magnetic resonance imaging (MRI) lesion activity in MS,[33–35] with an increased annualized relapse rate in the three months following in vitro fertilization (IVF).[34] Potential mechanisms include: GnRH-mediated increase in immune cell proliferation with increased cytokine, chemokine and endothelial growth factor production; GnRH-agonist-mediated rapid phasic changes in estrogen levels, with an increase followed by a decrease, similar to changes seen during pregnancy and postpartum, respectively; and discontinuation of MS disease-modifying treatments during fertility treatment.

Risk for MS in children

The risk for MS is about 2% for a child with one MS parent,[36] and MS has been observed in 6%–12% children when both parents had MS (conjugal MS).[37,38] Counseling should emphasize that MS in a child is likely many years away, its course can be benign, and continuous progress in MS research includes development of more effective treatments.

Small differences in MS risk according to month of birth have been reported (higher in spring, lower in autumn[39]) although the finding may be confounded by year and place of birth.[40] Lower vitamin D levels have been associated with a higher risk for MS,[41] and MS risk is lower among women born to mothers with high vitamin D intake during pregnancy.[42] Although safety of vitamin D supplementation in pregnancy is not established, supplementing vitamin D-deficient mothers might seem sensible,[42] but the dose given should achieve and not exceed a normal serum concentration (25-hydroxy vitamin D range 50–125 nmol/l).[43]

Impact of pregnancy on MS disease course

Changes in circulating pregnancy hormones (estrogen, progesterone, prolactin and others) have effects on immune responses that underlie MS pathology.[44] The number of acute MS relapses is approximately halved during pregnancy, especially in the third trimester, and approximately doubled during the three months postpartum.[45] Pregnancy probably has no impact on long-term course or the likelihood of secondary progressive MS.[46,47] Pregnancy and childbirth have even been associated with less long-term disability,[48] although interpretation of studies may be confounded by reverse causality when having MS affects reproductive decision making. Overall, the impact of pregnancy on MS course is not usually a concern when considering family planning.

Disease monitoring during pregnancy

While deleterious effects of MRI during pregnancy are not reported, its safety is not established sufficiently to support unrestricted use during pregnancy, with concern about the potential risk of heating effects from radiofrequency pulses, including teratogenicity, and effects of acoustic noise on the fetus.[49] It has been recommended to postpone elective

MRI until after the first trimester, but MRI may be used at any time when potential clinical benefits clearly outweigh uncertain risks. Unlike radiography—including computed tomography (CT)—MRI avoids radiation exposure.[50] Intravenous gadolinium-contrast agents should be used with extreme caution during pregnancy.[50] Lumbar puncture or electrophysiological tests are not associated with specific risks to mother or fetus but should be used minimally as they may cause discomfort in a pregnant woman.

Treatment before conception and during pregnancy

Pharmacological treatments for MS should be avoided where possible during pregnancy. This normally means discontinuing existing disease-modifying and symptomatic treatments when planning conception and during pregnancy, unless the balance of benefit and risk favors continuing a treatment.[51,52]

Management of relapses

A short course of high-dose corticosteroids to hasten recovery from relapses appears relatively safe during pregnancy, but generally should be limited to disabling relapses, and there is a possible increased risk of fetal cleft palate associated with corticosteroid treatment in the first trimester.[53]

Disease-modifying treatments

Reported experience of ß-interferon during pregnancy amounts to almost 1000 cases, most treated only during early weeks of the first trimester as treatment was discontinued when pregnancy was detected.[54–58] While two small studies of MS patients who became pregnant while being treated with ß-interferon-1a[59] and ß-interferon-1b[54] reported a higher than expected frequency of spontaneous abortions, no increase in spontaneous abortions was observed in subsequent reports of larger cohorts who were being treated with ß-interferon-1a. There was a low incidence of fetal abnormalities with no consistent pattern for any syndrome, though data are insufficient to exclude an association with rare fetal abnormalities.[55,56] ß-interferon treatment has been associated with premature delivery and reduced birth weight.[55,60] ß-interferon should not be started during pregnancy, and in women already receiving treatment it is standard practice to discontinue it to avoid pharmacological effects[61] prior to a planned conception. Some physicians may elect to continue treatment until pregnancy is confirmed if they feel it essential to avoid any delay between treatment discontinuation and becoming pregnant.

Pregnancy outcomes have been reported in about 400 glatiramer acetate-treated patients and no increase in fetal abnormality noted.[54,57,62,63] Although some physicians use glatiramer acetate during pregnancy when they feel its potential benefits outweighs risks, caution is advised as the reported numbers treated are not sufficient to exclude an uncommon fetal abnormality.

There is less or little information on pregnancy experience and fetal outcome with other disease-modifying treatments including natalizumab,[64,65] fingolimod,[66] dimethylfumarate[67] and alemtuzumab. Natalizumab shows increased abortions in animal studies,[68] while none so far has been detected in MS. Conception should be avoided until fingolimod is eliminated from the body, about two months after treatment discontinuation.[69] Teriflunomide has teratogenic effects in animals and must not be given during pregnancy;[70] it has a long plasma half-life, and cholestyramine is routinely used to eliminate it whenever treatment is discontinued, for instance prior to conception and pregnancy.[51,70] Mitoxantrone may cause amenorrhea (especially age >35 years[71]) and should be avoided during pregnancy because of potential for teratogenicity.[52]

In patients with previous highly active relapsing–remitting MS, cessation of disease-modifying treatment prior to conception may be associated with an increased relapse risk.[72] While it may be thought desirable to continue disease-modifying treatment in such patients, the potential for adverse effects on the fetus cannot be excluded, especially with newer, more potent treatments. In patients with highly active MS given natalizumab in the third trimester because of relapses, mild to moderate hematological abnormalities including thrombocytopenia and hemolytic anemia were seen in eight of nine newborns (K Hellwig, personal communication 2013).

There is little information regarding effects of MS disease-modifying treatments on human male fertility or pregnancy outcomes in fathers receiving treatment.[60] One study compared the outcome of pregnancies where fathers were treated (mainly with glatiramer acetate or ß-interferon) with outcomes from maternal MS cohorts with and without disease-modifying treatment and did not identify safety concerns for the offspring of the treated fathers.[73] Although some men discontinue glatiramer acetate or ß-interferon prior to conception, there is limited rationale for this approach. Teriflunomide is detected in semen and should be discontinued with cholestyramine washout in potential fathers.[70]

Symptomatic treatments

There is little information on most MS symptomatic therapies from which to provide evidence-based advice for use during pregnancy, apart from anticonvulsants.[74] Frequently used MS symptomatic agents (e.g. baclofen,[75] oxybutynin,[76] amantadine[77] and clonazepam[78]) carry United States Food and Drug Administration (FDA) class B, C or D risks.[79] A standard approach is to discontinue symptomatic therapies prior to conception, with an understanding of the potential functional impact; if continued, minimal effective doses should be used for the shortest time possible.

Delivery and post-pregnancy

Delivery and neonatal outcomes

Although not all reports concur,[80] there are probably no significant differences in gestational age, birth weight, length of birth hospitalization, and frequency of assisted vaginal delivery or cesarean section between women with MS and the general population.[81–83] A trend for more frequent labor induction in women with greater disability warrants further investigation.[82] Neither epidural anesthesia[84,85] nor cesarean section[85] has been associated with adverse effects on delivery or postpartum MS course.

Postpartum relapses

Disease-modifying therapies may be restarted soon after birth to potentially mitigate postpartum relapses. Poorly controlled clinical studies have suggested that monthly intravenous methylprednisolone[86] or immunoglobulin[87,88] may reduce postpartum relapses, but controlled studies are needed to confirm these effects.

Breastfeeding

Studies of the postpartum MS course[42,89,90] suggest no effect or a possible decrease in relapse rate associated with breastfeeding. Exclusive breastfeeding may be protective, although there have been only limited studies.[57,90] Because MS disease-modifying treatments may enter breast milk, they are normally withheld during breastfeeding. The decision whether to resume a disease-modifying treatment immediately after birth needs to be weighed against the potential benefits of breastfeeding. When patients receive high-dose methylprednisolone, brief suspension of breastfeeding for 24–48 hours has been recommended.[52]

Clinical trials of sex hormone therapies

A baseline cross-over trial of oral estriol in 10 women with relapsing–remitting MS showed an 80% decrease in gadolinium-enhancing lesions, a favorable Th1 to Th2 immune shift in peripheral blood mononuclear cells (PBMCs), and improved cognition.[91] A baseline crossover trial of transdermal testosterone in 10 men with relapsing–remitting MS showed no change in gadolinium-enhancing lesion frequency, but reduced brain atrophy and increased production of neurotropic factors by PBMCs.[3,92] These studies imply beneficial immunomodulatory and neuroprotective effects of estrogen in women and testosterone in men, respectively.

The effect of oral contraceptives (OCs) on MRI lesion activity was investigated in 149 women treated with subcutaneous ß-interferon 1a and randomized to receive ß-interferon 1a only, or ß-interferon 1a plus ethinylestradiol 20 mcg and desogestrel 150 mcg (low-dose estrogen group), or ethinylestradiol 40 mcg and desogestrel 125 mcg (high-dose estrogen group).[93] There were significantly fewer new lesions over two years in the high-dose estrogen group. Estrogen-containing OCs probably do not worsen MS disease course[94] and high-dose estrogen OCs may enhance the effect of ß-interferon in preventing new lesions in relapsing–remitting MS.

The Post Partum Progestin and Estriol in Multiple Sclerosis (POPARTMUS) trial investigated 12 weeks' treatment with 10 mg nomegestrol acetate versus placebo[95] and found no difference in postpartum relapse rate between study arms (C Confavreux, personal communication 2013).

Menopause

Any effects of menopausal hormone changes per se may be confounded by age-related changes in MS disease activity and comorbidities. Observations of patients who developed MS aged >50 years suggested a similar rate of disease progression in both sexes, while men progressed more rapidly when disease started between 18 and 49 years.[96] This highlights potentially complex contributions of age and sex together with genetic and environmental factors in such studies.

Recommendations for managing reproduction-related issues in MS

Counseling the mother and father is important before, during and following pregnancy. Helping a family to assess parenting abilities (physical, financial, emotional), and to understand short- and long-term consequences of pregnancy on MS in the mother and risks of MS in offspring, can guide realistic expectations of pregnancy outcomes (Table 1). Management issues for the prospective MS parents include fertility and conception; impact of pregnancy on MS course; implications for disease-modifying and symptomatic therapies; obstetric management and delivery; and breastfeeding (Table 2). Physicians should be aware of regulatory guidance regarding pharmacological treatments during pregnancy and the principle that medications will normally be avoided unless their benefits are considered to outweigh risks.

Future directions (Table 3)

The reasons underlying apparent changes of MS prevalence in women remain speculative. Future case-control studies to elucidate their cause(s) could yield major clinical insights and lead to new health care strategies for the prevention and treatment of MS.

Numerous studies have investigated effects of pregnancy on risk of MS or a first clinical or radiological

Table 1. Elements to be considered in counseling the patient/family at different stages of the reproductive "cycle" in MS.

There is a need for counseling provided in easily understood language supported by data (where possible) that are tailored to the individual patient and family clinical, psychological and socioeconomic status; different issues may emerge at different stages in the family planning and reproductive cycle of an MS patient:
Prior to conception: Issues of sexual function (male and female), MS impact on fertility and the risk of assistive reproductive techniques; use/impact of contraceptives; potential risks to offspring for developing MS; potential impact of MS treatments on fetal health; prior use of disease-modifying therapies and impact on pregnancy and fetal outcomes; influence of month of birth on development of MS in offspring; short-term and long-term impacts of pregnancy on MS status
During pregnancy: Management of MS during pregnancy (use and impact of disease-modifying and symptomatic therapies and treatment of relapses); use of MRI to assess MS disease status during pregnancy; short-term and long-term impacts of pregnancy on MS status
Postpartum: Expectations for postpartum MS relapse and management; restarting MS disease-modifying/symptomatic therapies that have been stopped during pregnancy; breastfeeding; parenting with a disability; long-term planning

MS: multiple sclerosis; MRI: magnetic resonance imaging.

Table 2. Recommendations related to management of MS around pregnancy.

1. Use assistive reproductive techniques (ART) to increase likelihood of a successful conception
   a. While about one in five assistive reproductive procedures in MS couples results in a successful pregnancy, there is a chance of the mother having an MS relapse while using ART; while more data are needed to understand and quantify this phenomenon, the information should be provided to MS parents considering ART to help them make an informed decision.
2. Use of MRI during pregnancy to monitor MS disease status
   a. While data are largely lacking, there is no obvious need to monitor MS with MRI during pregnancy; clinical assessment may suffice if increased disease activity is suspected
   b. Gadolinium-based contrast enhancing agents used in MRI procedures in MS have not been well studied in pregnancy or lactation and should be avoided where possible
   c. CT scans and X-rays are not generally recommended during pregnancy because of the potential risk of fetal radiation exposure
3. Impact of prior use of disease-modifying therapies on fetal development
   a. Animal studies indicate that use of teriflunomide carries teratologic risks and attempts at conception should await cessation of its use and washout both from the potential mother and father.
   b. For other MS disease-modifying agents there is limited evidence of impact on either fertility or fetal health, but the limited evidence base available does not preclude uncommon risks; standard practice is to discontinue treatment prior to conception unless it is felt that the benefits of continuing treatment outweigh the potential risks.
4. Impact of pregnancy on short- and long-term MS outcomes in the mother
   a. Ample evidence documents a short-term reduction in MS inflammatory activity (reflected in reduced relapse rate) during the second and third trimester of pregnancy with an increased risk of a relapse during the first three to six months postpartum; these data and their implications should be discussed with the prospective mother with MS and her partner prior to conception, during pregnancy and after delivery. There does not appear to be an effect of pregnancy on the long-term course of MS.
5. Impact on MS of disease-modifying therapies during pregnancy
   a. IV methylprednisolone for treatment of acute MS relapses is associated with potential fetal risks and side effects for the mother; it is best to avoid its use, especially in the first trimester of pregnancy and to restrict its use throughout pregnancy to only those relapses that have a significant impact on the mother's activities of daily living.
   b. Although use of IV immunoglobulin is probably safe during pregnancy, it cannot be recommended at this time because of lack of evidence of proven efficacy
   c. There is significant experience, but limited published evidence, of the impact of ß-interferons and glatiramer acetate during pregnancy. Neither appears to increase risk of spontaneous abortion, although animal studies have identified this as an effect of ß-interferon. Data on subcutaneous ß-interferons to date suggest no definite impact on fetal abnormalities but published information on intramuscular ß-interferon and glatiramer acetate in this regard is more limited; the overall data available are not sufficient to exclude rare adverse effects on the fetus. It is standard practice to discontinue these agents prior to and throughout pregnancy, unless there is considered to be a substantial risk to the pregnant woman of untreated MS becoming highly active such that the benefits of treatment outweigh potential (though uncertain) fetal risks.
   d. For more recently registered MS disease-modifying therapies, there are little available data. However:
      i. Natalizumab shows increased spontaneous abortions in animal studies, while none so far has been detected in MS. It may not cross the placenta during the first trimester. While discontinuation is recommended during pregnancy, this should be considered on a case-by-case basis, with full discussion of the potential benefit/risk of its continued use keeping in mind the potential for some patients with previous highly active disease to develop recurrence of highly active disease after treatment discontinuation.
      ii. Fingolimod should be discontinued two months before anticipated conception
      iii. Teriflunomide should be discontinued and washed out prior to conception and if an accidental pregnancy occurs during its use, it should be washed out (using recommended cholestyramine washout procedures).
      iv. Dimethylfumarate, the most recently approved MS disease-modifying agent, has been little studied in pregnancy and should probably be avoided pending availability of additional information.

(Continued)

Table 2. (Continued)

6. Use of symptomatic therapies during pregnancy
   a. Evidence of the impact of symptomatic therapies on pregnancy in MS is almost totally lacking. Almost all frequently used symptomatic agents for MS carry FDA category B, C or D risks. A conservative approach, while awaiting evidence would include:
      i. Stop all symptomatic therapies prior to conception, with an understanding and consideration of the impact on activities of daily living
      ii. If continued, use the minimal effective dose of symptomatic management agents, for the shortest time possible
      iii. Avoid use of agents for which there are no pregnancy-related data
   b. Pregnant MS patients should be provided with folic acid supplementation to reduce likelihood of neural tube defects in the fetus; use of vitamin D supplementation to a normal serum level should be considered.
7. Cesarean delivery and use of epidural anesthesia
   a. There is no evidence that either cesarean delivery or use of epidural anesthesia has an impact on MS in the mother; both can be used in delivery if advised.
8. Impact of breast feeding on maternal MS and the newborn
   a. There is no evidence that breastfeeding causes harm to the mother with MS and some evidence to suggest that it can be beneficial in controlling postpartum relapses. Data are generally lacking on the presence of disease-modifying or symptomatic therapies used by a nursing mother in breast milk and consequently the impact of such agents on the breastfeeding newborn. Generally the recommendation is to stop use of such agents if breastfeeding, or to avoid breastfeeding if the treatments are to be used.

MS: multiple sclerosis; MRI: magnetic resonance imaging; CT: computed tomography; IV: intravenous; FDA: United States Food and Drug Administration.

Table 3. Future directions.

1. Use of long-lasting population-based registries for:
   a. case-control studies to identify underlying environmental factors or gene-environment interactions responsible of sex ratio increase
   b. case-control studies to elucidate effects of pregnancies on MS risk and effects of MS on reproduction (reverse causality)
   c. evaluation of pregnancy effects on mother's long term MS course (development of disability, risk for secondary progressive MS)
   d. short- and long-term follow-up of children exposed in utero to disease-modifying treatments
2. Randomized controlled trials to assess the potential of sex hormone treatments for MS patients
   a. Estrogens (modulate inflammation)
   b. Testosterone (neuroprotection and repair)
3. Laboratory research to study relevant disease and therapeutic mechanisms
   a. Immunological effects of hormonal assisted reproduction treatments in women with MS
   b. Mechanisms of hormonal effects on inflammation, neuroprotection and repair

MS: multiple sclerosis.

demyelinating event,[26–29,97] outcomes of pregnancy for the mother and child,[82,83] and effects of drug exposure during pregnancy on the child,[55,56,60,63] but results are not always consistent and sometimes conflicting. Different study findings may reflect small sample sizes; heterogeneous methodologies and populations; and confounding factors such as co-morbidities, co-treatments, family history and maternal age. Using population-based registries with linkages to independent national databases, future studies should address the impact of pregnancy and MS therapies during pregnancy on long-term outcomes for mother and child. A challenge for all MS registry initiatives is to combine datasets to generate large international cohorts, with shared demographic and clinical information.[98,99]

Hormonal treatment trials with definitive clinical endpoints are warranted. A placebo-controlled trial of estrogen as add-on therapy to glatiramer acetate in women with relapsing–remitting MS is in progress.[100] Further laboratory investigation to elucidate mechanisms of potential beneficial (estrogens and testosterone) and adverse (gonadotropins) hormonal effects is needed.

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Conflict of interest

DHM has received honoraria through payments to his employer, UCL Institute of Neurology, for Advisory Committee and/or Consultancy advice in multiple sclerosis studies from Biogen Idec, GlaxoSmithKline, Novartis, Merck, Chugai, Mitsubishi Pharma Europe and Bayer Schering Pharma, and has also received grants through payments to his employer for performing central MRI analysis of multiple sclerosis trials from GlaxoSmithKline, Biogen Idec, Novartis and Merck. The Queen Square MS Centre at UCL Institute of Neurology is supported by the UK MS Society and UCL-UCLH Biomedical Research Centre.

FF serves on scientific advisory boards for Bayer-Schering, Biogen Idec, Genzyme, Merck Serono, Perceptive Informatics, Pfizer, Novartis and Teva Pharmaceutical Industries Ltd and has received speaker honoraria and support from Biogen Idec, Bayer Schering, Merck Serono, Novartis, Sanofi-Aventis and Teva Pharmaceutical Industries Ltd.

XM has received speaking honoraria and travel expense reimbursement for participation in scientific meetings, has been a steering committee member of clinical trials or participated in advisory boards of clinical trials in the past years with Bayer, Biogen Idec, Merck, Genentech, Genzyme, Novartis, Sanofi-Aventis, Teva Pharmaceuticals and Almirall.

SCR has served as a consultant to the National Multiple Sclerosis Society (USA) and the European Committee for Treatment and Research in MS; and has received honoraria and travel reimbursement for service on Data Safety Monitoring Boards or Advisory Boards for Bayer HealthCare, Coronado Biosciences Inc, Eli Lilly & Company, EMD Merck Serono, Genentech, F. Hoffmann-LaRoche, Ironwood Pharmaceuticals Inc, ISIS Pharmaecuticals Inc, MedImmune Inc, Novartis Pharmaceuticals Corporation, Observatoire Français de la Sclérosis en Plaques, Opexa Therapeutics, Sanofi-Aventis, SK Biopharmaceuticals, Synthon Pharmaceuticals Inc, and Teva Pharmaceutical Industries; and served as an editorial board member of the Multiple Sclerosis Journal.

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