Multiple Sclerosis

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This monograph is designed to enable the obstetrician–gynecologist to do the following:

- Learn the pathophysiology of multiple sclerosis
- Increase familiarity with clinical approaches for prevention and management
- Recognize signs and symptoms
- Evaluate patients
- Treat patients with uncomplicated multiple sclerosis and initiate appropriate referrals for more complicated cases
- Learn about reproductive concerns in patients with multiple sclerosis

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*See page vi for submission of CME credits.*
Multiple sclerosis (MS) disproportionately affects women and commonly is diagnosed during the childbearing years. Obstetrician–gynecologists play a critical role in the early recognition of this chronic inflammatory and demyelinating disease. However, early signs and symptoms typically are highly variable and subtle. Therefore, the Editorial Board has decided to rehabilitate the monograph from 2010 in the form of a completely revised overview. The authors of this revised monograph are neurologists with expertise in MS. They guide the reader through differential diagnosis, appropriate evaluation, and ultimate referral for neurologic consultation and treatment. Additionally, they provide an overview of the clinical MS subtypes, the myriad nonpharmacologic and medical options that are currently available for the management of specific MS symptoms, and the medical therapies that target this neurologic disorder directly. The sections that discuss the effects of MS and its various treatments on women across the entire life cycle also are included and should be particularly useful to practicing obstetrician–gynecologists.

Russell R. Snyder, MD
Editor
ABSTRACT: Multiple sclerosis (MS) is a chronic inflammatory and demyelinating disease of the central nervous system. The disease affects more women than men and often is diagnosed during a woman’s childbearing years. Typical clinical presentations of the disease are extensive and variable, with symptoms that include dysregulated mood, fatigue, vision problems, weakness, tremor, imbalance, abnormal sensations, bladder dysfunction, and heat sensitivity. If a woman aged 15–50 years experiences these neurologic symptoms in isolation or combination, and the symptoms are not explained by other underlying medical conditions, MS should be suspected. Multiple sclerosis can be divided into four clinical subtypes: 1) relapsing-remitting MS, 2) secondary progressive MS, 3) primary progressive MS, and 4) clinically isolated syndrome. Relapsing-remitting MS at the time of onset is the most common form and accounts for approximately 80% of all cases of MS (1). Relapsing-remitting MS does not affect life expectancy. However, because of the neurodegenerative and progressive course of the disease, patients accumulate physical and cognitive disabilities over time that result in impaired ability to work, increased financial burden, and slightly increased mortality (2–4). A variety of possible risk and prognostic indicators have been identified that may predict the course of disease, particularly the extent of relapses and disability. Multiple sclerosis currently is incurable, but many disease-modifying therapies are available that can reduce the frequency of clinically evident exacerbations and accumulation of disease burden as defined by the number of lesions identified on magnetic resonance imaging. The choice of disease-modifying therapies, contraception use, and treatment of symptoms should be individualized based on age at onset and disease activity and, during pregnancy, the gestational age. Proactive management of MS across the woman’s life cycle reduces morbidity, improves maternal and fetal health during pregnancy and the postpartum period, and increases quality-of-life measures for patients and their families.

Multiple sclerosis (MS) is an inflammatory and demyelinating disease of the central nervous system (CNS) that involves an immune-mediated disruption of the structural integrity of the brain, spinal cord, and optic nerves (5, 6). It is one of the most common neurologic disorders, and it is the leading cause of nontraumatic neurologic disability in young adults (7). Clinical manifestations of MS vary from subtle symptoms, such as cognitive impairment, sleep disturbance, fatigue, mood change, and abnormal sensations, to more severe symptoms, including vision loss, weakness, incoordination, impaired ambulation, and bladder dysfunction (Box 1). Although MS can cause many symptoms, not all individuals with the disease will manifest all possible symptoms. Furthermore, not all symptoms that manifest are caused by MS. Limited awareness and
appreciation of the seriousness of the disease, associated stigma, and lack of social support networks can delay diagnosis and treatment. If a woman aged 15–50 years experiences the described neurologic symptoms, and the symptoms are not explained by other underlying medical conditions, MS should be suspected and the health care provider should refer the patient for neurologic consultation to determine the cause of these symptoms and the treatment course as indicated.

Multiple sclerosis can be diagnosed at the time of a first episode based on clinical findings, magnetic resonance imaging (MRI) of the brain, and a cerebrospinal fluid (CSF) study using the McDonald criteria (discussed in the section “Diagnosis and Evaluation”). Lesions are stratified as either disseminated in space (damage in more than one place in the nervous system) and in time (damage has occurred more than once). Several disease-modifying therapies have been approved by the U.S. Food and Drug Administration (FDA) for the treatment of MS that can reduce clinical disease activity (eg, an exacerbation or “flare”) as well as development of new and enhancing lesions. However, none of these therapies has been proved safe during pregnancy, and patients with MS who plan to become pregnant should be counseled regarding initiation or discontinuation of disease-modifying therapies and the management of clinical relapse during pregnancy, in the immediate postpartum period, and during breastfeeding. The relapse rate decreases during pregnancy but increases in the first 3 months postpartum. Reproductive hormones may play an important role in regulating immune response during the course of MS (8). Women with MS also should be educated about the benefits of preventive care (9).

Obstetrician–gynecologists often provide primary health care to their patients and should be familiar with the basic pathophysiology, risk factors, clinical symptoms, and management of MS to provide optimal care, including counseling and education.
**Scope of the Problem**

Approximately 400,000 individuals in the United States and nearly 2.3 million individuals worldwide have MS (7, 10). The disease affects three times as many females as males. In the United States, the Eastern and Northern regions have the highest MS prevalence, and the Southern and Western regions have the lowest MS prevalence (11).

Multiple sclerosis can occur at any age from childhood to age 80 years, but the average age at onset is 34 years (7, 12). Thus, it is common for women to receive the diagnosis of MS during their reproductive years. For primary progressive MS, the average age at diagnosis is 40 years (13).

Environmental factors appear to play a significant role in the occurrence of MS. The prevalence of MS increases farther from the equator, although exceptions exist (14, 15). The prevalence is higher in Northern Europe, Canada, the Northern United States, New Zealand, and Australia; and lower in Asia, most of Africa, and South America (14). However, various ethnic groups, including the Samis, American Indians, Canadian Hutterites, New Zealand’s Maori, and Canada’s Inuits, are at low risk despite being far from the equator, whereas Sardinians, inland Sicilians, Palestinians, and Parsi have a relatively high risk although they live closer to the equator (16, 17). Geographic location is one explanation for the association of MS and vitamin D deficiency because patients who live far from the equator are exposed to less sunlight than those near the equator (18–20). Individuals who migrate in childhood from a high-risk location to a low-risk location adopt the risk of MS in the new location (a reduced risk). Those who migrate from a geographic area with a low prevalence of MS to a geographic area with a high prevalence of MS have an increased risk of developing MS (14, 21).

The causes of MS remain unknown. There are no definitive biomarkers that predict its development. Environmental, genetic, and epigenetic factors have a causal role in the course of MS and potentially interact with modifiable risk factors (Fig. 1). Although MS is not considered a hereditary disease, genetic factors appear to contribute to an individual’s risk of developing the disease. The probability of an identical twin developing MS is approximately 25–30% compared with 2.5–5% for a nonidentical twin (14, 22), and if both parents have MS, the risk of MS in their offspring is approximately 10 times higher than the risk in the general population (12).

The most important susceptibility region identified for MS is the major histocompatibility complex on chromosome 6p21. Human leukocyte antigens (HLAs), a group of alleles (genes), namely HLA-C554 and HLA-DRB1*11, have shown protective effects, and HLA-DR15 and HLA-DQ6 have shown an association with MS (14). Both the innate and adaptive immune systems, with their effector cells (eg, microglia, activated macrophages, and lymphocytes [ie, B cells and T cells]), are involved in regulating the pathogenesis of MS. Furthermore, from genome-wide association studies, non-HLA genes, such as IL2RA and IL7RA, have been identified as genetic variants with minor effects on MS (23, 24).
Subsequent genome-wide association studies and a meta-analysis have identified other associations, including the regions of CD58, TYK2, STAT3, and TNFRSF1A (25). More recently, B-cell-depleting antibodies have shown great success in limiting MS lesion formation and clinical disease activity, suggesting an important role of B cells in the pathogenesis of MS (26, 27).

Environmental risk factors, such as vitamin D deficiency, poor nutrition, obesity in early life, and cigarette smoking, are known to influence MS development. There is an inverse relationship between sun exposure, ultraviolet radiation exposure, and serum vitamin D levels and the risk of MS. High antiviral titers and oligoclonal bands have been reported in the CSF of MS patients. The risk of MS is low in individuals who have not been exposed to Epstein–Barr virus and increases markedly after Epstein–Barr virus infection (28, 29). There is no association between vaccines and the risk of MS (Fig. 1).

![Risk factors and modifiers](image.png)

**Risk factors and modifiers**
- Genetic factors (major histocompatibility complex and genome variants)
- Past Epstein–Barr virus infection
- Vitamin D deficiency
- Sun exposure
- Smoking
- Obesity
- Hormonal status

**Disease course**
- Inflammation → demyelination → degeneration

**Younger age**
- Early onset
- Inflammation—nonactive and low
- Spinal cord lesions—few
- Endogenous repair—good
- Axons and synapses—preserved
- Treatment—early

**Older age**
- Late onset
- Inflammation—chronic and active
- Spinal cord lesions—many
- Endogenous repair—poor
- Axons and synapses—extensive loss
- Treatment—delayed
- Frequent early relapses and incomplete recovery from relapses

**Low risk** → progression → **high risk**

**Figure 1.** Risk factors, modifiers, and disease course.
Disease Patterns

Four clinical types of MS have been described:

1. Relapsing-remitting MS
2. Secondary progressive MS
3. Primary progressive MS
4. Clinically isolated syndrome

Relapsing-remitting MS (Fig. 2A) is characterized by discrete clinically symptomatic attacks that generally evolve over days to weeks with complete or near complete symptomatic improvement. Patients remain neurologically stable between attacks. Multiple sclerosis usually starts as relapsing disease. Secondary progressive MS (Fig. 2B) requires a history of at least one clinical relapse. This clinical relapse must be followed by at least 6–12 months of continuous disability progression that is independent of apparent clinical relapses. Primary progressive MS (Fig. 2C) is characterized by a combination of disease progression for 1 year and positive CSF or MRI findings independent of clinically symptomatic relapses. Clinically isolated syndrome (Fig. 2D) refers to a single clinical attack of CNS inflammatory demyelinating symptoms that are suggestive of MS. A clinically isolated syndrome presentation can be monofocal or multifocal. The episode should last for at least 24 hours and should occur without fever, infection, or other obvious provoking etiologies and with no clinical features of encephalopathy (30–32).

Figure 2. Clinical subtypes of multiple sclerosis: A. relapsing-remitting, B. secondary progressive, C. primary progressive, and D. clinically isolated syndrome.
Demyelinating disease might be recognized even in the absence of clinical symptoms as radiologically isolated syndrome. First termed “radiologically isolated syndrome” in 2009 (33), this condition applies to individuals who are free of clinically apparent symptoms associated with CNS demyelination but have brain MRI changes consistent with MS. Radiologically isolated syndrome appears to indicate a risk of future demyelinating events. It is increasingly recognized that MRI evidence of disease activity may portend clinical presentations.

**Physiology and Pathophysiology**

Multiple sclerosis is an autoimmune disorder in which the target antigen of immune response is located in CNS myelin with resulting inflammation and demyelination (34). Experimental autoimmune encephalomyelitis models in animals have demonstrated that autoreactive myelin-specific T lymphocytes (CD4+ or CD8+) can result in CNS inflammatory demyelination (35–37). The presence of two or more oligoclonal bands in the CSF suggests intrathecal immunoglobulin G (IgG) synthesis and is indicative of immune response in the CNS. The molecular and cellular targets of oligoclonal bands in MS have not yet been identified, although many possible candidates, such as myelin oligodendrocyte glycoprotein, have been investigated extensively. Myelin-reactive T cells in patients with MS produce cytokines more consistent with a Th1 cytokine response, whereas myelin-reactive T cells in healthy individuals are more likely to produce Th2 cytokines (38).

Structurally, the myelinated nerve fiber is an axon surrounded by a myelin sheath formed by oligodendroglia cells in the CNS. Myelinated nerve fibers conduct nerve impulses by salutatory nerve conduction. In salutatory nerve conduction, the nerve impulse jumps from one node of Ranvier to another. The conduction velocities are approximately 70 m/s in myelinated fibers compared with 1 m/s in unmyelinated fibers. Normally, sodium channels are concentrated at nodes of Ranvier where depolarization occurs, and potassium channels are located underneath the myelin sheath. In the event of demyelination, voltage-dependent potassium channels are exposed, and the resting membrane becomes hyperpolarized, which results in conduction delay or blockage. Sodium channels will redistribute from nodes to naked segments. By the time the redistribution of sodium channels occurs, large leakage of current results in failure of the nerve impulse to jump. This failure is known as “conduction block.” In early phases of MS, oligodendrocytes attempt remyelination but are unable to completely or effectively rebuild the myelin sheath. Repeated attacks may result in axonal loss (39).

**Diagnosis and Evaluation**

The disease starts as a relapsing-remitting type of MS in approximately 80% of cases. Relapsing MS does not affect life expectancy. However, due to the neurodegenerative and progressive course of the disease, patients accumulate physical and cognitive disabilities over time that result in early retirement, increased financial burden, and
slightly increased mortality. Less commonly, the disease presents as a progressive MS phenotype (14).

Symptoms at initial presentation of MS can be varied, but traditionally the most apparent symptoms include visual, motor, ambulation, and sensory problems. The most common adverse effects of MS include cognitive impairment, fatigue, depression, sleep disorders, visual problems (optic neuritis, diplopia, and nystagmus), altered speech or swallowing, weakness, incoordination, tremor, imbalance, altered motor tone and pathological reflexes (hyperreflexia and Babinski sign), and bowel and bladder dysfunction (Box 1). Uhthoff phenomenon, a worsening of neurologic symptoms caused by exposure to higher temperatures resulting in a transient conduction block, is seen in patients with MS. Lhermitte sign, an electric-like sensation that passes down the spine when flexing the neck forward with the chin moving toward the chest, also occurs in patients with MS (14) (Fig. 3, Box 1). Atypical clinical features of MS are listed in Box 2. If patients present with these atypical features, other etiologies should be considered.

**Figure 3.** Structural lesions and typical clinical manifestations in patients with multiple sclerosis.
Commonly used tests for the diagnosis of MS include neuroimaging, CSF studies, and evoked potential studies. Evoked potential studies are electric waves generated by visual, auditory, or sensory stimulation and recorded by electrodes placed on the scalp. These waves are generated at specific intervals and by specific brain regions. A delay or absence of waves helps to determine integrity and location of lesions. Magnetic resonance imaging of the brain and spine with and without contrast are performed before other neuroimaging studies.

Magnetic resonance imaging is key to the diagnosis and follow-up of patients with MS. Lesions in patients with MS are well characterized on fluid attenuated inversion recovery sequence. Fluid attenuated inversion recovery is a T2-weighted image with attenuation of CSF. Persistent hypodensity on a T1-weighted image correlates with axonal damage. Contrast enhancement on T1 sequence for MS lesions is seen in patients with acute demyelination. Lesions that are nonspecific because of edema, inflammation, gliosis, and axonal loss contribute to T2 lesion formation. Characteristic lesions of MS are ovoid, greater than 3 mm, well circumscribed, and homogenous in nature (40, 41). They are located specifically in the periventricular, juxtacortical, and infratentorial regions of the brain and in the spinal cord (Fig. 3 and Fig. 4) (42). The rate of development of apparent or new T2-hyperintense lesions commonly is used to quantify disease activity in MS. Neurodegeneration and axonal loss result in the formation and evolution of chronic or persistent T1-hypointense lesions also known as black holes, which are another measure of disease activity (43, 44). Lesions in MS patients frequently are perpendicular to the ventricular surface, correlating with perivenous demyelination (“Dawson fingers”) (45) (Fig. 4). Early in the course of MS, because of inflammation, breakdown of the blood brain barrier is detected by gadolinium enhancement in the MRI T1 sequence (46).

On electrophoresis, the CSF contains oligoclonal bands of IgG, which are present in 75–85% of MS patients (46, 47). The presence of oligoclonal bands confirms MS in patients with previous clinical suspicion. In cerebrospinal fluid, white blood cell counts greater than $0.05 \times 10^9$/L (50 cells per microliter), the presence of polymorphonuclear cells, or a protein level greater than 100 mg/dL should raise suspicion for an alternative
Multiple sclerosis demyelination affecting optic nerves and sensory nerves can be examined using visual-evoked and somatosensory-evoked potentials (48). Other tests, such as CSF analysis and the serum neurofilament light chain blood test, can reflect axonal pathologic processes in the CNS, and the level of serum neurofilament light chains has been proposed as a prognostic biomarker for MS. Patients who are experiencing relapse and have MRI activity also have higher serum levels of neurofilament light chains compared with those without disease activity (49, 50).

The diagnosis of relapsing-remitting MS is established when a patient presents with typical neurologic symptoms or manifestations that are discrete episodes disseminated in time and space and other explanations or diagnoses are not identified. In 2001, the International Panel on MS Diagnosis introduced the McDonald criteria, which are diagnostic criteria integrating MRI assessment with clinical and other paraclinical methods (46). The McDonald criteria were revised in 2005 and again in 2010 to provide guidance for rapid diagnosis with equivalent or improved specificity, sensitivity, or both. In 2017, the panel reviewed the 2010 criteria and revised them to specify the diagnosis of clinically isolated syndrome and delineate the diagnostic criteria for dissemination in time and in
Multiple Sclerosis

The criteria also emphasize the need to explore, identify, and exclude alternative explanations for the clinical presentation. Unlike the 2010 criteria, the 2017 criteria do not discriminate between symptomatic and asymptomatic MRI lesions (6). Primary progressive MS can be diagnosed based on the criteria in Box 3.

Relapse, flare, or exacerbation is defined as a monophasic clinical episode with patient-reported symptoms and objective findings typical of MS, reflecting a focal or multifocal inflammatory demyelinating event in the CNS, developing acutely or subacutely, having a duration of at least 24 hours, with or without recovery, and occurring without infection or fever (6).

### Table 1. The 2017 McDonald Criteria for Diagnosis of Multiple Sclerosis in Patients With an Attack at Onset

<table>
<thead>
<tr>
<th>Number of Clinical Attacks</th>
<th>Number of Lesions With Objective Clinical Evidence</th>
<th>Additional Data Needed for Diagnosis of Multiple Sclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>More than two</td>
<td>More than two</td>
<td>None</td>
</tr>
<tr>
<td>More than two</td>
<td>One (additional clear evidence of previous attack involving a lesion in a distinct anatomical location)</td>
<td>None</td>
</tr>
<tr>
<td>More than two</td>
<td>One</td>
<td>Dissemination in space* demonstrated by an additional clinical attack implicating a different CNS site or by MRI and dissemination in time† by an additional clinical attack implementing a different CNS site or by MRI or demonstration of cerebrospinal fluid-specific oligoclonal bands‡</td>
</tr>
<tr>
<td>One</td>
<td>One</td>
<td>Dissemination in space* demonstrated by an additional clinical attack implicating a different CNS site or by MRI or demonstration of cerebrospinal fluid-specific oligoclonal bands‡</td>
</tr>
</tbody>
</table>

*Dissemination in space can be demonstrated by one or more T2-hyperintense lesions that are characteristic of multiple sclerosis in two or more of four areas of CNS: 1) periventricular, 2) cortical or juxtacortical, 3) infratentorial brain regions, and 4) the spinal cord. In individuals older than 50 years or those with vascular risk factors, it might be prudent to seek a higher number of periventricular lesions.

†Dissemination in time can be demonstrated by the simultaneous presence of gadolinium-enhancing lesions and nonenhancing lesions at any time or by a new T2-hyperintense or gadolinium-enhancing lesion on follow-up MRI, with reference to a baseline scan, irrespective of the timing of baseline MRI.

‡Presence of cerebrospinal fluid-specific oligoclonal bands does not demonstrate dissemination in time but can substitute for the requirement for demonstration of this measure.

Abbreviations: CNS, central nervous system; MRI, magnetic resonance imaging.

Neuromyelitis Optica Spectrum Disorder

Neuromyelitis optica spectrum disorder is a rare autoimmune disease that affects the optic nerves and spinal cord. It represents a distinct clinical and pathophysiologic entity from MS. Aquaporin 4, a plasma membrane water-transporting protein, is present on astrocyte foot processes. Antibody to aquaporin 4 receptor is pathogenic and expressed in the optic nerves, brainstem, and spinal cord. Neuromyelitis optica spectrum disorder is associated with significant morbidity. Worldwide mortality rates range from 9% to 23% (51). Core clinical characteristics include the following six conditions:

1. Optic neuritis, which typically presents as a sudden, severe bilateral visual impairment frequently with chiasmal involvement with a poor recovery even with prompt intervention
2. Acute myelitis, which has longitudinally extensive involvement of the spinal cord (eg, at least three contiguous segments) and often results in complete spinal cord syndrome and sphincter involvement (compared with partial syndrome in MS)
3. Area postrema syndrome, which presents with intractable hiccups, nausea, and vomiting, and usually responds well to treatment with corticosteroids (compared with optic neuritis)
4. Acute brainstem syndrome
5. Symptomatic narcolepsy or acute diencephalic syndrome
6. Symptomatic cerebral syndrome

For the diagnosis of primary progressive multiple sclerosis, 1 year of disease progression (retrospectively or prospectively determined) plus two of the three following criteria are necessary:

1. Evidence of dissemination in space in the brain based on greater than one T2 lesion in at least one area characteristic for multiple sclerosis (ie, periventricular, juxtacortical, or infratentorial)
2. Evidence of dissemination in space in the spinal cord based on greater than two T2 lesions in the spinal cord
3. A positive finding in the cerebrospinal fluid (ie, isoelectric-focusing evidence of oligoclonal bands, increased immunoglobulin G index, or both)

If an individual has brainstem or spinal cord syndrome, all symptomatic lesions are excluded from the criteria.

**Aggressive Multiple Sclerosis**

A uniform definition of aggressive multiple sclerosis does not exist, but the condition is characterized by repeated severe attacks, early disability, highly active lesions on MRI, and failure of conventional treatment to control disease. According to a 2013 study from British Columbia, an aggressive MS diagnosis can be established based on Expanded Disability Status Scale, duration of the disease, and progression of the disease (52, 53). Patients with aggressive MS require an aggressive approach to treatment (54). Characteristics typically associated with a poor prognosis or severe course include male gender, African American race, older age at onset (older than 40 years), motor symptoms or ataxia at onset, incomplete recovery from relapses, frequent early relapses (more than two relapses in the first 2 years) and brainstem or spinal cord lesion at onset (Fig. 1).

**The Marburg Type Multiple Sclerosis**

The Marburg type MS has a rapidly progressive disease course from the onset. Typically, it is a monophasic illness and results in death within a short period (55).

**Tumefactive Multiple Sclerosis**

Tumefactive MS is characterized by atypical radiologic findings, including lesions larger than 2 cm with a mass effect, edema, and ring enhancement (Fig. 4). Patients present with a variety of symptoms, including motor, cognitive, sensory, cerebellar, and brainstem symptoms (56). Differential diagnoses include brain neoplasm and cerebral abscess. Brain biopsy is warranted in patients with suspicious lesions.

**Schilder Disease**

Schilder disease usually occurs in childhood but also can affect adults. Imaging studies reveal one or two roughly symmetrical plaques larger than 2 cm, and pathologic analysis reveals subacute or chronic myelinoclastic diffuse sclerosis in the absence of other etiologies (57).

**Differential Diagnosis**

Other etiologies of neurologic diseases must be evaluated before confirming a diagnosis of MS. Even if patients with an established diagnosis of MS develop progressive worsening, further evaluation is warranted to exclude superimposed conditions, such as vitamin deficiency, cervical stenosis, myelopathy, or leukencephalopathy. Important conditions to consider are listed in Box 4. Many clinical, MRI, and serologic findings can resemble symptoms of relapsing-remitting MS.
Structural Causes
- Cervical stenosis (e.g., disc herniation, stenosis, or ossification of posterior longitudinal ligament)
- Cerebral or spinal cord tumor (e.g., intramedullary, intradural, or extradural)
- Vascular malformation, such as dural arteriovenous fistula, or arteriovenous malformation
- Ischemic cerebrovascular disease (e.g., small vessel disease or ischemic optic neuropathy)

Infectious Causes
- Human immunodeficiency virus
- Lyme disease
- Neurosyphilis
- Human T cell lymphotropic virus type 1
- Progressive multifocal leukoencephalopathy

Nutritional Causes
- Vitamin B₁₂ deficiency
- Vitamin E deficiency
- Copper deficiency

Rheumatologic and Autoimmune Causes
- Neurosarcoidosis
- Systemic lupus erythematosus
- Neurologic involvement in patients with Behçet syndrome
- Leukodystrophies and leukoencephalopathies
- Acute disseminated encephalomyelitis
- Mitochondrial encephalopathy with lactic acidosis and stroke
- Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids
- Sjögren syndrome
- Antiphospholipid syndrome
- Vasculitis (Wegener granulomatosis)

Other Causes
- Primary lateral sclerosis
- Paraneoplastic myelopathy
- Hereditary spastic paraparesis
Management

Disease-Modifying Therapies

Disease-modifying therapies that were approved by the FDA for use in patients with MS are listed in Box 5. Daclizumab was initially approved for the treatment of relapsing-remitting MS but was removed from the market in March 2018 because of reports of liver toxicity, CNS inflammation, and death. Siponimod and cladribine are the most recently approved oral MS disease-modifying therapies. Siponimod, in addition to treating clinically isolated syndrome and relapsing-remitting disease, is the first oral disease-modifying therapy approved for the treatment of active secondary progressive disease. Cladribine is used to treat relapsing forms of MS including relapsing-remitting disease and active secondary progressive disease in adults. It is not recommended for use in individuals with clinically isolated syndrome of MS. Each medication offers different efficacy, tolerability, and adverse effect profiles. Careful consideration is required when choosing the correct treatment. Health care providers must weigh the adverse effects against the benefits of the treatment and choose individualized MS medication as clinically appropriate. Education about the risks and benefits of the initiation and continuation of disease-modifying therapy in women with MS before pregnancy and in those who become pregnant is important. For most disease-modifying therapies, limited safety information is available regarding use during prepregnancy and pregnancy. The mechanisms of action, recommended timelines for the last dose of medication before pregnancy, teratogenicity and

Box 5. Disease-Modifying Therapies for Patients With Multiple Sclerosis

- Injectables
  - Interferon β-1a
  - Interferon β-1b
  - Peginterferon β-1a
  - Glatiramer acetate
- Oral medications
  - Fingolimod
  - Dimethyl fumarate
  - Teriflunomide
  - Siponimod
  - Cladribine
- Infusions
  - Natalizumab
  - Alemtuzumab
  - Ocrelizumab
  - Mitoxantrone
embryo-lethality profiles, and adverse effects of these disease-modifying therapies are listed in Table 2.

There are three approaches to initiating disease-modifying therapy:

1. The tried and true approach: injection therapy with interferon β-1a, interferon β-1b, and glatiramer acetate
2. The convenient approach: oral therapy with fingolimod, dimethyl fumarate, and teriflunomide
3. The efficacy approach: infusion therapy with natalizumab and ocrelizumab

In April 2018, the American Academy of Neurology issued a new guideline for initiating, switching, and stopping disease-modifying therapies for the treatment of patients with MS (58). Included are the following four Level A recommendations for clinicians:

1. Discuss treatment preferences in terms of safety, route of administration, lifestyle, cost, efficacy, common adverse effects, and tolerability
2. Engage in an ongoing dialogue regarding treatment decisions throughout the disease course
3. Counsel patients with MS who use disease-modifying treatments to notify the clinician of new or worsening symptoms
4. Counsel individuals with MS considering natalizumab discontinuation and regarding the increased risk of relapse or MRI-detected disease activity within 6 months of discontinuation.

Switching disease-modifying therapies should be considered after patients experience one or more relapses, two or more new brain lesions, or increased disability during a 1-year disease-modifying therapy treatment period (Level B recommendation).

**CASE NO. 1.** A 34-year-old Caucasian patient without significant past medical history presents with tingling and numbness, weakness, and visual disturbance. The patient was born and lived in Canada and moved to Texas in her 20s. Her mother has primary progressive MS. Two weeks before her clinic visit, the patient developed left upper extremity numbness, tingling, and weakness, which resolved in 2 days; however, she then developed right hemibody numbness and tingling with left eye pain and blurry vision. On physical examination, she has decreased visual acuity in her left eye (20/200) and afferent pupillary defect. She also has brisk deep-tendon reflex and positive Hoffman sign in the left eye. Her vitamin D (25-OH-D) level is 70 nmol/L (28 ng/mL). Cerebrospinal fluid reveals increased IgG index and prominent oligoclonal IgG bands. Cerebrospinal fluid white blood cell count is $0.02 \times 10^9/L (20 \text{ cells per microliter}) (90\% \text{ lymphocyte predominance})$, and a workup for infectious causes yields negative results. Brain MRI shows more than 30 foci of hyperintense T2/FLAIR signal within the deep white matter, in the corpus callosum, and along the ventricular surface oriented perpendicular to the orientation of the lateral ventricles (**Fig. 5A**). Two areas of white matter hyperintensity were visualized on contrast enhancement. Magnetic resonance imaging also shows contrast enhancement within the left aspect of the optic chiasm extending into the intraconal portion of the left optic nerve (**Fig. 5B**). Her cervical spine MRI reveals linear T2 hyperintense, mildly
expansile signals in the left ventral cord spanning the C5–C6 spinal segments with associated patchy enhancement (Fig. 5C). She is treated with intravenous methylprednisolone, 1,000 mg/d, for 5 days for the acute attack. A diagnosis of MS is established, and the patient is prescribed subcutaneous glatiramer acetate, 40 mg/mL, three times a week. After starting glatiramer acetate, she has been doing well without clinical relapse, and her brain MRI and cervical spine MRI show decreased lesions 2 years after initiating treatment (Fig. 5D, Fig. 5E, and Fig. 5F).

This case illustrates the risk factors and clinical presentations of MS and importance of early diagnosis and treatment of the disease in women. This patient has several risk factors that include migration from Canada (a high prevalence area) to a low prevalence area in adulthood (therefore, she will not adopt the low risk in the new location), a suboptimal vitamin D level, and a family history of MS. She presented with typical symptoms of MS, such as blurry vision, tingling and numbness, and weakness. Multiple sclerosis was diagnosed at her first clinic presentation based on revised 2017 McDonald diagnostic criteria (dissemination in space: periventricular, cortex, cervical spine; and dissemination in time: contrast-enhanced lesions and presence of oligoclonal bands in the cerebrospinal fluid) (Table 1). Based on the safety and efficacy profile and her reproductive status, she is treated with glatiramer acetate, which she tolerates well, and neuroimaging surveillance after 2 years shows improvement of the MS lesions in the brain and spine (Fig. 5D, Fig. 5E, and Fig. 5F).

Figure 5. Brain and cervical spine affected by multiple sclerosis. Magnetic resonance imaging results before treatment (A, B, and C) and 2 years after treatment (D, E, and F).

**Treatment of Acute Relapse**

*Attacks* in MS are defined as episodes of focal neurologic disturbances lasting longer than 24 hours with a preceding period of clinical stability of at least 30 days and without an alternate explanation, such as infection or fever. Treatment has no effect on the long-term
prognosis of MS; therefore, the aim of relapse treatment is to accelerate recovery of the clinical symptoms. The recommended initial approach for an acute MS exacerbation is systemic corticosteroids (59). The current treatment of choice is methylprednisolone 1 g/d for 3–7 days (60). In a 2012 study, the route of administration—whether oral or intravenous—did not demonstrate significant differences in clinical, imaging, or pharmacologic outcomes (61). Likewise, a 2015 landmark study demonstrated that oral methylprednisolone (500 mg/d for 5 days) was not inferior to intravenous methylprednisolone (1,000 mg/day for 3 days) (62). The second-line treatment for patients with acute MS relapse who have a poor response to high-dose corticosteroids is plasma exchange (63). Patients with relapsing-remitting MS who have current disease activity manifested by clinical symptoms or MRI lesions should be offered disease-modifying therapy as discussed at the end of the section “Disease-Modifying Therapies.”

**Symptom Management**

Symptoms in MS can evolve over time and must be evaluated and addressed on a routine basis. The treatment of MS symptoms is important because they can adversely affect quality of life, the ability to perform or complete daily activities, and independence. Multiple sclerosis often causes a clustering and magnification of symptoms (symptoms reinforce one another). A multifactorial approach for symptom management should be considered (Table 3).

**Fatigue**

Fatigue is the most common symptom of MS and often occurs before the diagnosis. It can be caused by psychosocial factors, cognitive impairment, mood changes, poor sleep, disordered breathing, or other physical factors. Fatigue can be primary or secondary. Primary fatigue worsens with heat but may not be associated with precipitating activities. Patients with primary fatigue can be treated with pharmacologic agents, such as CNS stimulants, amantadine, modafinil, armodafinil, and nonpharmacologic measures, such as environment modification and exercise. Secondary fatigue is due to other comorbidities (ie, anemia or thyroid disease), mood or sleep disorders, or adverse effects of medication use. Sleep disorders are common in patients with MS. Secondary fatigue is managed by controlling the associated comorbidities.

**Sensory Problems**

Sensory problems can be positive (ie, pain and paresthesia) or negative (ie, numbness or loss of sensation). Pain associated with MS can be classified as acute neuropathic pain (trigeminal and glossopharyngeal neuralgia, Lhermitte sign, and dysesthesias), chronic pain (bilateral constant burning pain), acute inflammatory pain (optic neuritis), or a secondary pain syndrome (bladder spasm, spasticity, and musculoskeletal pain). Trigeminal neuralgia or other types of neuralgia are controlled with neuropathic pain medications, such as carbamazepine, oxcarbazepine, lamotrigine, and gabapentin. Surgical intervention, such as a gasserian ganglion block, gamma knife surgery, or microvascular decom
pression, can be considered for cases that do not respond to traditional management. Chronic pain syndrome also can be managed with neuropathic pain medications, such as tricyclic antidepressants, antiepileptic medication, and serotonin norepinephrine reuptake inhibitors, and nonpharmacologic interventions, such as biofeedback, nerve stimulation, and relaxation techniques.

**Cognitive Deficits**

Cognitive deficits occur in patients with any type of MS but are most notable in those with secondary progressive MS. Cognitive deficits are seen mainly in the domains of information processing speed; working, verbal, or visual memory; and executive functioning. Treatment of other comorbidities, such as mood disorders and sleep disturbance, should be considered. Neuropsychologic testing should be performed to evaluate for the presence, type, and degree of cognitive impairment and change over time. Preventive measures to reduce cognitive deficits may include the use of effective MS disease-modifying therapies, medications for attention problems, cognitive remediation therapy, adaptive strategies, health and wellness maintenance, and control of vascular risk factors. Choline esterase inhibitors and N-methyl-d-aspartate receptor antagonists have been used with success in some studies. However, there are no proven therapies to prevent cognitive impairment related to MS (64).

**Mood Changes**

Depression is the most prevalent mood disorder seen in MS patients. It has been reported that patients with MS have two or three times the rate of depression of the general population, and that suicide is twice as common (65). Anxiety is the second most common mood disorder reported in patients with MS, but apathy, impulse control disorders, emotional lability, and other mood disorders also are noted to occur. Depression can be reactive because of structural injury to the hypothalamic–pituitary–adrenal axis or can be related to adverse effects of medications. Mood disorders are managed with antidepressants and antipsychotics along with nonpharmacologic interventions, such as psychotherapy, exercise, and transcranial magnetic stimulation.

**Bladder Dysfunction**

Three types of neurogenic bladder dysfunction are seen in patients with MS: 1) detrusor muscle overactivity with suprapontine or spinal cord lesions (most common), 2) detrusor muscle dyssynergia with suprasacral cord lesions, and 3) detrusor muscle hypoactivity with sacral cord or conus lesions or disruption of the descending bulbospinal pathways. Bladder dysfunction has a negative effect on quality of life and causes social isolation. Also, it increases the risk of kidney infections. Pharmacologic treatment for detrusor hyperactivity includes antimuscarinic agents, intranasal desmopressin, β3-receptor agonist, and onabotulinumtoxinA. Sacral nerve modulation and posterior tibial nerve stimulation can be considered in refractory cases. Detrusor muscle dyssynergia is managed with α1-adrenergic receptor antagonists and antispasticity agents. Detrusor muscle
hypoactivity is managed by indwelling or intermittent scheduled catheterization. Potential adverse medication profiles must be reviewed in patients with bladder dysfunction (66). Health care providers should educate patients regarding bladder training, which includes scheduled or planned voiding, the Credé maneuver or abdominal vibration, and pelvic floor or Kegel exercises.

**Bowel Dysfunction**

Neurogenic bowel dysfunction in patients with MS may result from upper and lower motor neuron impairment and can be divided into disorders of storage and disorders of elimination. Constipation is seen more commonly than fecal urgency or fecal incontinence (67). Management of constipation includes a high-fiber diet, hydration, exercise, mobilization, and the use of laxatives. Increasing the amount of fiber in the patient’s diet can help in the management of fecal incontinence.

**Spasticity**

Spasticity is an increase in muscle tone that is velocity dependent. Spasticity results from disruption of supranuclear pathways controlling the spinal inhibitory interneurons. Fixed spasticity results in contractures, and intermittent spasticity results in spasms. Mild spasticity is sometimes beneficial because it provides support to antigravity muscles. Spasticity causes pain, bowel and bladder dysfunction, sleep disturbance, impaired ambulation, and pressure ulcers. Management of spasticity includes use of pharmacologic and nonpharmacologic interventions and the control of triggers. Pharmacologic treatments include the use of oral or intrathecal baclofen, tizanidine, benzodiazepines, gabapentin, dantrolene, naltrexone, and onabotulinumtoxinA. Nonpharmacologic interventions, such as stretching exercises, bracing, physical therapy, cryotherapy, hydrotherapy, and transcutaneous electrical stimulation, also play a major role in the management of spasticity.

**Heat Intolerance**

Heat and humidity worsen MS symptoms. Transient conduction block is seen in Uhthoff phenomenon. Environmental cooling with fans and air conditioning helps to reduce heat intolerance. Use of cold drinks, ice packs, and lightweight clothing also is helpful.

**Sleep Disturbance**

A variety of sleep disorders has been reported in individuals with MS, including obstructive sleep apnea, restless leg syndrome, rapid-eye-movement sleep behavioral disorder, narcolepsy, and periodic limb movement disorder. Sleep plays an important role in memory consolidation and normal brain function. Impaired sleep results in poor memory, poor performance, and increased stress. Consultation with a sleep expert is helpful to establish an accurate diagnosis and management of sleep disorders. Use of melatonin, improved sleep hygiene, treatment of coexisting mood disorders, avoidance of stimulants, and regular exercise can help manage sleep disturbance.
Gait Impairment

Gait impairment in patients with MS usually is multifactorial. Cerebellar involvement results in ataxia. Sensory deficits, motor deficits, spasticity, fatigue, and medication adverse reactions can result in gait impairment. Dalfampridine is the only medication indicated to improve walking in patients with MS. Other treatment options currently are being developed or undergoing clinical trials (68). Regular exercise, physical therapy, balance training, management of spasticity, and use of appropriate assistive devices help improve gait.

Visual Changes

Visual changes in patients with MS include blurred vision, diminished acuity, decreased color perception, vision loss, and double vision. Optic neuritis and internuclear ophthalmoplegia commonly are seen in patients with MS. Nystagmus and skew deviations also can manifest with cerebellar or brainstem involvement. Ophthalmologic consultation can be considered for the management of diplopia or errors of refraction.

Tremor

Tremor can be classified as postural, rest, or action. It can affect the patient’s head, voice, trunk, or limbs. Tremor may be seen with cerebellar or brainstem involvement and is difficult to manage with medications. Trials of propranolol and clonazepam can be considered. The use of wrist weights or tremor “spoons” or “forks” also can be helpful.

Vertigo

Vertigo usually occurs with brainstem involvement. It may display characteristics of central vertigo and other brainstem findings, such as trigeminal or facial nerve involvement. Antihistamines and anticholinergics alleviate symptoms. Vestibular rehabilitation and balance training are helpful.

Speech, Swallow, and Respiratory Dysfunction

Speech, swallow, and respiratory dysfunction can be seen with brainstem involvement or facial nerve weakness. Spinal cord involvement can cause respiratory impairment. Speech and swallow therapy, physical therapy, and aspiration precautions are useful in the management of speech and swallow dysfunction. Respiratory dysfunction is managed with invasive and noninvasive respiratory support, chest percussion, and with treatment of associated medical conditions, such as pneumonia.

Sexual Dysfunction

Sexual dysfunction is common in women with MS. Women note decreased orgasmic response and vaginal lubrication, low sexual desire, and impaired genital sensation. Intercourse can be difficult or even painful with associated adductor spasm and incontinence.
Lubricants can be used for vaginal dryness. Management of coexisting bowel and bladder dysfunctions, spasticity, and mood disorders can help alleviate sexual dysfunction symptoms.

**Nonpharmacologic Treatment**

Patients with MS may benefit from comprehensive care delivered by a multidisciplinary team. Neuropsychologic therapy can be helpful with adaptive strategies and coping skills targeting cognitive problems. Social work or care management intervention can identify the psychosocial effects of the disease on patients and implement strategies to reduce adverse effects. Occupational therapy can improve upper extremity fine motor skills, cognition, and energy conservation. Physical therapy can strengthen muscles and improve gait and balance. Orthotics may further improve gait and balance. Speech and swallow therapy can improve speech, language, and communication and help patients avoid aspiration.

Obesity or high body mass index is a risk factor for pediatric-onset and adult-onset MS (69) and often is a result of a sedentary lifestyle and unhealthy diet. High sodium intake is associated with higher relapse rates and increased MRI lesions (70). Because vitamin D deficiency is associated with MS activity and progression, levels should be checked annually, and supplements should be used to maintain serum levels above 60 ng/mL (71). Dietary counseling can provide guidance to maintain a healthy nutritional intake. A healthy diet facilitates slower cognitive decline (72). Exercise improves muscle strength, mobility, spasticity, fatigue, depression, cognition, and quality of life (73, 74). Both aerobic and resistance training are beneficial. Patients should be encouraged to participate in a regular exercise program on several days a week.

Tobacco use leads to increased cognitive impairment and mortality. Smoking cessation should be discussed with all MS patients (75, 76).

Psychological stress affects MS activity (77). Relaxation and mindfulness therapy are beneficial for patients with MS. Patients who are mentally active demonstrate better cognitive function and less brain atrophy than those who are not (78). Participating in hobbies, such as reading, writing, art, playing music, and playing games can alleviate symptoms in MS patients.

Education is important to reinforce concepts of care, including ongoing monitoring, evaluation for disease relapse, and addressing any new symptoms. Adherence to treatment plans also must be reinforced.

**Future Treatment**

The goal of future therapies for MS is not only to treat symptoms and disease activity, but also to offer a path to regenerate myelin and preserve axon integrity, which could eventually restore neuronal function. Currently, stem cell therapy appears promising in
experimental MS animal models. Other therapies under investigation include monoclonal antibodies that may provide targeted remyelination. Ongoing MS clinical trials and information on how to participate in these trials are listed at www.clinicaltrials.gov.

Approximately 30% of patients with MS use complementary and alternative medicine (CAM). The three most frequently used types of CAM for MS patients are 1) chiropractic adjustment, 2) massage, and 3) acupuncture (79). No high-quality clinical trials provide evidence that CAM therapies can modify disease progression or eliminate all MS symptoms. Therefore, MS should not be managed initially or exclusively with CAM. However, it is reasonable to use CAM in some circumstances as an adjunct for symptom relief. In March 2014, the American Academy of Neurology published a comprehensive literature review and evidence-based practice guidelines for CAM use in patients with MS (80, 81). Level A and Level B recommendations are highlighted in Box 6. Additionally, there are several Level C recommendations regarding the effectiveness of the following therapies:

- Gingko biloba is possibly effective for fatigue.
- Reflexology is possibly effective for MS-related paresthesias.
- The Cari Loder regimen is possibly ineffective for MS-related disability, symptoms, depression, and fatigue.
- Bee sting therapy is possibly ineffective for MS relapses, disability, fatigue, MRI outcomes, and health-related quality of life.

Reproductive Concerns

Contraception, infertility treatment, pregnancy, and breastfeeding can produce hormonal changes in women with MS that can affect both the course of the disease (eg, relapse rate) and the severity of symptoms. It is largely unknown whether there are significant differences in gene expression that may contribute to pathogenesis of MS during pregnancy and other reproductive stages.

Prepregnancy Consultation

For all reproductive-aged women with MS, counseling regarding disease-modifying therapy safety and disease activity during pregnancy, delivery, postpartum care, and breastfeeding should be discussed. Information should be provided to allow patients to participate in an informed decision-making process to improve satisfaction and care outcomes.
Pregnancy does not increase the risk of developing MS or appear to affect the type or severity of MS exacerbation. Studies have reported a decrease in MS relapse rate during pregnancy and an increase in relapse rate during the first 3 months postpartum (82, 83). Stress, exhaustion, infection, and the loss of antenatal immunosuppression may account...
for the increased relapse rate during the first 3 months of the postpartum period. The
long-term disability or disease progression caused by MS is not altered by pregnancy.

Current literature does not provide a consensus regarding the effect of MS on preg-
nancy. In some reports, MS in pregnant women has been associated with a higher risk of
cesarean birth and lower infant birth weight compared with women without MS (84). Other
studies show a typical birth weight to be equal to that in the general population (85, 86).
In a large national database study of pregnancy outcomes in women with MS, rates of
intrauterine growth restriction and cesarean birth were only marginally higher than
in the general obstetric population, without increases in other adverse outcomes (87).
The offspring of MS patients are at higher risk of developing MS compared with the
general population (ranging from 2% to 5% higher than the 0.1–0.2% risk in the general
population) (88, 89). Some literature also indicates that pregnant women with MS had
increased rates of induction of labor and operative interventions during delivery (90).
Epidural anesthesia has been used safely in patients with MS during labor and cesarean
birth (91).

All disease-modifying therapies have potential adverse effects on fertility and preg-
nancy outcomes, but the level of risk varies among agents. Generally, the use of disease-
modifying therapies in patients with MS should be avoided in pregnancy. If first-trimester
exposure to MS disease-modifying therapy has occurred, detailed ultrasonography with
fetal echocardiography may be indicated.

The importance of effective contraception should be addressed in women of childbear-
ing age with MS. Long-acting reversible contraception methods (eg, intrauterine devices)
are reliable and effective for MS patients (92). Contraception is recommended if a male
partner is taking teriflunomide because it is detectable in human semen, and it is unclear
whether this affects fertility or fetal development. Further details regarding contraception
in patients with MS are provided in the section “Contraception.”

Cessation of disease-modifying therapies before pregnancy should be considered unless
the benefits outweigh the risks (58). Oral medications, such as teriflunomide, dimethyl
fumarate, and fingolimod, are contraindicated for use before and during pregnancy (58,
93, 94). A washout period is recommended for certain disease-modifying therapies, but
several observational studies and registry data suggest that interferon β and glatiramer
acetate can be used before pregnancy and can be continued during pregnancy to reduce
the risk of relapse (93, 95–97). Of note, glatiramer acetate is the only pregnancy category B
medication. Animal studies of glatiramer acetate have failed to demonstrate fetal risk.

Disease-modifying therapy generally is not started in newly diagnosed patients with
mild MS if they are planning pregnancy within the next year, because these therapies
take weeks to months to take full effect (Table 2). However, in patients with severe MS,
disease-modifying therapy can be started to control or stabilize disease activity before
pregnancy. The B-cell depletion agent ocrelizumab can be used in these patients before
pregnancy, but infusion should be discontinued during pregnancy. Teriflunomide is known to cause teratogenic effects. Women actively treated with teriflunomide who wish to become pregnant can be treated with a rapid elimination using oral cholestyramine to decrease the blood level of teriflunomide to less than 0.02 micrograms per milliliter (93). Long-acting monoclonal antibodies, such as ocrelizumab, provide sustained disease control even after treatment. For MS patients who are currently well-controlled with fingolimod or natalizumab and desire pregnancy, consider a switch to ocrelizumab before stopping birth control to prevent rebound disease activity and minimize risk to the developing fetus (98, 99). Management of pregnant women with MS should involve a multidisciplinary team approach consisting of maternal–fetal medicine subspecialists, neurologists, and anesthesiologists. Furthermore, these patients should give birth in a tertiary medical center. Antenatal surveillance should be considered on an individual basis.

**CASE NO. 2.** A 27-year-old woman with a diagnosis of MS who is not being treated with disease-modifying therapy presents for consultation about becoming pregnant, pregnancy, and family planning. Her symptoms, including isolated facial weakness, began 1.5 years before this visit. Magnetic resonance imaging of the brain and cervical spine showed MS lesions, and the cerebrospinal fluid test yielded positive results for oligoclonal banding. Based on these findings, the diagnosis of MS was established. Because of financial issues and incomplete insurance coverage, she was unable to continue care and has not been treated. Since the diagnosis, the patient has had fatigue and intermittent burning pain in her hands and feet. A neurologic examination yielded normal results. Repeat MRI of the brain and cervical spine again demonstrates lesions, but no contrast-enhancing lesions or new lesions are evident since the previous imaging. The patient has three children, anticipates having additional children, and recently had her contraceptive implant removed by her obstetrician–gynecologist. Disease-modifying therapy risks and benefits during fertilization and pregnancy are discussed, and by mutual agreement, treatment initiation is deferred.

In many patients, MS is adequately controlled without treatment or with only modestly effective disease-modifying therapy. This patient has not been treated with a disease-modifying therapy, and she has not had a clinical relapse since she received the diagnosis 1.5 years ago. The recent neuroimaging did not show active contrast-enhancing lesions or new lesions. Therefore, considering her young age at onset, mild symptoms and anatomic involvement, and stable neuroimaging test result, she is at low risk of disease progression (Fig. 1). Because she is attempting pregnancy and had her contraceptive implant removed, the best management approach is to defer treatment and monitor the course of the disease closely during pregnancy.

**Contraception**

Studies exist with positive and negative outcomes regarding the effects of combined oral contraceptives (OCs) on MS activity. A meta-analysis suggested neither a protective nor a negative effect of combined OCs (100). However, it also has been reported that low doses
of estrogen associated with combined OCs may have protective effects against developing MS (101), may delay the onset of symptoms (102), and may slow the progression of MS (103). Studies have found the incidence of MS to be decreased with use of combined OCs (101, 104). Some studies have demonstrated that patients who used OCs had less physical disability (103, 105). Currently, no data link negative interactions between combined OCs and disease-modifying therapies, and one study has suggested that use of combined OCs with interferon β-1a reduced annualized relapse rates and diminished MRI activity in relapsing-remitting MS (106). There are limited data to determine whether intrauterine contraceptive devices or implants affect MS-related disease exacerbation or activity. Most contraceptive methods appear to be safe for women with MS.

Disease-modifying therapies do not appear to decrease the effectiveness of hormonal contraception, although formal drug–drug interaction studies are limited. For women with MS taking potentially teratogenic medications, long-acting reversible contraceptive methods (eg, intrauterine devices or implants) may be the best option (107). Some medications commonly used to treat MS symptoms (eg, gabapentin or benzodiazepines) do not alter the efficacy of combined OCs (108); however, it is postulated that modafinil used for treatment of fatigue in women with MS might reduce the efficacy of combined OCs (109). Teriflunomide can interact with combined OCs to increase estrogen levels (110).

**CASE NO. 3.** A 23-year-old woman with MS has concerns and questions about disease management and contraceptive use. She has been using disease-modifying therapy for MS and combined OCs. Her initial MS symptoms were diplopia and arm weakness that occurred 1 year before this visit. Magnetic resonance imaging of the brain demonstrates brainstem lesions, and her cerebrospinal fluid analysis is positive for oligoclonal bands. The disease is well controlled with oral dimethyl fumarate. She has no plans for pregnancy in the near future but is concerned that the combined OC she uses may affect the disease course, disease progression, or efficacy of her MS treatment and that the dimethyl fumarate will affect the efficacy of her OC.

The patient is reassured that combined OC use does not appear to be associated with an increased risk of relapse in women with newly diagnosed MS (111). Moreover, combined OC use does not increase the risk of either developing MS or an MS relapse (92, 112–115). Studies of fingolimod and dimethyl fumarate in MS patients have found no evidence that combined OCs reduce the efficacy of these agents (116, 117). No data confirm or refute that combined OCs decrease efficacy of dimethyl fumarate. This patient is advised to continue dimethyl fumarate and combined OCs and stop dimethyl fumarate when she discontinues contraception.

**Assisted Reproductive Technology**

Patients with MS have increased rates of sexual dysfunction (118), endocrine abnormalities, and endometriosis (119). Women with MS generally do not have more difficulty becoming pregnant compared with healthy women (120). However, MS may be associated
with a higher frequency of childlessness (22% in the MS population versus 13% in the healthy population). There is no difference in the reported rates of infertility and miscarriage, although elective abortions are more frequent in patients with MS (20% in the MS population versus 12% in the healthy population) (121). According to one study, patients with MS may have low levels of antimüllerian hormone (122), but other studies have shown normal antimüllerian hormone levels in MS patients with low disease activity (annualized relapse rate lower than 0.5) (123). Data do not indicate that women with MS seek assisted reproductive technology (ART) more than women in control groups (82). However, disease activity is increased in patients receiving gonadotropin-releasing hormone (GnRH) agonists and recombinant follicle-stimulating hormone (124). The rate of relapse increases with unsuccessful ART cycles (125) and with the use of a GnRH agonist (126, 127). Therefore, GnRH agonists should be avoided in patients with relapsing-remitting MS undergoing infertility treatment with ART. It is unclear whether the exogenously administered hormones (eg, GnRH agonist, follicle-stimulating hormone, or progesterone), or the rapid changes in reproductive hormone levels in women undergoing ART, or both, are responsible for the increased disease activity for MS patients undergoing ART therapy.

**Acute Relapse During Pregnancy**

Frequency of relapses decreases during pregnancy, and the treatment approach often should be more conservative. Pseudorelapse during pregnancy due to infection, fever, or other coexisting medical conditions should be considered when a pregnant woman with MS has worsening symptoms. For example, during pregnancy, symptomatic or asymptomatic urinary tract infections in a patient with MS can present with increased neurologic symptoms. It is important to perform screening for a urinary tract infection and treat the infection even if the patient is asymptomatic. Magnetic resonance imaging studies often are not required to determine management of relapse. However, if needed, MRI without the contrast agent gadolinium is considered safe during pregnancy (128). Magnetic resonance imaging with gadolinium should be avoided due to teratogenic effects reported in animal studies (129). Gadolinium crosses the placenta immediately in primates, but the clinical significance of this in women is uncertain (130). Less than 0.1% of gadolinium enters breast milk, but suspension of breastfeeding for 24 hours is recommended (Box 7) (131).

Use of corticosteroids during the first trimester should be avoided if possible because of an increased risk of cleft palate (132). Prednisone, prednisolone, or methylprednisolone is considered safe during the second trimester and third trimester because minimal amounts cross the placenta, although there is an increased risk of preterm labor and low birth weight (133). Minimal amounts of corticosteroids transfer to breast milk, but it is recommended to pump and discard milk for up to 4 hours after each treatment (134) (Box 8).
Multiple sclerosis relapse occurs in 15–22% of women during pregnancy.*

Corticosteroid use for acute MS relapse:
- Intravenous methylprednisolone is appropriate.
- Dexamethasone is contraindicated.

Severe or corticosteroid refractory MS relapses can be managed with intravenous immunoglobulin or plasmapheresis.

Pregnancy and the Postpartum Period

The 1998 prospective Pregnancy in Multiple Sclerosis trial (known as PRIMS) was the first study to examine the relationship between pregnancy and MS (137). This study found decreased annualized relapse rates during pregnancy with a significant nadir in the third trimester and significantly increased relapse rates in the first 3 months of the postpartum period. Approximately 28% of cohort-experienced relapses occurred in the postpartum period (83, 137). A follow-up study demonstrated that relapses occurred most often in patients who had a relapse a year before pregnancy or during pregnancy (64). Patients who had used disease-modifying therapy in the 2 years before pregnancy were found to have a 45% reduction in the postpartum relapse rate (138).

During pregnancy the immune system shifts from an inflammatory Th1 and Th2 response to a more protective Th1 and Th2 profile to accept and maintain the pregnancy. During the postpartum period, the immune system returns to an inflammatory Th1 and Th2 state. Because of this shift, some studies suggest that pregnancy decreases the risk of developing MS and its progressive course (139–141).

Patients with MS may have increased rates of cesarean birth due to MS-related neuromuscular perineal weakness and spasticity (87). Women with MS might have difficulty pushing during the later stages of delivery because of neurologic deficits. However, a 2002 population-based cohort study showed that women with MS did not have an increased number of pregnancy or delivery complications, stillbirth, ectopic pregnancies, offspring with birth defects, preterm births, or spontaneous abortions (85). Epidural anesthesia and spinal anesthesia are safe for delivery in women with MS (86, 87). Epidural anesthesia does not increase the risk of relapse (137).

Breastfeeding

The data regarding breastfeeding and its effect on MS disease activity in postpartum women are limited, and results appear to be conflicting. However, available evidence suggests that women with mild forms of MS are more likely to breastfeed than women with more severe MS (142). Postpartum relapse rates mostly reflect the severity of antepartum MS disease activity, and breastfeeding is inversely proportional to the underlying disease severity (143). Some studies have found that the effect of breastfeeding is either neutral (137, 144) or beneficial (145, 146). A meta-analysis of 12 studies demonstrated a 47% decrease in annualized relapse rates during the postpartum period in MS patients who were breastfeeding (147). Furthermore, breastfeeding is known to provide beneficial health effects in the neonate. Breastfeeding generally is encouraged and supported in women with MS.

Most women decline MS disease-modifying therapy while breastfeeding, but women with severe disease are likely to forego breastfeeding and restart disease-modifying therapy in the postpartum period. The use of interferon β-1a or glatiramer acetate is probably safe for breastfeeding (148). Interferon β-1a is secreted at minimal levels in
breast milk, and no adverse effects have been observed in breastfed infants (149). There are no reported adverse effects of glatiramer acetate on breastfed infants (148). Drugs best avoided during breastfeeding include dimethyl fumarate (unknown if secreted), natalizumab (secreted at low levels), mitoxantrone (secreted), fingolimod (secreted), and teriflunomide (secreted).

**CASE NO. 5.** A 35-year-old woman with relapsing-remitting MS gives birth to a healthy boy weighing 3.4 kg (7.5 lb). No relapses were reported during pregnancy. She is interested in resuming her previous treatment with glatiramer acetate, 40 mg/mL, three times a week. She is concerned about the safety of this disease-modifying therapy during breastfeeding and the affect breastfeeding may have on disease activity.

According the PRIMS trial, breastfeeding itself had no effect on postpartum disease activity (83, 137). Exclusive breastfeeding for at least 2 months postpartum was associated with a reduced rate of MS relapses. This protective affect might be related to the lactational suppression of menses during exclusive breastfeeding. Because breastfeeding provides beneficial health effects for the neonate, women with MS should not be discouraged from breastfeeding (115). Hormonal signaling during breastfeeding may modulate immune activity and susceptibility of MS flares. Although MS itself is not a contraindication to breastfeeding, use of medication during this time should be reviewed. The use of glatiramer acetate likely is safe during breastfeeding, and no adverse effects have been reported using glatiramer acetate in breastfed infants. This patient was advised to resume glatiramer acetate.

**Perimenopause, Menopause, and Disease Activity**

The menopausal transition may affect MS disease course, and there is potential for a modulatory role of hormone therapy (HT) (150). Antimüllerian hormone can be a marker of ovarian aging, and lower antimüllerian hormone levels have been associated with increased disability and gray matter loss in women with MS independent of chronological age and disease duration. Some studies have demonstrated decreased serum antimüllerian hormone levels in women of childbearing age with MS (122), but others found low antimüllerian hormone levels only in patients with higher disease activity (123). After menopause, there is a reduction in the relapse rate, but the disability progression continues at a similar rate compared with the premenopausal period (151).

Most women develop MS before menopause, and MS does not influence the timing of menopause (152). Long-term treatment with methylprednisolone and interferon β-1b may change menopausal age (153). Symptomatic overlap can be seen in MS and menopause. Clinical history can help distinguish between MS activity and menopausal symptoms. The course of MS may slightly worsen after menopause, possibly because of the effects of estrogen loss on inflammation of the CNS and neurodegeneration. The neuroprotective effects of estrogen in the CNS may include increasing antiinflammatory cytokines, decreasing demyelination, and enhancing oxidative and mitochondrial function (8).
Therefore, HT potentially can alleviate symptoms or even reverse some of the underlying pathology associated with MS. Estriol combined with glatiramer acetate has been shown to reduce annualized relapse rates and MRI activity in patients with relapsing-remitting MS (154).

Limited objective data exist regarding the effect of HT on the course of MS (155). Some studies have suggested that the rate of disability accumulation in women with MS after menopause is increased (72). Patients with MS also have a risk of heart disease, low bone mass (formerly referred to as osteopenia) and osteoporosis (probably due to physical inactivity), psychosocial issues, and marital problems during menopause and perimenopause (156–158). Women with MS receive less preventive care than healthy women and only one half of women with MS see a health care provider regularly (159). Women with MS should be counseled proactively to view menopause as a time to reassess health-related goals and to consider a multidisciplinary approach for optimal management of symptoms, including cardiovascular examinations, osteoporosis prevention, routine screening, neuropsychologic evaluation, and rehabilitation and wellness programs.

**CASE NO. 6.** A 53-year-old woman who has had MS for more than 10 years reports worsening of tingling and numbness in her arms and legs and increased muscle spasms. Additional symptoms include anxiety, sleep disturbance, cognitive concerns, and hot flushes. Updated MRI studies do not show new or increased disease burden or contrast-enhancing lesions. Current disease-modifying therapy includes glatiramer acetate, 40 mg/mL, three times a week. Before glatiramer acetate, natalizumab had been prescribed but was discontinued due to concerns related to John Cunningham virus seropositivity.

There is frequent overlap between menopause-related and MS-related symptoms, with common comorbidities, such as sexual dysfunction, mood disorders, and changes in bladder function (152). Furthermore, some MS symptoms may be exacerbated by perimenopausal changes, such as hot flushes or sleep disturbance. Low estrogen status, such as during menopause and the postpartum period, can produce exacerbations of MS. Therefore, clinical observation and neuroimaging surveillance are warranted to monitor disease progression and to guide treatment of symptoms (ie, with corticosteroids), and to determine whether to switch medication. This patient presents with worsening residual paresthesia and muscle spasm along with anxiety and insomnia, but MRI did not show new or increased disease burden or contrast enhancing lesions. Therefore, glatiramer acetate is continued, and amitriptyline (a tricyclic antidepressant), 25 mg nightly at bedtime, is initiated for symptom treatment. Her anxiety, insomnia, and paresthesia are significantly improved. The decision to start a patient on hormone therapy should be based on gynecologic indications. Moreover, cardiac check-up, osteoporosis prevention and screening, and treatment protocols should be considered as a standard part of treatment plans for all women with MS.
Multiple sclerosis is one of the most common neurologic disorders worldwide. In many countries, it is the leading cause of nontraumatic neurologic disability in young adults. The disease affects women more often than men. Obstetrician-gynecologists should be familiar with the effects of MS on women’s health as well as on maternal and fetal outcomes. The following key points should be useful to obstetrician-gynecologists in screening, diagnosis, and initial management of patients with MS:

- Environmental risk factors, such as vitamin D deficiency, unhealthy diet, obesity in early life, and cigarette smoking play a partial role in the development of MS. Therefore, lifestyle modification is important to decrease the risk of developing MS.

- Waxing and waning neurologic deficits are the hallmark signs of MS. If a woman aged 15–50 years experiences unexplained waxing and waning neurologic symptoms, MS should be suspected, and a referral to a neurologist is warranted.

- No specific tests or biomarkers for MS are available, but brain and spinal MRI and analyses of CSF and vision provoked potential can be used to support the diagnosis. The diagnosis of MS mainly relies on recognition of symptoms in the patient’s clinical history and neurologic examination.

- Most women with MS will have normal pregnancies and will breastfeed. Pregnancy may facilitate a better outcome in long-term disability in a woman with MS. Multiple sclerosis does not increase the risks of infertility and adverse pregnancy outcomes, and infants born to women with MS are not at increased risk of prematurity or congenital anomalies.

- Women with MS should begin disease-modifying therapy. The choice of a specific agent should be individualized according to safety; efficacy; tolerability; reproductive status; disease activity; and patient values, preferences, and resources.

- Disease-modifying therapy should be avoided during pregnancy. Glatiramer acetate and interferon β are modestly effective and are preferred for women who are not using reliable birth control. Ocrelizumab is a highly effective disease-modifying agent for a woman who is planning to become pregnant or who is not using reliable birth control.

- Pregnancy in women with MS is not considered high-risk. A woman’s hormonal status may affect MS disease activity and symptoms.

- Women with MS should be counseled to view menopause as a time to reassess health-related goals and to consider a multidisciplinary approach for overall health and wellbeing.
Test Your Clinical Skills

Complete the answer sheet at www.clinicalupdates.org under “Test Your Clinical Skills” and receive 5 continuing medical education credits. The answers appear on page 43.

Directions: Select the one best answer or completion.

1. The male-to-female ratio of incidence of MS is
   A. 1:1
   B. 1:2
   C. 1:3
   D. 1:4

2. If both parents have MS, the risk for their offspring is how many times higher than that for the general population?
   A. Two
   B. Four
   C. Six
   D. Ten

3. Which clinical type of MS is the usual initial presentation?
   A. Clinically isolated syndrome
   B. Primary progressive
   C. Relapsing-remitting
   D. Secondary progressive

4. Which finding in cerebrospinal fluid is indicative of MS in patients with clinical suspicion?
   A. Oligoclonal bands of immunoglobulin G on electrophoresis
   B. Presence of polymorphonuclear cells
   C. Protein level greater than 100 mg/dL
   D. White blood cell count greater than $0.05 \times 10^9$/L (50 cells per microliter)

5. Which of the following demyelinating diseases is associated with the shortest life span after diagnosis?
   A. Aggressive MS
   B. The Marburg type MS
   C. Schilder disease
   D. Tumefactive MS

6. An attack in a patient with MS is defined as a focal neurologic disturbance occurring after at least 30 days of stability in the absence of alternate explanation and lasting how long?
   A. 24 hours
   B. 48 hours
   C. 3 days
   D. 7 days

7. The most common symptom of MS is
   A. fatigue
   B. numbness
   C. paresthesia
   D. visual disturbance
8. The most common bowel dysfunction seen in patients with MS is
   A. constipation
   B. diarrhea
   C. fecal incontinence
   D. fecal urgency

9. Tobacco use by patients with MS is associated with increased
   A. dizziness
   B. mortality
   C. spasticity
   D. visual changes

10. The effect of pregnancy on women with MS results in decreased
    A. disease progression
    B. long-term disability
    C. relapse rate during pregnancy
    D. relapse rate postpartum

11. Which of the following medications used to treat MS is associated with the lowest risk in the fetus?
    A. Dimethyl fumarate
    B. Fingolimod
    C. Glatiramer acetate
    D. Teriflunomide

12. Which of the following factors is associated with increased rate of relapses in patients with MS?
    A. Use of combined oral contraceptives
    B. Use of gonadotropin-releasing hormone agonist
    C. Use of long-acting reversible contraceptives
    D. Pregnancy

13. In the PRIMS study, exclusive breastfeeding for at least how long was associated with a reduced rate of MS relapses?
    A. 1 month
    B. 2 months
    C. 3 months
    D. 6 months

14. In patients with MS, hormone therapy is associated with decreased
    A. antiinflammatory cytokine levels
    B. disability accumulation rate
    C. mitochondrial function
    D. relapse rates in relapsing-remitting MS
The following list is for information purposes only. Referral to these sources and websites does not imply the endorsement of the American College of Obstetricians and Gynecologists. This list is not meant to be comprehensive. The exclusion of a source or website does not reflect the quality of that source or website. Please note that websites are subject to change without notice.


54. Freedman MS, Rush CA. Severe, highly active, or aggressive multiple sclerosis [published erratum appears in Continuum (Minneap Minn) 2018;24:967]. Continuum (Minneap Minn) 2016;22:761–84. (Level III)


131. Administration of contrast media to women who are breastfeeding. In: ACR Committee on Drugs and Contrast Media, editor. ACR manual on contrast media version 10.3. Reston, VA: American College of Radiology; 2018. (Level III)


Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

I  Evidence obtained from at least one properly designed randomized controlled trial.

II-1 Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.

III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Answers

Each monograph in Clinical Updates in Women’s Health Care is an overview of a topic of importance to obstetrician–gynecologists in practice. Upcoming titles include the following:

- Aging Women and the Office Assessment

If not previously completed, earn CME credits for back issues of Clinical Updates in Women’s Health Care. Online access to the complete title list is available at www.clinicalupdates.org.

Updates

Also available at www.clinicalupdates.org are the following content updates:

- Anorectal Disorders (May 2015)
- Common Dermatologic Conditions (January 2018)
- Complementary and Alternative Medicine (June 2015)
- Memory Loss and Dementia (January 2019)
- Metabolic Bone Disease (October 2019)
- Obesity (October 2013)
- Obesity (August 2017)
- Occupational Diseases and Injuries (July 2016)
- Sleep Disorders (September 2015)
- Upper Gastrointestinal Tract, Biliary, and Pancreatic Disorders (June 2017)

List of Titles

2020
Overactive Bladder (Vol. XIX, No. 1, January 2020)
Multiple Sclerosis (Vol. XIX, No. 2, March 2020)

2019
Surgical Considerations (Vol. XVIII, No. 1, January 2019)
Evaluation and Management of Lipid Disorders (Vol. XVIII, No. 2, March 2019)
Acute Cough (Vol. XVIII, No. 3, May 2019)
Migraine and Other Headache Disorders (Vol. XVIII, No. 4, July 2019)
Back Pain (Vol. XVIII, No. 5, September 2019)
Diabetes Mellitus (Vol. XVIII, No. 6, November 2019)

2018
Common Dermatologic Conditions (Vol. XVII, No. 1, January 2018)
Arthritis (Vol. XVII, No. 2, March 2018)
Asthma (Vol. XVII, No. 3, May 2018)
Incidental Radiologic Findings (Vol. XVII, No. 4, July 2018)
The Role of Physical Therapy in Obstetric–Gynecologic Practice (Vol. XVII, No. 5, September 2018)
Perioperative Pain Management (Vol. XVII, No. 6, November 2018)

2017
Liver Disease: Reproductive Considerations (Vol. XVI, No. 1, January 2017)
Structural Heart Disease (Vol. XVI, No. 2, March 2017)
Arrhythmias (Vol. XVI, No. 3, May 2017)
Gynecologic and Obstetric Care for Breast Cancer Survivors (Vol. XIV, No. 4, July 2017)
Mood and Anxiety Disorders (Vol. XVI, No. 5, September 2017)
Ischemic Heart Disease (Vol. XVI, No. 6, November 2017)

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Challenging Patient Encounters (Vol. XV, No. 5, September 2016)
Liver Disease: General Pathophysiology, Diagnosis, and Management
(Vol. XV, No. 6, November 2016)
Liver Disease: General Pathophysiology, Diagnosis, and Management Supplement
(Vol. XV, No. 6, November 2016)

2015
Metabolic Bone Disease (Vol. XIV, No. 2, April 2015)
Benign Breast Disease (Vol. XIV, No. 3, July 2015)
Hormone Therapy and Alternative Therapies for Menopause (Vol. XIV, No. 4, October 2015)
Lower Gastrointestinal Tract Disorders (Vol. XIV, No. 5, November 2015)

2014
Sexuality and Sexual Disorders (Vol. XIII, No. 2, April 2014)
Nutrition (Vol. XIII, No. 3, July 2014)
Adverse Drug Reactions (Vol. XIII, No. 4, October 2014)
Memory Loss and Dementia (Vol. XIII, No. 5, November 2014)

2013
Obesity (Vol. XII, No. 1, January 2013)
Exercise (Vol. XII, No. 2, April 2013)
Allergies (Vol. XII, No. 4, October 2013)
Thyroid Disorders (Vol. XII, No. 5, November 2013)

2012
Sleep Disorders (Vol. XI, No. 3, July 2012)
Upper Gastrointestinal Tract, Biliary, and Pancreatic Disorders (Vol. XI, No. 4, October 2012)
Anemia (Vol. XI, No. 5, November 2012)

2011
Complementary and Alternative Medicine (Vol. X, No. 4, October 2011)

2010
Anorectal Disorders (Vol. IX, No. 1, January 2010)
Anorectal Disorders Supplement (Vol. IX, No. 1, January 2010)
Occupational Diseases and Injuries (Vol. IX, No. 3, July 2010)

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### Table 2. Disease-Modifying Agents for Multiple Sclerosis

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism of Action</th>
<th>Last Dose Before Conception</th>
<th>Evidence of Teratogenicity and Embryonal Lethality Based on Animal Data*</th>
<th>Evidence of Birth Defects and Abortion Based on Human Data*</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferons</td>
<td>• Suppression of Th1 cells</td>
<td>2 months</td>
<td>Teratogenicity—no</td>
<td>No evidence</td>
<td>Headache, flu-like symptoms, and injection site reactions</td>
</tr>
<tr>
<td></td>
<td>• Reduction in the number of cells crossing blood–brain barrier</td>
<td></td>
<td>Embryonal lethality—yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>• Upregulation of T regulatory cells</td>
<td>2 weeks</td>
<td>Teratogenicity—no</td>
<td>No evidence</td>
<td>Flushing and injection site reactions</td>
</tr>
<tr>
<td></td>
<td>• Shift to Th2 cytokine milieu</td>
<td></td>
<td>Embryonal lethality—no</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fingolimod</td>
<td>• Sphingosine-1-phosphate (SIP) antagonist effects</td>
<td>2 months</td>
<td>Teratogenicity—yes</td>
<td>Birth defects; no pattern</td>
<td>Headache, flu-like symptoms, increased levels of liver function markers, and abdominal pain</td>
</tr>
<tr>
<td></td>
<td>• Shift to Th2 cytokine milieu</td>
<td></td>
<td>Embryonal lethality—yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dimethyl fumarate</td>
<td>• Antiinflammatory and neuroprotective effects via nuclear factor kappa B and nuclear factor erythroid 2-related factor 2 pathways</td>
<td>Few days or weeks because of a short half-life</td>
<td>Teratogenicity—no</td>
<td>Contraindicated in pregnancy</td>
<td>Flushing, dyspepsia, and progressive multifocal leukoencephalopathy</td>
</tr>
<tr>
<td>Teriflunomide</td>
<td>• Inhibition of pyrimidine synthesis</td>
<td>Washes out with elimination process</td>
<td>Teratogenicity—yes</td>
<td>Contraindicated in pregnancy</td>
<td>Increased levels of liver function markers, reactivation of tuberculosis, thinning of hair, and diarrhea</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>• Alpha-4 integrin antagonist effects</td>
<td>2 months</td>
<td>Teratogenicity—no</td>
<td>Possibly increased risk of abortion</td>
<td>Headache, fatigue, diarrhea, rash, and progressive multifocal leukoencephalopathy</td>
</tr>
<tr>
<td>Alemzumab</td>
<td>• Anti-CD52 monoclonal antibody effects</td>
<td>4 months</td>
<td>Teratogenicity—no</td>
<td>No evidence</td>
<td>Autoimmunity, injection site reactions, and malignancy</td>
</tr>
<tr>
<td>Rituximab</td>
<td>• Anti-CD20 monoclonal antibody effects</td>
<td>12 months</td>
<td>Teratogenicity—no</td>
<td>B-cell depletion and hematologic issues</td>
<td>Injection site reactions, hepatitis B reactivation, muco-cutaneous reactions, and progressive multifocal leukoencephalopathy</td>
</tr>
<tr>
<td>Ocrelizumab</td>
<td>• Anti-CD20 monoclonal antibody effects</td>
<td>6 months</td>
<td>Teratogenicity—unknown</td>
<td>Unknown</td>
<td>Infusion reactions and upper respiratory tract infections; should be avoided in patients with hepatitis B</td>
</tr>
<tr>
<td>Siponimod</td>
<td>• Sphingosine-1-phosphate (SIP) Receptor modulator</td>
<td>10 days</td>
<td>Teratogenicity—yes</td>
<td>Unknown</td>
<td>Headache, hypertension, and increases in transaminase levels</td>
</tr>
<tr>
<td>Cladribine</td>
<td>Purine analog effects (mimics the nucleoside adenosine)</td>
<td>6 months</td>
<td>Teratogenicity—yes</td>
<td>Contraindicated</td>
<td>Upper respiratory infections, headache, and low white blood cell counts</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Embryonal lethality—yes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Data from the specific medication’s package insert.*
<table>
<thead>
<tr>
<th>Symptom</th>
<th>Pharmacologic Treatment</th>
<th>Nonpharmacologic Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>• Amantadine, 100 mg twice per day</td>
<td>• Environmental manipulation (ie, cooling techniques)</td>
</tr>
<tr>
<td></td>
<td>• Modafinil, 200 mg–400 mg per day</td>
<td>• Aerobic and strength training exercise</td>
</tr>
<tr>
<td></td>
<td>• Armodafinil, 150–250 mg per day</td>
<td>• Energy conservative techniques (ie, use of assistive devices)</td>
</tr>
<tr>
<td></td>
<td>• Central nervous system stimulants (amphetamine or methylphenidate)</td>
<td>• Cognitive behavioral therapy</td>
</tr>
<tr>
<td></td>
<td>• Modafinil, 200 mg–400 mg per day</td>
<td>• Relaxation therapy</td>
</tr>
<tr>
<td></td>
<td>• Armodafinil, 150–250 mg per day</td>
<td>• Transcranial magnetic stimulation</td>
</tr>
<tr>
<td>Trigeminal neuralgia</td>
<td>• Carbamazepine</td>
<td>• Gasserian ganglion procedures</td>
</tr>
<tr>
<td></td>
<td>• Oxcarbazepine</td>
<td>• Gamma knife surgery</td>
</tr>
<tr>
<td></td>
<td>• Lamotrigine</td>
<td>• Microvascular decompression</td>
</tr>
<tr>
<td>Chronic neuropathic pain</td>
<td>• Tricyclic antidepressants</td>
<td>• Transcutaneous electrical nerve stimulation</td>
</tr>
<tr>
<td></td>
<td>• Duloxetine</td>
<td>• Meditation</td>
</tr>
<tr>
<td></td>
<td>• Antiepileptic drugs</td>
<td>• Biofeedback techniques</td>
</tr>
<tr>
<td></td>
<td>• Intrathecal baclofen</td>
<td></td>
</tr>
<tr>
<td>Cognitive deficits</td>
<td>• Stimulants* (amphetamine, modafinil, and methylphenidate)</td>
<td>• Cognitive–behavioral treatment</td>
</tr>
<tr>
<td></td>
<td>• Cholinesterase inhibitors* (donepezil, rivastigmine, and galantamine)</td>
<td>• Exercise and yoga</td>
</tr>
<tr>
<td></td>
<td>• N-methyl-D-aspartate receptor antagonist* (memantine)</td>
<td></td>
</tr>
<tr>
<td>Depression and anxiety</td>
<td>• Antidepressants</td>
<td>• Psychologic therapy</td>
</tr>
<tr>
<td></td>
<td>• Anxiolytics</td>
<td>• Web-based initiatives</td>
</tr>
<tr>
<td></td>
<td>• Antiepileptic drugs</td>
<td>• Exercise</td>
</tr>
<tr>
<td></td>
<td>• Gabapentin</td>
<td>• Transcranial magnetic stimulation</td>
</tr>
<tr>
<td>Detrusor muscle hyperactivity</td>
<td>• Antimuscarinic</td>
<td>• Percutaneous posterior tibial nerve stimulation</td>
</tr>
<tr>
<td></td>
<td>• Intranasal desmopressin</td>
<td>• Sacral neuromodulation</td>
</tr>
<tr>
<td>Detrusor muscle dysynergia</td>
<td>• Alpha 1-adrenergic receptor antagonist</td>
<td>• None</td>
</tr>
<tr>
<td>Detrusor muscle hypoactivity</td>
<td>• None</td>
<td>• Indwelling or intermittent catheterization</td>
</tr>
<tr>
<td>Constipation</td>
<td>• Natural or other laxatives</td>
<td>• High-fiber diet</td>
</tr>
<tr>
<td></td>
<td>• Fluids</td>
<td>• Fluids</td>
</tr>
<tr>
<td></td>
<td>• Exercise and mobilization</td>
<td>• Exercise and mobilization</td>
</tr>
<tr>
<td>Fecal incontinence</td>
<td>• None</td>
<td>• Reduction in dietary fiber intake</td>
</tr>
<tr>
<td>Spasticity</td>
<td>• Baclofen (oral and intrathecal)</td>
<td>• Cold beverages</td>
</tr>
<tr>
<td></td>
<td>• Tizanidine</td>
<td>• Lightweight clothing</td>
</tr>
<tr>
<td></td>
<td>• Benzodiazepines</td>
<td>• Fans or air conditioning</td>
</tr>
<tr>
<td></td>
<td>• Gabapentin</td>
<td>• Cool suits, gel packs, or ice packs</td>
</tr>
<tr>
<td></td>
<td>• Dantrolene</td>
<td>• Correction or eliminate of triggers (eg, bladder distension or pressure sore)</td>
</tr>
<tr>
<td></td>
<td>• Naltrexone†</td>
<td>• Range of motion stretching</td>
</tr>
<tr>
<td></td>
<td>• OnabotulinumtoxinA injection</td>
<td>• Physical therapy</td>
</tr>
<tr>
<td></td>
<td>• OnabotulinumtoxinA injection</td>
<td>• Cryotherapy</td>
</tr>
<tr>
<td></td>
<td>• OnabotulinumtoxinA injection</td>
<td>• Transcutaneous electrical nerve stimulation</td>
</tr>
<tr>
<td>Heat intolerance</td>
<td>• None</td>
<td>• Relaxation therapy</td>
</tr>
<tr>
<td></td>
<td>• Cool beverages</td>
<td>• Hydrotherapy</td>
</tr>
<tr>
<td></td>
<td>• Lightweight clothing</td>
<td>• Bracing</td>
</tr>
<tr>
<td></td>
<td>• Fans or air conditioning</td>
<td>• Noninvasive brain stimulation</td>
</tr>
<tr>
<td>Sleep Hygiene</td>
<td>• Melatonin</td>
<td>• Control of underlying sleep disorders</td>
</tr>
<tr>
<td></td>
<td>• Control of associated mood disorders</td>
<td>• Exercise</td>
</tr>
<tr>
<td></td>
<td>• Avoidance of stimulants</td>
<td>• Exposure to natural light</td>
</tr>
<tr>
<td></td>
<td>• Exercise and mobilization</td>
<td>• Regular relaxing bedtime routine</td>
</tr>
<tr>
<td></td>
<td>• Wrist weights</td>
<td>• Avoidance of daytime naps</td>
</tr>
<tr>
<td>Gait impairment</td>
<td>• 4-Aminopyridine</td>
<td>• Exercise</td>
</tr>
<tr>
<td></td>
<td>• Management of spasticity</td>
<td>• Management of associated conditions, such as optic neuritis</td>
</tr>
<tr>
<td></td>
<td>• Balance training</td>
<td>• Correction of diplopia with prism</td>
</tr>
<tr>
<td></td>
<td>• Use of assistive devices</td>
<td>• Surgical correction</td>
</tr>
<tr>
<td>Visual changes</td>
<td>• None</td>
<td>• Balance training</td>
</tr>
<tr>
<td>Tremors</td>
<td>• Clonazepam</td>
<td>• Symmetric treatment with Anticholinergics or antihistamines</td>
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<td></td>
<td>• Wrist weights</td>
<td>• Balance training</td>
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<tr>
<td>Vertigo</td>
<td>• Symmetric treatment with Anticholinergics or antihistamines</td>
<td>• Speech therapy</td>
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<tr>
<td></td>
<td>• Wrist weights</td>
<td>• Swallow therapy</td>
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<td></td>
<td>• Balance training</td>
<td>• Aspiration precautions</td>
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<tr>
<td></td>
<td>• Symmetric treatment with Anticholinergics or antihistamines</td>
<td>• Physical therapy</td>
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<tr>
<td></td>
<td>• balance training</td>
<td>• Chest percussion</td>
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<tr>
<td></td>
<td>• Symmetric treatment with Anticholinergics or antihistamines</td>
<td>• Noninvasive or invasive respiratory support</td>
</tr>
<tr>
<td>Sexual dysfunction</td>
<td>• Sildenafil for maintenance of erections</td>
<td>• Treatment of associated conditions, such as spasticity, bowel dysfunction</td>
</tr>
<tr>
<td></td>
<td>• Treatment of associated conditions, such as spasticity, bowel dysfunction</td>
<td>• Lubricants</td>
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</tbody>
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