Management strategies for female patients of reproductive potential with multiple sclerosis

An evidence-based review

Coyle, Patricia K.; Oh, Jiwon; Magyari, Melinda; Oreja-Guevara, Celia; Houtchens, Maria

Published in:
Multiple Sclerosis and Related Disorders

DOI:
10.1016/j.msard.2019.04.003

Publication date:
2019

Document version
Publisher's PDF, also known as Version of record

Multiple Sclerosis and Related Disorders 32 (2019) 54–63

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Review article

Management strategies for female patients of reproductive potential with multiple sclerosis: An evidence-based review

Patricia K Coyle[a,*], Jiwon Oh[b], Melinda Magyari[c], Celia Oreja-Guevara[d], Maria Houtchens[e]

[a] Department of Neurology, Stony Brook University, Stony Brook, NY, USA
[b] St. Michael's Hospital, University of Toronto, Toronto, Ontario, Canada
[c] Danish Multiple Sclerosis Center, Department of Neurology, Copenhagen University Hospital, Copenhagen, Denmark
[d] Hospital Clínico San Carlos, Universidad Complutense de Madrid, IdISSC, Madrid, Spain
[e] Brigham and Women's Hospital, Harvard Medical School, Brookline, MA, USA

ARTICLE INFO

Keywords:
Multiple sclerosis
Pregnancy
Disease modifying therapy
Family Planning
Postpartum

ABSTRACT

Multiple sclerosis (MS) is an inflammatory, demyelinating, neurodegenerative, immune-mediated disease primarily diagnosed in early adulthood. Multiple sclerosis mostly impacts women of reproductive potential, with pregnancy and birth outcomes being major concerns for many patients. While there is ample evidence that the disease itself has no impact on pregnancy, many women living with MS still question their ability to have children, and the impact of childbearing on their disease in the short and long term. Such questions emphasize the importance of proper guidance from healthcare professionals, particularly neurologists. Management considerations are also complicated by the growing list of available treatment options. This review will summarize current evidence and expert opinion around the management of female MS patients of reproductive potential, from family planning to the postpartum period. Current guidelines on the use of disease-modifying therapies throughout pregnancy will be discussed, as well as other general medical recommendations, to minimize MS disease activity in the peripartum period.

1. Introduction

Multiple sclerosis (MS) is the most common chronic neurological immune-mediated disorder of young adults, and is more commonly seen in women (Hauser and Oksenberg, 2006). The prevalence of MS has been increasing over the past few decades and is now approximately three times more common in women than in men (Harbo et al., 2013; Koch-Henriksen et al., 2018). Owing to both the increasing incidence of MS in women, as well as an increasing number of available therapies, MS is becoming a substantial and growing clinical burden for women of reproductive potential (Altintas et al., 2015; MS International Federation, 2013; Nguyen et al., 2019).

Adequate guidance for female MS patients who plan to conceive remains an unmet medical need (Borisow et al., 2014). Obstetricians often lack experience in MS, and neurologists frequently have limited knowledge about the obstetric and pregnancy implications of MS (Borisow et al., 2014; Coyle et al., 2004). Moreover, the increasing number of distinct disease-modifying therapies (DMTs), and potential side effects, complicate the management of women with MS considering pregnancy. They need a treatment plan which minimizes the likelihood of relapses, while balancing risk to the fetus and mother (Vukusic and Marignier, 2015).

There are a lack of robust clinical studies and evidence-based guidelines on clinical decision-making and therapeutic choices during pregnancy (Wundes et al., 2014). Furthermore, there are uncertainties pertaining to appropriate management strategies in female MS patients throughout the stages of pre-conception, pregnancy, and the postpartum period. This overview of current knowledge and clinical practice, by specialist neurologists experienced in the treatment of women with MS, provides guidance on the management and care of female MS

Abbreviations: AAN, American Academy of Neurology; ACOG, American College of Obstetricians and Gynecologists; ART, assisted reproductive technology; CDC, US Center for Disease Control; DDI, drug–drug interaction; DMF, dimethyl fumarate; DMT, disease-modifying therapy; EAN, European Academy of Neurology; ECTRIMS, European Committee for Treatment and Research in Multiple Sclerosis; FSRH, Faculty of Sexual and Reproductive Health; GA, glatiramer acetate; GnRH, gonadotropin-releasing hormone; GWAS, genome-wide association studies; GYNs, gynecologists; HCP, healthcare professional; IFNβ, interferon beta; kD, kilodalton; LARC, long-acting reversible contraceptive; MRI, magnetic resonance imaging; MS, multiple sclerosis; NICE, National Institute for Health and Care Excellence; OB, obstetricians; US MEC, US Medical Eligibility Criteria; WHO, World Health Organization

* Corresponding author.
E-mail address: Patricia.Coyle@Stonybrookmedicine.edu (P.K. Coyle).

https://doi.org/10.1016/j.msard.2019.04.003
Received 6 December 2018; Received in revised form 8 March 2019; Accepted 2 April 2019

Table 1
Patient concerns and advice before, during, and after pregnancy.

Concern	Guidance
Pre-pregnancy	
Fertility and fetal development	In general, there is no evidence of an association between maternal MS and adverse effects on fetal development. The effect of MS on fertility is uncertain; blood hormone abnormalities have been observed in female patients with MS which may affect fertility, but this still requires substantiation (Hellwig and Correale, 2013; Lombardi et al., 2011; Roux et al., 2015; Yalcin et al., 2017)
Assisted reproductive technology/*in vitro* fertilization	Use of gonadotropin-releasing hormone agonists and antagonists, if pregnancy does not occur, may be associated with temporary increased risk of relapses (Hellwig, 2014)
Contraceptive use	No evidence for negative impact on MS disease course. LARC methods may be particularly effective, as they do not require proactive user compliance (Houtchens et al., 2017)
Sexual dysfunction	Observed in up to 63% of women; may require specific counseling and treatments (Kim et al., 2018; Lew-Starowicz and Gianotten, 2015)
Genetic risk	MS is not considered to be inherited, but risk of developing MS is modestly increased when a parent has MS (Coyle, 2016)
DMT use and washout	Therapy dependent; no washout is reasonable for glatiramer acetate (GA), interferon beta (IFNβ), dimethyl fumarate (DMF), or natalizumab (Coyle, 2016)
Lifestyle	Women should be counseled to take prenatal vitamins, avoid alcohol and smoking, and maintain a healthy diet (Coyle, 2016)
During pregnancy	
Impact of pregnancy on MS prognosis	Pregnancy is associated with a marked decrease in disease activity during the third trimester, followed by an increase in the postpartum period. No long-term negative impact on relapsing MS (Confavreux et al., 1998; Coyle, 2016)
Impact of MS on pregnancy outcome	No increase in ectopic pregnancies, birth defects, miscarriage, or stillbirths (Hellwig, 2014; Oreja-Guevara et al., 2014)
Treatment with DMTs during pregnancy	Typically, DMTs are not used during pregnancy. Symptomatic treatment should be for short periods when appropriate and necessary. Glucocorticoids can be used for relapses at any time during pregnancy. Magnetic resonance imaging (MRI) may be carried out if there is good reason. Use of contrast should be avoided (unless absolutely necessary) (Airas and Kaaja, 2012; Alroughani et al., 2016)
At delivery and postpartum	
Delivery and anesthesia	Use of anesthesia should be based solely on experienced obstetric clinical decision-making (Lu et al., 2013a; Pasto et al., 2012)
Breastfeeding	Data on DMT transfer to breast milk and negative effects in newborns are lacking. Since patients with more active disease would benefit from early DMT resumption after delivery, the potential risk of DMT exposure to the infant during breastfeeding should be considered (Almas et al., 2016)
Disease activity	The first 3 months postpartum are a high-risk period for increased clinical and MRI disease activity, after which time activity reverts to the pre-pregnancy level (Alroughani et al., 2018; Confavreux et al., 1998)
Use of DMTs	DMTs can usually be reinstated soon after delivery (Coyle, 2016)
Economic/social impact	Pregnancy does not produce disability; choosing to have a child should not be directed by a diagnosis of MS (Coyle, 2016)
Child development	Maternal MS is not thought to have a negative impact on the mental health status of the child (Andersen et al., 2018)

DMT, disease-modifying therapy; LARC, long-acting reversible contraceptive; MRI, magnetic resonance imaging; MS, multiple sclerosis.

patients from family planning through to the postpartum period.

2. Patients not planning on pregnancy

For female patients who are not actively planning a pregnancy, healthcare professionals (HCPs) should provide helpful information about available contraception. There are existing guidelines, such as those provided by the American College of Obstetricians and Gynecologists (ACOG) (The American College of Obstetricians and Gynecologists, 2015), the US Center for Disease Control and Prevention (CDC) (Centers for Disease Control and Prevention, 2018), the Faculty of Sexual and Reproductive Health (FSRH) (Faculty of Sexual and Reproductive Health, 2016), and the World Health Organization (WHO) (World Health Organization, 2015), on contraceptive use in women of reproductive potential. These include information on specific contraceptives, as well as family planning. However, there is a clear need for additional guidance for use of contraceptives in women with specific neurologic conditions. The US Medical Eligibility Criteria for Contraceptive Use (US MEC), the FSRH UK MEC, and the WHO MEC provide evidence-based guidance on contraceptive use in the general population (Curtis et al., 2016; Faculty of Sexual and Reproductive Health, 2016; World Health Organization, 2015). More recently, the US MEC has been updated to include similar recommendations for patients with MS (Curtis et al., 2016). The MS Trust, an online resource in the UK, also provides guidance for the use of hormonal contraceptives based on potential interactions with DMTs (https://www.mstrust.org.uk/a-z/contraception). Since female patients with MS first discuss their family planning with their neurologist, the ability of the neurologist to provide accurate information about contraceptive options is important (Bove et al., 2014; Siroos and Harirchian, 2014).

Guidelines provided by the WHO and ACOG indicate that all patients, depending on their medical eligibility, should have access to all contraceptive methods, including long-acting reversible contraceptive (LARC) methods (intrauterine devices, implantable rods), tubal sterilization, hormonal contraceptives, and barrier methods (The American College of Obstetricians and Gynecologists, 2015; World Health Organization, 2015). Most contraceptive methods appear effective and safe for women with MS. LARC methods may be particularly appropriate in female patients because, once positioned, they do not require proactive user compliance (Houtchens et al., 2017; The American College of Obstetricians and Gynecologists, 2015). According to the WHO, UK MEC and US MEC, progestin-only and combined hormonal contraceptives are not recommended for patients with prolonged immobility, because of increased risk of venous thromboembolism and concerns about decreased bone mineral density (Curtis et al., 2016; Faculty of Sexual and Reproductive Health, 2016; Houtchens et al., 2017; World Health Organization, 2015).

Primary care providers and obstetricians/gynecologists (OB/GYNs) may benefit from additional up-to-date education about the use of contraceptives in women living with MS. In general, there is no interaction between DMTs and oral contraceptives. Formal drug–drug interaction (DDI) studies are limited; however, DDI studies have been carried out to assess the efficacy of oral contraceptives with concurrent delayed-release dimethyl fumarate (DMF) and fingolimod therapy (David et al., 2012; Zhu et al., 2017). In these studies, there were no reciprocal pharmacokinetic effects between DMF or fingolimod and oral contraceptives. Teriflunomide has also not shown any clinically relevant effect on the pharmacokinetics of oral contraceptives (Genzyme Corp., 2016). While increases in mean ethinylestradiol and levonorgestrel levels have been observed following repeat doses of teriflunomide, this interaction has not been shown to impact contraceptive efficacy (Genzyme Corp., 2016; Miller, 2015).

3. Family planning

HCPs advising female MS patients considering pregnancy must address several factors, including fertility, treatment choice, delivery, and the potential effects of pregnancy on MS disease activity and course (Table 1). Living with MS can have a significant impact on family planning decisions; in surveys of patients with MS, up to 77% have reported that their intended number of pregnancies changed as a result of their diagnosis (Carvalho et al., 2014). MS symptoms that may interfere with parenting, and fear of disability worsening, are the most common reasons contributing to these pregnancy-related decisions. Lack of education, specifically with regard to treatment possibilities during pregnancy, is a significant concern among both men and women with MS. In a recent Danish survey of 590 patients with MS, 47% of patients felt inadequately informed about DMT use during pregnancy (Rasmussen et al., 2018). More 'holistic' concerns of women living with MS, including the well-being of the child, ability to cope with parenting, societal attitudes, and genetic counseling (Prunty et al., 2008; Skinner et al., 2015), also contribute, although these are beyond the scope of this paper.

3.1. Fertility

Blood hormone abnormalities have been observed in female patients with MS which may affect fertility, but this still requires substantiation (Hellwig and Correale, 2013; Lombardi et al., 2011; Roux et al., 2015). Women with MS also tend to have fewer pregnancies and childbirths before they first experience clinical symptoms; however, it is not known if this lower number of pregnancies is a direct result of having MS (Magyari et al., 2013). Sexual dysfunction is also common among patients with MS. In a recent meta-analysis of 14,538 patients living with all types of MS, 63% of women and 61% of men reported challenges with sexual dysfunction (Kim et al., 2018). Despite its prevalence, pharmacologic treatment and advice for managing sexual dysfunction in patients with MS is lacking (Lew-Starowicz and Gianotten, 2015).

The prevalence of impaired fecundity ranges from 10 to 15% percent in the US general population (in women between the ages of 15–44) to over 30% in the European general population (in women between the ages of 35–44) (Chandra et al., 2013; ESHRE Capri Workshop Group, 2010). In comparison, approximately 10% of women living with MS have difficulty becoming or staying pregnant (Coyle, 2016). Assisted reproductive technology (ART) can be used, which includes *in vitro* fertilization and fertility treatments in which eggs and embryos are handled, with success rates as high as 31% in the US and 22% in the European general population (Calhaz-Jorge et al., 2017; Centers for Disease Control and Prevention, 2018). In a recent study from the New England Pregnancy Prospective Cohort Study (PREG-MS), 14% of patients successfully conceived through the use of fertility treatments (Manieri et al., 2018). While there are a limited number of studies on the effect of ART in female MS patients, there is an association with increased relapse risk, particularly in the first 3 months after unsuccessful cycles (Rankin et al., 2018). This has also been observed when gonadotropin-releasing hormone (GnRH) agonists are used; in a French, retrospective study of 32 patients with MS, significant increases in relapse rates three months after IVF treatment were observed in patients receiving GnRH agonists (Hellwig, 2014; Michel et al., 2012). Similar risks have not been observed after use of GnRH antagonists (Coyle, 2016; Michel et al., 2012). Recent reports suggest that continued DMT use may prevent this relapse risk and have questioned whether both agonists and antagonists carry a risk (Brzosko et al., 2018). Ultimately, a loss of pregnancy may be more of a trigger for MS activity than the type of ART used, but further research is needed (Kaplan et al., 2018). Low Vitamin D levels are also commonly reported in patients with MS and can impact fertility, and while not a clinical requirement, Vitamin D level assessment prior to and during pregnancy may be beneficial (Duan et al., 2014).

3.2. Pre-conception

Discussions on the risks and benefits of DMTs should occur as early as possible with a patient and before any planned pregnancy (Vukusic and Marignier, 2015). The US Food and Drug Administration's decision to update labelling by referencing the Pregnancy Lactation and Labelling Rule will help US HCPs evaluate benefit/risk (Office of the Federal Register (US), 2014). DMTs are generally not recommended for use during pregnancy unless the benefits outweigh the risks to the fetus, and recommended washout periods for some DMTs should be considered prior to conception (Houtchens et al., 2017). Since pharmacotherapy should be limited during pregnancy, adequate control of MS symptoms should be considered prior to conception (Coyle, 2016).

There are many considerations involved with family planning, in both patients with MS and the general population, such as female age, fertility status, and duration of non-conception (Cuello et al., 2017). In general, the probability of conceiving decreases with age, particularly in women over 33 years old (Wesselink et al., 2017). In patients with MS, disease activity should be stable in patients for 1 year prior to conception to diminish the risk of postpartum relapses (Wesselink et al., 2017). Early initiation of DMTs following an MS diagnosis, and subsequent DMT adherence, is a critical component of MS management, as higher relapse rates pre-pregnancy are associated with higher relapse rates in the postpartum period (Alroughani et al., 2018). Consequently, prolonged washouts prior to conception should be avoided to minimize time off therapy (Coyle, 2016). A potential (albeit unproven) alternative for women with a high risk of relapse is the use of monthly pulsed corticosteroids, which may be used until pregnancy is achieved (Bove et al., 2014).

DMT washout periods should be as short as possible (Table 2) (Coyle, 2016). Given the teratogenic effects observed with fingolimod (Novartis Pharmaceuticals Corp., 2018) and teriflunomide (Genzyme Corp., 2016) in animal studies, use of these therapies should be terminated prior to conception, and washout periods should be considered. DMTs with a short half-life, such as DMF which has a terminal half-life of 1 h (Biogen, 2017), do not require a washout; however, washout periods should be considered for DMTs with longer half-lives (e.g., teriflunomide and ocrelizumab). Teriflunomide-treated patients should undergo an accelerated elimination procedure to rapidly decrease plasma drug levels (Genzyme Corp., 2016). For natalizumab, a washout period is not specified, and its use during pregnancy should be reserved for patients only with significant disease activity following a benefit–risk evaluation (Montalban et al., 2018). While reproductive toxicity (i.e., negative effects on embryofetal development) and hematologic abnormalities in newborns have been observed following natalizumab exposure, the rate of these adverse events is comparable with the general population (Haghikia et al., 2014; Hellwig et al., 2011). As a precaution, given the high frequency of hematological abnormalities, natalizumab use during the third trimester should only be considered as a last resort (Haghikia et al., 2014). Routine screening for these abnormalities should be performed as long as natalizumab is being used during pregnancy. Extended interval dosing every 6–8 weeks may also be performed to reduce exposure to natalizumab while preventing breakthrough disease activity (Bomprezzi and Pawate, 2014). Alternatively, glatiramer acetate (GA) and interferon beta (IFNβ) may be used in patients who wish to become pregnant, as neither therapy has been associated with negative pregnancy effects in humans (Coyle, 2016).

Patients receiving DMTs with non-continuous dosing regimens, such as cladribine, should avoid pregnancy until the washout period following the last dose is complete. Women receiving cladribine should use effective contraception during treatment and for at least 6 months after the last dose. Patients should also consider both a hormonal and barrier contraceptive method for at least 4 weeks after the last dose in each treatment year (Merck Serono Europe Ltd., 2018).

In patients receiving alemtuzumab, low to undetectable concentrations of the drug have been detected in serum 30 days following each treatment course (Genzyme Corp., 2017). Hypothyroidism, which has been observed in patients on alemtuzumab, may result in an increased risk of miscarriage or other fetal effects; thyroid function tests are required prior to treatment initiation and every 3 months thereafter (Genzyme Therapeutics, 2018). Neonatal Graves' disease has also been noted due to placental transfer of anti-thyroid antibodies (Genzyme Corp., 2017). For these reasons, women on alemtuzumab should avoid pregnancy during treatment and for at least 4 months after the last infusion (Genzyme Corp., 2017). A six-month washout period is recommended in patients receiving ocrelizumab in the US (12 months in Europe) (Genentech Inc., 2018; Roche Registration GmbH, 2018). If ocrelizumab use is continued during pregnancy, and due to the risk of B-cell depletion, B-cell counts should be checked in newborns. Live or live-attenuated vaccines should not be administered prior to confirming recovery of B-cell counts in these infants (Genentech Inc., 2018). Rituximab, which is indicated for hematologic malignancies and rheumatoid arthritis, has been used off-label for MS treatment in some countries (Chakravarty et al., 2011). As there have been reported incidences of congenital malformations and neonatal infections associated with its use, patients should avoid pregnancy for up to 12 months after rituximab exposure (Salzer et al., 2016).

3.3. Genetic risk

The risk of passing MS to children is a significant concern among women living with MS. In a large North American Research Committee on MS (NARCOMS) registry study, 35% of patients with MS cited this potential risk as the reason for why they chose not to have children after an MS diagnosis (Alwan et al., 2013). While the risk of inheriting MS from a parent with the disease is low (2–3%), there are genetic risk factors, such as HLA-associated variants, that may be inherited and increase the risk of developing MS (Coyle, 2016; Olsson et al., 2016; Xia et al., 2016). Recent genome-wide association studies (GWAS) have also demonstrated that families with multiple MS cases carry more MS-associated susceptibility variants than families with fewer affected relatives (Isobe et al., 2013). However, there are many additional factors that play a role in MS pathogenesis, such as environmental factors, incomplete penetrance, and epigenetic changes (Kucukali et al., 2015). Despite this, regular pre-conception genetic testing for risk factors associated with MS is not currently available (Buraga and Popovici, 2014).

4. Pregnancy

4.1. General medical management

While not a requirement, given the association between Vitamin D deficiency and increased MS risk, women with MS should be advised to take prenatal vitamins including Vitamin D and folic acid (Coyle, 2016; Jalkanen et al., 2015). To ensure adequate supplementation, Vitamin D levels should be monitored throughout pregnancy (Lerchbaum and Rabe, 2014). As in the general population, patients should also avoid alcohol and smoking, and ensure adequate sleep and a balanced diet during pregnancy (Coyle, 2016). Since women with MS may be more susceptible to urinary tract infections, special attention should be given to the detection and treatment of such infections in pregnant women with MS (Mahadeva et al., 2014).

While the amount of data available on DMT safety in patients who become pregnant are increasing, those who have received DMTs at the time of conception should still be encouraged to participate in a formal pregnancy registry (Coyle, 2016). In newly diagnosed patients, pregnancy should be delayed until the disease is adequately controlled with a DMT (1–2 years depending on disease activity) unless there is a concern about rapidly declining fertility due to advanced age. HCPs need to explain the pregnancy-related risks of DMTs within the context

Table 2
Guidelines for use of approved multiple sclerosis (MS) disease-modifying therapy (DMTs) pre-pregnancy, during pregnancy, and during breastfeeding.

DMT	*Washout period*	*Pregnancy use*	*Breastfeeding*	*Special concerns*
Alemtuzumab[a]	4 months after last course of treatment	EU/US: Limited data; use only if benefit outweighs potential risk to fetus	EU: Discontinue during each course of treatment and 4 months after last infusion US: Limited data; discontinue either breastfeeding or therapy	Risk of thyroid disease; women with hypothyroidism should be treated during pregnancy; risk of neonatal Grave's disease (transplacental passage of anti-thyroid antibodies)
Cladribine[b] ***(EU only)***	6 months after the last course of treatment	Do not use	Do not use	Based on human experience with other DNA inhibitors, could cause congenital malformations during pregnancy
Dimethyl fumarate[c] *Coyle, 2016*	Not required	EU/US: Limited data; use only if benefit outweighs potential risk to fetus	EU/US: Limited data; use caution when nursing	N/A
Fingolimod[d]	6–8 weeks	EU: Contraindicated for use during pregnancy US: Limited data; use only if benefit outweighs potential risk to fetus	EU/US: Do not use	Potential risk of fetal loss and vascular malformations
GA[e]	Not required	EU/US: Limited data; use only if benefit outweighs potential risk to fetus	EU/US: Limited data; use caution when nursing	N/A
Interferon beta (Thiel et al., 2016; Vaughn et al., 2018)	Not required	EU: Contraindicated for use during pregnancy US: Limited data; use only if benefit outweighs potential risk to fetus	EU/US: Limited data; consider the mother's clinical need and any potential adverse effects on the breastfed child	N/A
Natalizumab[f]	Not required	EU: Use only if benefit outweighs potential risk to fetus US: No adequate data	EU: Do not use US: Use only if benefit outweighs potential risk to infant	Mild to moderate hematologic alterations
Ocrelizumab[g]	EU: 12 months US: 6 months	EU: Use only if benefit outweighs potential risk to fetus US: Limited data; do not use	EU: Do not use US: Use only if benefit outweighs potential risk to infant	B-cell depletion in infants
Teriflunomide[h]	Use accelerated elimination procedure to lower serum level concentrations to below 0.02 mg/L	EU/US: Contraindicated for use during pregnancy	EU: Do not use US: Use only if benefit outweighs potential risk to infant	Potential for serious birth defects

EU, European Union; GA, glatiramer acetate; N/A, not available; US, United States. From European Summaries of Product Characteristics and US full Prescribing Information for [a]Lemtrada®, [b]Mavenclad®, [c]Tecfidera®, [d]Gilenya®, [e]Copaxone®, [f]Tysabri®, [g]Ocrevus®, and [h]Aubagio®.

Table 3
Disease-modifying therapy recommendations in patients with mild/moderate and high disease activity.

	Mild/moderate disease activity (≤1 relapses in prior year)	High disease activity (≥2 relapses in prior year)
Treatment-naïve	Delay pregnancy until 1 year of stability is achieved	Delay pregnancy until disease is adequately controlled (1–2 years) (Hughes et al., 2014)
On-treatment	Discontinue treatment prior to pregnancy (with the exception of GA 20 and 40 mg/mL and IFNβ, DMF, and natalizumab, which can be continued if necessary)(Biogen, 2017, 2018a,b,c; Montalban et al., 2018)	Treatment with natalizumab during pregnancy, or alemtuzumab or cladribine prior to pregnancy may be considered after discussion of the potential implications. Conception should be delayed 6 (US) to 12 (EU) months after the last dose of ocrelizumab (Genentech Inc., 2018; Montalban et al., 2018; Roche Registration GmbH, 2018)

DMF, dimethyl fumarate; EU, European Union; GA, glatiramer acetate; IFNβ, interferon beta; US, United States.

of the background rates of miscarriage and congenital abnormalities. No DMT is considered entirely safe for use during pregnancy. However, pregnant women who have been exposed to a variety of DMTs thus far report obstetric and neonatal complications (e.g., malformations or pregnancy complications) at rates similar to the general population (Cree, 2013; Davenport et al., 2016; Dung and Panda, 2014; Fragoso et al., 2010; Kieseier and Benamor, 2014; Salminen et al., 2010; Vukusic et al., 2017). The decision to continue DMT use depends on disease severity and the DMT in question (Table 3).

Data on pregnancy outcomes are starting to emerge for most DMTs. However, only GA and the IFNβs (as a class) have more than a thousand human exposures (Jesus-Ribeiro et al., 2017; Romero et al., 2015; Sandberg-Wollheim et al., 2011). GA displays a favorable safety profile, with congenital anomaly rates similar to those in the general population in over 7000 exposures (Sandberg-Wollheim et al., 2018). There have been over 2000 pregnancy exposures with IFNβ. In a study of 445 pregnant women with MS in the German Multiple Sclerosis and Pregnancy Registry, early exposure to IFNβ prevented significantly more relapses compared to untreated patients and had no apparent effect on pregnancy outcomes (Thiel et al., 2016). The long-term impact of natalizumab treatment on pregnancy outcomes is unclear. In an observational study of 376 MS or Crohn's disease patients in the Tysabri Pregnancy Exposure Registry, there was no specific pattern of birth defects that would suggest a drug association (Friend et al., 2016). In patients receiving natalizumab, the combination of avoiding washout prior to conception along with early resumption after delivery is most effective for preventing maternal disease worsening (Portaccio et al., 2018).

Overall, European Committee for Treatment and Research in Multiple Sclerosis/European Academy of Neurology (ECTRIMS/EAN) guidelines recommend IFNβ or GA use until the pregnancy is confirmed (Montalban et al., 2018). Those with persistent high-disease activity may also continue treatment with natalizumab, but only after a thorough discussion of the potential implications with the patient. In very active cases, alemtuzumab may continue to be used as long as conception is avoided for at least 4 months after the last infusion (Montalban et al., 2018). Pregnancy-related American Academy of Neurology (AAN) practice guidelines are much less specific. Clinicians are told to monitor reproductive plans, and counsel regarding reproductive risks and use of birth control (Rae-Grant et al., 2018).

Relapse frequency typically decreases during pregnancy. In a recent, retrospective, administrative claims US database study of 2867 women with MS and live births, relapse rates decreased from approximately 1.7% in the 3 months before pregnancy to 1% in the first trimester (Houtchens et al., 2018). Patients who continue to experience relapses may benefit from corticosteroids. There are conflicting data suggesting that corticosteroids may increase the risk of birth defects and miscarriage and so their use should be restricted to the treatment of acute relapses that substantially impact daily life (Bjorn et al., 2015; Smets et al., 2017). Different corticosteroids reach the fetus to different degrees. Approximately 100% of dexamethasone reaches the fetus, and therefore should be avoided (Hellwig, 2014). Corticosteroids are safe even during the first trimester and use does not increase risk for cleft lip or palate (Skuladottir et al., 2014). Those with severe relapses throughout pregnancy may benefit from methylprednisolone or prednisolone; these are metabolized and inactivated in the placenta (Brookings and Lee, 2009). While data are limited, plasma exchange may also be safe in women who experience severe relapses (Correia et al., 2018; Cox et al., 2017). Overall, general pharmacotherapy for MS symptoms during pregnancy (e.g., corticosteroids, analgesics, spasticity treatment options, and antidepressants) should be evaluated carefully and used at the minimum effective dose, for as short a time as possible.

4.2. Impact on MS disease activity and course

Pregnancy in MS does not appear to increase the risk of exacerbations; in fact, a reduction in disease activity appears coincident with increasing concentrations of gestation-related steroid hormones, among other factors (Sicotte et al., 2002), which are most evident during the final trimester (Coyle, 2016). In addition, studies have shown that disability worsening is more rapid in nulliparous women compared to multiparous women with MS (Teter et al., 2014). Previous choice of DMT, however, can have an adverse impact; rebound disease activity has been observed in patients after treatment discontinuation with fingolimod or natalizumab (Clerico et al., 2017; Meinl et al., 2018).

The impact of pregnancy on relapse rates was first reported in the seminal Pregnancy in Multiple Sclerosis study, a multi-center, prospective, observational study examining the impact of pregnancy and the postpartum state on MS disease activity in untreated patients (Confavreux et al., 1998). Of the 254 pregnancies in this study, relapse rates during the third trimester were reduced by 70% compared to the year before pregnancy. Similar results have been observed in more recent studies. In a retrospective, administrative claims database study, which followed 2158 women living with MS and a live birth, adjusted relapse rates per month were significantly lower during pregnancy compared to the pre-pregnancy period; however, monthly adjusted relapse rates increased from 0.99% in the third trimester of pregnancy to 2.56% in the 6-week puerperium period (Houtchens et al., 2018).

Relapses before and during pregnancy are associated with an increased risk of postpartum relapse (Hughes et al., 2014; Jesus-Ribeiro et al., 2017). The potential influence of DMT treatment on postpartum relapse rate was assessed in a prospective study of MS patients in the Italian Pregnancy dataset; in this study, early introduction or resumption of DMTs within the first 3 months post-birth was associated with a reduced, albeit marginal, risk of postpartum relapses (Portaccio et al., 2014). In an MSBase study of 893 pregnancies in women with MS, DMT use in the 2 years prior to conception was protective against postpartum relapses after delivery (Hughes et al., 2014).

The association between relapses and postpartum disease activity prompts the need for standardized treatment guidelines (Jesus-Ribeiro et al., 2017). International or country-specific guidance, such as ECTRIMS/EAN (Montalban et al., 2018), AAN (Rae-Grant et al., 2018),

and the UK National Institute for Health and Care Excellence (NICE) guidelines, emphasize the need for discussion of how pregnancy might reduce relapse rates, with the possibility of a transient increase after delivery (National Institute for Health and Care Excellence, 2014). Treatment plans should balance the risk posed by the DMT to the fetus and/or mother with regard to teratogenicity, fetotoxicity, and the potential of further disease progression (Vukusic and Marignier, 2015).

4.3. Peripartum care guidelines

MS confers no increased risk for miscarriage or congenital malformation. The course of a typical pregnancy in women with MS is similar to that in women without MS, albeit with a tendency towards increased use of assisted delivery/Caesarean section and possibly lower neonatal birth weights (Hellwig, 2014; Oreja-Guevara et al., 2014). Caesarean sections are not mandatory for women with relapsing remitting MS, and any anesthetic choice or delivery method is acceptable (Pasto et al., 2012). Epidural and spinal anesthesia are acceptable for obstetric pain management in MS patients (Conradi et al., 2013; Ragnedda et al., 2015), as their use has no impact on future disability or disease activity; no correlation has been made between epidural analgesia use and postpartum relapses or disability progression (Lu et al., 2013a; Pasto et al., 2012). Having MS does not create a high-risk pregnancy, and duration of birth hospitalization is not extended (Lu et al., 2013b). However, supportive care and counseling from MS HCPs should be provided throughout all stages of pregnancy (Baird and Dalton, 2013).

5. Postpartum

5.1. Disease activity

As mentioned previously, the first 3 months postpartum are a high-risk period for increased clinical and magnetic resonance imaging (MRI) disease activity, after which activity declines to pre-pregnancy levels (Alroughani et al., 2018). In women at relatively high risk of postpartum relapse (very active disease pre-pregnancy, poor prognostic profile, relapse during pregnancy, and/or no prior DMT use), rapid re-initiation of a DMT after delivery may be advisable (Coyle, 2016). Use of corticosteroids can be considered for symptomatic treatment during acute postpartum exacerbations of MS (Alroughani et al., 2016); however, while methylprednisolone transfer to breastmilk is minimal, breastfeeding should be delayed between 2 and 4 h after treatment to minimize infant exposure (Boz et al., 2017).

5.2. Breastfeeding

While the benefits of breastfeeding on infant health are well known, its potential benefit of reducing disease activity in patients with MS is inconclusive (Langer-Gould and Hellwig, 2013; Vukusic and Confavreux, 2013). Mothers without relapses during pregnancy, or with no active disease as indicated by MRI 2–4 months after delivery, may choose to breastfeed for the WHO-recommended 6 months (Alroughani et al., 2016; Hellwig et al., 2015). While some studies have found that exclusive breastfeeding for at least 2 months after delivery can decrease postpartum relapse risk (Hellwig et al., 2015), other researchers found that breastfeeding had no influence on postpartum relapses (Jesus-Ribeiro et al., 2017). Evidence also suggests that exclusive breastfeeding by mothers with MS may offer the infant protection from MS later in life (Conradi et al., 2013; Coyle, 2016; Ragnedda et al., 2015).

The decision to restart DMTs after delivery or breastfeeding is an important issue for women living with MS. There is limited information available on the safety of DMT use during lactation, as well as the extent of DMT transfer to breastmilk (Table 2) (Almas et al., 2016). IFNβ and GA may be considered during lactation, as GA is considered safe, with no known transfer to breastmilk, and negligible levels of IFNβ in breastmilk have been detected (0.006% of the maternal dose) (Hale et al., 2012; Teva Neuroscience, 2018). While the transfer of other DMTs (e.g., fingolimod, cladribine, and DMF) to breastmilk has not been confirmed, it is considered highly likely, and thus not recommended in breastfeeding mothers (Almas et al., 2016). With the exception of natalizumab, which has been detected in breastmilk at concentrations ranging from 2 to 412 ng/mL, it is unknown whether other monoclonal antibodies (such as alemtuzumab and ocrelizumab) are transferred into breastmilk (Almas et al., 2016; Biogen, 2018b; Genentech Inc., 2018; Proschmann et al., 2018). Currently, women are advised to discontinue monoclonal antibody use while breastfeeding.

6. Progressive forms of MS

There are limited data on the impact of progressive MS on obstetric outcomes and vice versa. In a study of 973 women with clinically definite MS, results suggested that pregnancy at a younger age and use of oral contraceptives might adversely affect patients with progressive MS (D'Hooghe et al., 2012). However, until further studies resolve this question, pregnant women with progressive MS should be managed in a similar manner to patients with relapsing MS (Coyle, 2016). In very disabled patients, assisted vaginal delivery or Caesarean section may need to be considered (Coyle, 2016).

Few studies have investigated the safety of DMTs in pregnant patients with progressive forms of MS. Ocrelizumab is indicated for use in patients with primary progressive MS (Genentech Inc., 2018; Roche Registration GmbH, 2018), although women of reproductive potential are advised to continue to use contraception while receiving treatment, and for 6–12 months after the last infusion (Genentech Inc., 2018; Roche Registration GmbH, 2018).

7. Conclusions

While the care of women living with MS during pregnancy and the peripartum period can be complex, this review attempts to summarize the evidence and expert recommendations about specific issues in each of these periods. Most patients with MS can safely become pregnant and deliver healthy children, without adversely affecting their own health or MS disease course (Coyle, 2016). As the prevalence of MS continues to increase among women of reproductive potential, neurologists will play a growing role in managing these MS patients during all stages of family planning and pregnancy. Neurologists, primary care physicians, and OB/GYNs will continue to help these patients make informed decisions and choices related to pregnancy (Rasmussen et al., 2018). Physician and patient education will be critical to increase comfort level with pregnancy planning and improve safety and outcomes in this group of patients.

Conflicts of interest

Patricia K Coyle: Consulting fees from Accordant, Bayer, Biogen Idec, Celgene, Genentech/Roche, Genzyme/Sanofi, Novartis, Serono, Teva; research support from Actelion, Alkermes, Genentech/Roche, MedDay, NINDS, Novartis. **Jiwon Oh:** Consulting or speaking fees (Biogen Idec, Celgene, EMD Serono, Genzyme, Novartis, Roche), Grant/research support (Biogen Idec, MS Society of Canada, National MS Society, Brain Canada). **Melinda Magyari:** Consulting and speaking fees (Biogen, Sanofi, Teva, Roche, Novartis, Merck). **Celia Oreja-Guevara:** Consulting or speaking fees (Merck, Sanofi-Genzyme, Biogen Idec, Teva, Celgene, Novartis, Roche). **Maria Houtchens:** Consulting fees from Biogen, Genentech, Genzyme, Serono, Teva; research support from Genzyme, Biogen, Serono.

Financial support

Development of this manuscript was supported by Sanofi.

Author contributions

1 **Patricia K Coyle**: Conception and design, data analysis and interpretation, manuscript review and critique.
2 **Jiwon Oh:** Conception and design, data analysis and interpretation, manuscript review and critique.
3 **Melinda Magyari:** Conception and design, data analysis and interpretation, manuscript review and critique.
4 **Celia Oreja-Guevara:** Conception and design, data analysis and interpretation, manuscript review and critique.
5 **Maria Houtchens:** Conception and design, data analysis and interpretation, manuscript review and critique.

All authors have read, commented on the manuscript and approved the final manuscript.

Acknowledgments

Medical writing and editorial support, under the direction of the authors, was provided by Laura Geuss, PhD (Onyx, New York, USA), funded by Sanofi, according to Good Publication Practice guidelines (Link). The manuscript was reviewed for scientific accuracy by Darren P Baker, PhD, Jonathan Valenzano, PharmD, and Karyn Liu, PhD, of Sanofi. The authors were responsible for all content and editorial decisions, and received no honoraria related to the development of this publication.

References

Airas, L., Kaaja, R., 2012. Pregnancy and multiple sclerosis. Obstet. Med. 5 (3), 94–97.
Almas, S., Vance, J., Baker, T., Hale, T., 2016. Management of multiple sclerosis in the breastfeeding mother. Mult. Scler. Int. 2016, 6527458.
Alroughani, R., Alowayesh, M.S., Ahmed, S.F., Behbehani, R., Al-Hashel, J., 2018. Relapse occurrence in women with multiple sclerosis during pregnancy in the new treatment era. Neurology 90 (10), e840–e846.
Alroughani, R., Altintas, A., Al Jumah, M., Sahraian, M., Alsharoqi, I., AlTahan, A., Daif, A., Dahdaleh, M., Deleu, D., Fernandez, O., Grigoriadis, N., Inshasi, J., Karabudak, R., Taha, K., Totolyan, N., Yamout, B.I., Zakaria, M., Bohlega, S., 2016. Pregnancy and the use of disease-modifying therapies in patients with multiple sclerosis: benefits versus risks. Mult. Scler.Mult. Scler. Int. 2016, 1034912.
Altintas, A., Najar, B., Gozubatik-Celik, G., Menku, S.F., 2015. Pregnancy data in a Turkish multiple sclerosis population. Eur. Neurol. 74 (5–6), 296–302.
Alwan, S., Yee, I.M., Dybalski, M., Guimond, C., Dwosh, E., Greenwood, T.M., Butler, R., Sadovnick, A.D., 2013. Reproductive decision making after the diagnosis of multiple sclerosis (MS). Mult. Scler. 19 (3), 351–358.
Andersen, J.B., Moberg, J.Y., Niclasen, J., Laursen, B., Magyari, M., 2018. Mental health among children of mothers with multiple sclerosis: a Danish cohort and register-based study. Brain Behav. e1098.
Baird, S.M., Dalton, J., 2013. Multiple sclerosis in pregnancy. J. Perinat. Neonatal. Nurs. 27 (3), 232–241.
Biogen, 2017. Tecfidera (dimethyl fumarate) [package insert]. https://www.tecfidera.com/content/dam/commercial/multiple-sclerosis/tecfidera/pat/en_us/pdf/full-prescribing-info.pdf. Accessed 13 July 2018.
Biogen, 2018. Tecfidera (dimethyl fumarate) [summary of product characteristics]. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002601/WC500162069.pdf. Accessed 13 July 2018.
Biogen, 2018. Tysabri (natalizumab) [package insert]. https://www.tysabri.com/content/dam/commercial/multiple-sclerosis/tysabri/pat/en_us/pdfs/tysabri_prescribing_information.pdf. Accessed 13 July 2008.
Biogen, 2018. Tysabri (natalizumab) [summary of product characteristics]. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000603/WC500044686.pdf. Accessed 13 July 2018.
Bjorn, A.M., Ehrenstein, V., Nohr, E.A., Norgaard, M., 2015. Use of inhaled and oral corticosteroids in pregnancy and the risk of malformations or miscarriage. Basic Clin. Pharmacol. Toxicol. 116 (4), 308–314.
Bomprezzi, R., Pawate, S., 2014. Extended interval dosing of natalizumab: a two-center, 7-year experience. Ther. Adv. Neurol. Disord. 7 (5), 227–231.
Borisow, N., Paul, F., Ohlraun, S., Pach, D., Fischer, F., Dorr, J., 2014. Pregnancy in multiple sclerosis: a questionnaire study. PLoS One 9 (6), e99106.
Bove, R., Alwan, S., Friedman, J.M., Hellwig, K., Houtchens, M., Koren, G., Lu, E., McElrath, T.F., Smyth, P., Tremlett, H., Sadovnick, A.D., 2014. Management of multiple sclerosis during pregnancy and the reproductive years: a systematic review. Obstet. Gynecol. 124 (6), 1157–1168.
Boz, C., Terzi, M., Zengin Karahan, S., Sen, S., Sarac, Y., Emrah Mavis, M., 2017. Safety of IV pulse methylprednisolone therapy during breastfeeding in patients with multiple sclerosis. Mult. Scler. Epub ahead of print.
Brookings, W., Lee, M., 2009. Management of multiple sclerosis during pregnancy. Progress Neurol. Psychiatry 13 (6), 9–11.
Brzosko, B., Thiel, S., Gold, R., Hellwig, K., 2018. Low Relapse Risk Under Disease Modifying Treatment During ART in Women With Relapsing Remitting Multiple Sclerosis (P356). AAN, Los Angeles, CA.
Buraga, I., Popovici, R.E., 2014. Multiple sclerosis and pregnancy: current considerations. Sci.WorldJ. 2014, 513160.
Calhaz-Jorge, C., De Geyter, C., Kupka, M.S., de Mouzon, J., Erb, K., Mocanu, E., Motrenko, T., Scaravelli, G., Wyns, C., Goossens, V., 2017. Assisted reproductive technology in Europe, 2013: results generated from European registers by ESHRE. Hum. Reprod. 32 (10), 1957–1973.
Carvalho, A.T., Veiga, A., Morgado, J., Tojal, R., Rocha, S., Vale, J., Sa, M.J., Timoteo, A., 2014. Multiple sclerosis and motherhood choice: an observational study in Portuguese women patients. Rev. Neurol. 59 (12), 537–542.
Centers for Disease Control and Prevention, 2018. Assisted Reproductive Technology (ART) Data. http://nccd.cdc.gov/drh_art. Accessed 4 October 2018.
Chakravarty, E.F., Murray, E.R., Kelman, A., Farmer, P., 2011. Pregnancy outcomes after maternal exposure to rituximab. Blood 117 (5), 1499–1506.
Chandra, A., Copen, C.E., Stephen, E.H., 2013. Infertility and impaired fecundity in the United States, 1982-2010: data from the National Survey of Family Growth. Natl. Health Stat. Rep. 14 (67), 1–18.
Clerico, M., Artusi, C.A., Liberto, A.D., Rolla, S., Bardina, V., Barbero, P., Mercanti, S.F., Durelli, L., 2017. Natalizumab in multiple sclerosis: long-term management. Int. J. Mol. Sci. 18 (5).
Confavreux, C., Hutchinson, M., Hours, M.M., Cortinovis-Tourniaire, P., Moreau, T., 1998. Rate of pregnancy-related relapse in multiple sclerosis. Pregnancy in multiple sclerosis group. N. Engl. J. Med. 339 (5), 285–291.
Conradi, S., Malzahn, U., Paul, F., Quill, S., Harms, L., Then Bergh, F., Ditzenbach, A., Georgi, T., Heuschmann, P., Rosche, B., 2013. Breastfeeding is associated with lower risk for multiple sclerosis. Mult. Scler. 19 (5), 553–558.
Correia, I., Ribeiro, J.J., Isidoro, L., Batista, S., Nunes, C., Macario, C., Borges, C., Tomaz, J., Sousa, L., 2018. Plasma exchange in severe acute relapses of multiple sclerosis - results from a Portuguese cohort. Mult. Scler. Relat. Disord. 19, 148–152.
Cox, J.L., Koepsell, S.A., Shunkwiler, S.M., 2017. Therapeutic plasma exchange and pregnancy: a case report and guidelines for performing plasma exchange in a pregnant patient. J. Clin. Apher. 32 (3), 191–195.
Coyle, P.K., 2016. Management of women with multiple sclerosis through pregnancy and after childbirth. Ther. Adv. Neurol. Disord. 9 (3), 198–210.
Coyle, P.K., Christie, S., Fodor, P., Fuchs, K., Giesser, B., Gutierrez, A., Lynn, J., Weinstock-Guttman, B., Pardo, L., Women Neurologists MS Initiative, 2004. Multiple sclerosis gender issues: clinical practices of women neurologists. Mult. Scler. 10 (5), 582–588.
Cree, B.A., 2013. Update on reproductive safety of current and emerging disease-modifying therapies for multiple sclerosis. Mult. Scler. 19 (7), 835–843.
Cuello, J., Romero Delgado, F., Lozano Ros, A., Salgado Camara, P., Garcia Dominguez, J., Higueras, Y., Goicochea Briceño, H., Garcia-Tizon Larroca, S., De Leon-Luis, J., Martinez Gines, M., 2017. Time to pregnancy in multiple sclerosis: a case-control study. Austin J. Clin. Neurol. 4 (6), 1123–1127.
Curtis, K.M., Tepper, N.K., Jatlaoui, T.C., Berry-Bibee, E., Horton, L.G., Zapata, L.B., Simmons, K.B., Pagano, H.P., Jamieson, D.J., Whiteman, M.K., 2016. U.S. medical eligibility criteria for contraceptive use, 2016. MMWR Recomm. Rep. 65 (3), 1–103.
D'Hooghe, M.B., Haentjens, P., Nagels, G., D'Hooghe, T., De Keyser, J., 2012. Menarche, oral contraceptives, pregnancy and progression of disability in relapsing onset and progressive onset multiple sclerosis. J. Neurol. 259 (5), 855–861.
Davenport, L., Beyer, B., Truffinet, P., Mandel, M., 2016. Nonclinical data demonstrate high sensitivity of rats versus humans to embryo foetal toxicity when exposed to teriflunomide. Mult. Scler. 18 (S4), EP1420.
David, O.J., Ocwieja, M., Meiser, K., Emotte, C., Jakab, A., Wemer, J., den Daas, I., Schmouder, R., 2012. Pharmacokinetics of fingolimod (FTY720) and a combined oral contraceptive coadministered in healthy women: drug-drug interaction study results. Int. J. Clin. Pharmacol. Ther. 50 (8), 540–544.
Duan, S., Lv, Z., Fan, X., Wang, L., Han, F., Wang, H., Bi, S., 2014. Vitamin D status and the risk of multiple sclerosis: a systematic review and meta-analysis. Neurosci. Lett. 570, 108–113.
Dung, A.A., Panda, A.K., 2014. Interferon beta-1a therapy for multiple sclerosis during pregnancy: an unresolved issue. In: BMJ Case Rep 2014.
ESHRE Capri Workshop Group, 2010. Europe the continent with the lowest fertility. Hum. Reprod. Update 16 (6), 590–602.
Faculty of Sexual and Reproductive Health, 2016. UK Medical Eligibility Criteria for Contraceptive Use (UKMEC). United Kingdom.
Fragoso, Y.D., Finkelsztejn, A., Kaimen-Maciel, D.R., Grzesiuk, A.K., Gallina, A.S., Lopes, J., Morales, N.M., Alves-Leon, S.V., de Almeida, S.M., 2010. Long-term use of glatiramer acetate by 11 pregnant women with multiple sclerosis: a retrospective, multicentre case series. CNS Drugs 24 (11), 969–976.
Friend, S., Richman, S., Bloomgren, G., Cristiano, L.M., Wenten, M., 2016. Evaluation of pregnancy outcomes from the Tysabri(R) (natalizumab) pregnancy exposure registry: a global, observational, follow-up study. BMC Neurol. 16 (1), 150.
Genentech Inc., 2018. Ocrevus (ocrelizumab) [package insert]. https://www.gene.com/download/pdf/ocrevus_prescribing.pdf. Accessed 30 November 2018.
Genzyme Corp., 2016. Aubagio (teriflunomide) [package insert]. http://products.sanofi.us/aubagio/aubagio.html. Accessed 13 July 2018.
Genzyme Corp., 2017. Lemtrada (alemtuzumab) [package insert]. http://products.sanofi.us/lemtrada/lemtrada.html. Accessed 13 July 2018.
Genzyme Therapeutics, 2018. Lemtrada (alemtuzumab) [summary of product characteristics]. https://www.ema.europa.eu/documents/product-information/lemtrada-epar-product-information_en.pdf. Accessed 4 December 2018.
Haghikia, A., Langer-Gould, A., Rellensmann, G., Schneider, H., Tenenbaum, T., Elias-

Hamp, B., Menck, S., Zimmermann, J., Herbstritt, S., Marziniak, M., Kumpfel, T., Meinl, I., Plavina, T., Gold, R., Hellwig, K., 2014. Natalizumab use during the third trimester of pregnancy. JAMA Neurol. 71 (7), 891–895.
Hale, T.W., Siddiqui, A.A., Baker, T.E., 2012. Transfer of interferon beta-1a into human breastmilk. Breastfeed Med. 7 (2), 123–125.
Harbo, H.F., Gold, R., Tintore, M., 2013. Sex and gender issues in multiple sclerosis. Ther. Adv. Neurol. Disord. 6 (4), 237–248.
Hauser, S.L., Oksenberg, J.R., 2006. The neurobiology of multiple sclerosis: genes, inflammation, and neurodegeneration. Neuron 52 (1), 61–76.
Hellwig, K., 2014. Pregnancy in multiple sclerosis. Eur. Neurol. 72 (Suppl 1), 39–42.
Hellwig, K., Correale, J., 2013. Artificial reproductive techniques in multiple sclerosis. Clin. Immunol. 149 (2), 219–224.
Hellwig, K., Haghikia, A., Gold, R., 2011. Pregnancy and natalizumab: results of an observational study in 35 accidental pregnancies during natalizumab treatment. Mult. Scler. 17 (8), 958–963.
Hellwig, K., Rockhoff, M., Herbstritt, S., Borisow, N., Haghikia, A., Elias-Hamp, B., Menck, S., Gold, R., Langer-Gould, A., 2015. Exclusive breastfeeding and the effect on postpartum multiple sclerosis relapses. JAMA Neurol. 72 (10), 1132–1138.
Houtchens, M.K., Edwards, N.C., Phillips, A.L., 2018. Relapses and disease-modifying drug treatment in pregnancy and live birth in US women with MS. Neurology 91 (17), e1570–e1578.
Houtchens, M.K., Zapata, L.B., Curtis, K.M., Whiteman, M.K., 2017. Contraception for women with multiple sclerosis: guidance for healthcare providers. Mult. Scler. 23 (6), 757–764.
Hughes, S.E., Spelman, T., Gray, O.M., Boz, C., Trojano, M., Lugaresi, A., Izquierdo, G., Duquette, P., Girard, M., Grand'Maison, F., Grammond, P., Oreja-Guevara, C., Hupperts, R., Bergamaschi, R., Giuliani, G., Lechner-Scott, J., Barnett, M., Edite Rio, M., van Pesch, V., Amato, M.P., Iuliano, G., Slee, M., Verheul, F., Cristiano, E., Fernandez-Bolanos, R., Poehlau, D., Saladino, M.L., Deri, N., Cabrera-Gomez, J., Vella, N., Herbert, J., Skromne, E., Savino, A., Shaw, C., Moore, F., Vucic, S., Petkovska-Boskova, T., McDonnell, G., Hawkins, S., Kee, F., Butzkueven, H., MSBase study group, 2014. Predictors and dynamics of postpartum relapses in women with multiple sclerosis. Mult. Scler. 20 (6), 739–746.
Isobe, N., Damotte, V., Re, V.L., Ban, M., Pappas, D., Guillot-Noel, L., Rebeix, I., Compston, A., Mack, T., Cozen, W., Fontaine, B., Hauser, S.L., Oksenberg, J.R., Sawcer, S., Gourraud, P.A., 2013. Genetic burden in multiple sclerosis families. Genes Immun. 14 (7), 434–440.
Jalkanen, A., Kauko, T., Turpeinen, U., Hamalainen, E., Airas, L., 2015. Multiple sclerosis and vitamin D during pregnancy and lactation. Acta Neurol. Scand. 131 (1), 64–67.
Jesus-Ribeiro, J., Correia, I., Martins, A.I., Fonseca, M., Marques, I., Batista, S., Nunes, C., Macario, C., Almeida, M.C., Sousa, L., 2017. Pregnancy in Multiple Sclerosis: a Portuguese cohort study. Mult. Scler. Relat. Disord. 17, 63–68.
Kaplan, T., Bove, R., Galetta, K., Healy, B., Chitnis, T., Houtchens, M., 2018. Effect of pregnancy loss on MS disease activity (P4.370). Neurology 90 (15 Supplement).
Kieseier, B.C., Benamor, M., 2014. Pregnancy outcomes following maternal and paternal exposure to teriflunomide during treatment for relapsing-remitting multiple sclerosis. Neurol. Ther. 3 (2), 133–138.
Kim, D., Leurer, C., So, B., Casserly, C., Seyman, E., Baral, S., Oh, J., 2018. Sexual Dysfunction in Multiple Sclerosis: a Systematic Review and Meta-Analysis of Prevalence (P692). ECTRIMS, Berlin, Germany.
Koch-Henriksen, N., Thygesen, L.C., Stenager, E., Laursen, B., Magyari, M., 2018. Incidence of MS has increased markedly over six decades in Denmark particularly with late onset and in women. Neurology 90 (22), e1954–e1963.
Kucukali, C.I., Kurtuncu, M., Coban, A., Cebi, M., Tuzun, E., 2015. Epigenetics of multiple sclerosis: an updated review. Neuromolecular. Med. 17 (2), 83–96.
Langer-Gould, A., Hellwig, K., 2013. One can prevent post-partum MS relapses by exclusive breast feeding: yes. Mult. Scler. 19 (12), 1567–1568.
Lerchbaum, E., Rabe, T., 2014. Vitamin D and female fertility. Curr. Opin. Obstet. Gynecol. 26 (3), 145–150.
Lew-Starowicz, M., Gianotten, W.L., 2015. Sexual dysfunction in patients with multiple sclerosis. Handb. Clin. Neurol. 130, 357–370.
Lombardi, G., Celso, M., Bartelli, M., Cilotti, A., Del Popolo, G., 2011. Female sexual dysfunction and hormonal status in multiple sclerosis patients. J. Sex Med. 8 (4), 1138–1146.
Lu, E., Zhao, Y., Dahlgren, L., Preston, R., van der Kop, M., Synnes, A., Sadovnick, A.D., Traboulsee, A., Tremlett, H., 2013a. Obstetrical epidural and spinal anesthesia in multiple sclerosis. J. Neurol. 260 (10), 2620–2628.
Lu, E., Zhao, Y., Zhu, F., van der Kop, M.L., Synnes, A., Dahlgren, L., Sadovnick, A.D., Sayao, A.L., Tremlett, H., British Columbia Multiple Sclerosis Clinic, N., 2013b. Birth hospitalization in mothers with multiple sclerosis and their newborns. Neurology 80 (5), 447–452.
Magyari, M., Koch-Henriksen, N., Pfleger, C.C., Sorensen, P.S., 2013. Reproduction and the risk of multiple sclerosis. Mult. Scler. 19 (12), 1604–1609.
Mahadeva, A., Tanasescu, R., Gran, B., 2014. Urinary tract infections in multiple sclerosis: under-diagnosed and under-treated? A clinical audit at a large University Hospital. Am. J. Clin. Exp. Immunol. 3 (1), 57–67.
Manieri, M.C., Mahlanza, T.D., Houtchens, M., 2018. Disease-Modifying Therapies, Fertility, and Postpartum Multiple Sclerosis Course: Interim Report from the PREG-MS Group. ECTRIMS, Berlin, Germany.
Meinl, I., Havla, J., Hohlfeld, R., Kumpfel, T., 2018. Recurrence of disease activity during pregnancy after cessation of fingolimod in multiple sclerosis. Mult. Scler. 24 (7), 991–994.
Merck Serono Europe Ltd., 2018. Mavenclad (cladribine) [summary of product characteristics]. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004230/WC500234561.pdf. Accessed 13 July 2018.
Michel, L., Foucher, Y., Vukusic, S., Confavreux, C., de Seze, J., Brassat, D., Clanet, M., Clavelou, P., Ouallet, J.C., Brochet, B., Pelletier, J., Labauge, P., Lebrun, C., Lepage, E., Le Frere, F., Jacq-Foucher, M., Barriere, P., Wiertlewski, S., Laplaud, D.A., Club Francophone de la Sclerose En Plaques, 2012. Increased risk of multiple sclerosis relapse after *in vitro* fertilisation. J. Neurol. Neurosurg. Psychiatry 83 (8), 796–802.
Miller, A.E., 2015. Teriflunomide: a once-daily oral medication for the treatment of relapsing forms of multiple sclerosis. Clin. Ther. 37 (10), 2366–2380.
Montalban, X., Gold, R., Thompson, A.J., Otero-Romero, S., Amato, M.P., Chandraratna, D., Clanet, M., Comi, G., Derfuss, T., Fazekas, F., Hartung, H.P., Havrdova, E., Hemmer, B., Kappos, L., Liblau, R., Lubetzki, C., Marcus, E., Miller, D.H., Olsson, T., Pilling, S., Selmaj, K., Siva, A., Sorensen, P.S., Sormani, M.P., Thalheim, C., Wiendl, H., Zipp, F., 2018. ECTRIMS/EAN guideline on the pharmacological treatment of people with multiple sclerosis. Mult. Scler. 24 (2), 96–120.
MS International Federation, 2013. Atlas of MS. https://www.msif.org/about-us/who-we-are-and-what-we-do/advocacy/atlas/. Accessed 7 March 2018.
National Institute for Health and Care Excellence, 2014. Multiple sclerosis in adults: management. Clinical guideline [CG186]. https://www.nice.org.uk/guidance/cg186. Accessed 7 March 2018.
Nguyen, A.L., Havrdova, E.K., Horakova, D., Izquierdo, G., Kalincik, T., van der Walt, A., Terzi, M., Alroughani, R., Duquette, P., Girard, M., Prat, A., Boz, C., Sola, P., Ferraro, D., Lugaresi, A., Lechner-Scott, J., Barnett, M., Grand'Maison, F., Grammond, P., Ramo-Tello, C., Turkoglu, R., McCombe, P., Pucci, E., Trojano, M., Granella, F., Spitaleri, D., Van Pesch, V., Soysal, A., Oreja-Guevara, C., Verheul, F., Vucic, S., Hodgkinson, S., Slee, M., Ampapa, R., Prevost, J., Menoyo, J.L.S., Skibina, O., Solaro, C., Olascoaga, J., Shaw, C., Madsen, K.G., Naidoo, K., Hyde, R., Butzkueven, H., Jokubaitis, V., Group, M.S.S., 2019. Incidence of pregnancy and disease-modifying therapy exposure trends in women with multiple sclerosis: a contemporary cohort study. Mult. Scler. Relat. Disord. 28, 235–243.
Novartis Pharmaceuticals Corp., 2018. Gilenya (fingolimod) [package insert]. https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/gilenya.pdf. Accessed 13 July 2018.
Office of the Federal Register (US), 2014. Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling. https://www.federalregister.gov/documents/2014/12/04/2014-28241/content-and-format-of-labeling-for-human-prescription-drug-and-biological-products-requirements-for. Accessed 20 April 2018.
Olsson, T., Barcellos, L.F., Alfredsson, L., 2016. Interactions between genetic, lifestyle and environmental risk factors for multiple sclerosis. Nat. Rev. Neurol. 13, 25.
Oreja-Guevara, C., Wiendl, H., Kieseier, B.C., Airas, L., NeuroNet Study, G., 2014. Specific aspects of modern life for people with multiple sclerosis: considerations for the practitioner. Ther. Adv. Neurol. Disord. 7 (2), 137–149.
Pasto, L., Portaccio, E., Ghezzi, A., Hakiki, B., Giannini, M., Razzolini, L., Piscolla, E., De Giglio, L., Pozzilli, C., Paolicelli, D., Trojano, M., Marrosu, M.G., Patti, F., La Mantia, L., Mancardi, G.L., Solaro, C., Totaro, R., Tola, M.R., Di Tommaso, V., Lugaresi, A., Moiola, L., Martinelli, V., Comi, G., Amato, M.P., MS Study Group of the Italian Neurological Society, 2012. Epidural analgesia and cesarean delivery in multiple sclerosis post-partum relapses: the Italian cohort study. BMC Neurol. 12, 165.
Portaccio, E., Ghezzi, A., Hakiki, B., Sturchio, A., Martinelli, V., Moiola, L., Patti, F., Mancardi, G.L., Solaro, C., Tola, M.R., Pozzilli, C., De Giglio, L., Totaro, R., Lugaresi, A., De Luca, G., Paolicelli, D., Marrosu, M.G., Comi, G., Trojano, M., Amato, M.P., MS Study Group of the Italian Neurological Society, 2014. Postpartum relapses increase the risk of disability progression in multiple sclerosis: the role of disease modifying drugs. J. Neurol. Neurosurg. Psychiatry 85 (8), 845–850.
Portaccio, E., Moiola, L., Martinelli, V., Annovazzi, P., Ghezzi, A., Zaffaroni, M., Lanzillo, R., Brescia Morra, V., Rinaldi, F., Gallo, P., Tortorella, C., Paolicelli, D., Pozzilli, C., De Giglio, L., Cavalla, P., Cocco, E., Marrosu, M.G., Solaro, C., Uccelli, A., Laroni, A., Pasto, L., Giannini, M., Trojano, M., Comi, G., Amato, M.P., MS Study Group of the Italian Neurological Society, 2018. Pregnancy decision-making in women with multiple sclerosis treated with natalizumab: II: maternal risks. Neurology 90 (10), e832–e839.
Proschmann, U., Thomas, K., Thiel, S., Hellwig, K., Ziemssen, T., 2018. Natalizumab during pregnancy and lactation. Mult. Scler. 24 (12), 1627–1634.
Prunty, M., Sharpe, L., Butow, P., Fulcher, G., 2008. The motherhood choice: themes arising in the decision-making process for women with multiple sclerosis. Mult. Scler. 14 (5), 701–704.
Rae-Grant, A., Day, G.S., Marrie, R.A., Rabinstein, A., Cree, B.A.C., Gronseth, G.S., Haboubi, M., Halper, J., Hosey, J.P., Jones, D.E., Lisak, R., Pelletier, D., Potrebic, S., Sitcov, C., Sommers, R., Stachowiak, J., Getchius, T.S.D., Merillat, S.A., Pringsheim, T., 2018. Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology 90 (17), 777–788.
Ragnedda, G., Leoni, S., Parpinel, M., Casetta, I., Riise, T., Myhr, K.M., Wolfson, C., Pugliatti, M., 2015. Reduced duration of breastfeeding is associated with a higher risk of multiple sclerosis in both Italian and Norwegian adult males: the EnvIMS study. J. Neurol. 262 (5), 1271–1277.
Rankin, K., Zhao, C., Correale, J., Hellwig, K., Michel, L., Laplaud, D., Chitnis, T., Bove, R., 2018. Assisted reproductive technologies and multiple sclerosis relapses: a new case series, and pooled analyses of existing studies. (P4.366). Neurology 90 (15 Supplement).
Rasmussen, P.V., Magyari, M., Moberg, J.Y., Bogelund, M., Jensen, U.F.A., Madsen, K.G., 2018. Patient awareness about family planning represents a major knowledge gap in multiple sclerosis. Mult. Scler. Relat. Disord. 24, 129–134.
Roche Registration GmbH, 2018. Ocrevus (ocrelizumab) [Summary of Product Characteristics]. https://www.gene.com/download/pdf/ocrevus_prescribing.pdf. Accessed 13 July 2018.
Romero, R.S., Lunzmann, C., Bugge, J.P., 2015. Pregnancy outcomes in patients exposed

to interferon beta-1b. J. Neurol. Neurosurg. Psychiatry 86 (5), 587–589.
Roux, T., Courtillot, C., Debs, R., Touraine, P., Lubetzki, C., Papeix, C., 2015. Fecundity in women with multiple sclerosis: an observational mono-centric study. J. Neurol. 262 (4), 957–960.
Salminen, H.J., Leggett, H., Boggild, M., 2010. Glatiramer acetate exposure in pregnancy: preliminary safety and birth outcomes. J. Neurol. 257 (12), 2020–2023.
Salzer, J., Svenningsson, R., Alping, P., Novakova, L., Bjorck, A., Fink, K., Islam-Jakobsson, P., Malmestrom, C., Axelsson, M., Vagberg, M., Sundstrom, P., Lycke, J., Piehl, F., Svenningsson, A., 2016. Rituximab in multiple sclerosis: a retrospective observational study on safety and efficacy. Neurology 87 (20), 2074–2081.
Sandberg-Wollheim, M., Alteri, E., Moraga, M.S., Kornmann, G., 2011. Pregnancy outcomes in multiple sclerosis following subcutaneous interferon beta-1a therapy. Mult. Scler. 17 (4), 423–430.
Sandberg-Wollheim, M., Neudorfer, O., Grinspan, A., Weinstock-Guttman, B., Haas, J., Izquierdo, G., Riley, C., Ross, A.P., Baruch, P., Drillman, T., Coyle, P.K., 2018. Pregnancy outcomes from the branded glatiramer acetate pregnancy database. Int. J. MS Care 20 (1), 9–14.
Sicotte, N.L., Liva, S.M., Klutch, R., Pfeiffer, P., Bouvier, S., Odesa, S., Wu, T.C., Voskuhl, R.R., 2002. Treatment of multiple sclerosis with the pregnancy hormone estriol. Ann. Neurol. 52 (4), 421–428.
Siroos, B., Harirchian, M.H., 2014. Multiple sclerosis and pregnancy; What a neurologist may be asked for? Iran J. Neurol. 13 (2), 57–63.
Skinner, S., Guimond, C., Butler, R., Dwosh, E., Traboulsee, A.L., Sadovnick, A.D., 2015. An assessment of genetic counseling services for individuals with multiple sclerosis. J. Genet. Couns. 24 (1), 46–57.
Skuladottir, H., Wilcox, A.J., Ma, C., Lammer, E.J., Rasmussen, S.A., Werler, M.M., Shaw, G.M., Carmichael, S.L., 2014. Corticosteroid use and risk of orofacial clefts. Birth. Defects Res. A Clin. Mol. Teratol. 100 (6), 499–506.
Smets, I., Van Deun, L., Bohyn, C., van Pesch, V., Vanopdenbosch, L., Dive, D., Bissay, V., Dubois, B., Belgian Study Group for Multiple Sclerosis, 2017. Corticosteroids in the management of acute multiple sclerosis exacerbations. Acta Neurol. Belg. 117 (3), 623–633.
Teter, B., Kavak, K.S., Kolb, C., Coyle, P.K., Weinstock-Guttman, B., 2014. Parity associated with long-term disease progression in women with multuple sclerosis. J. Mult. Scler. 1 (1), 1–6.
Teva Neuroscience, 2018. Copaxone (glatiramer acetate) [package insert]. https://www.copaxone.com/interactivepi/index. Accessed 13 July 2018.
The American College of Obstetricians and Gynecologists, 2015. Committee opinion no. 642: increasing access to contraceptive implants and intrauterine devices to reduce unintended pregnancy. Obstet. Gynecol. 126 (4), e44–e48.
Thiel, S., Langer-Gould, A., Rockhoff, M., Haghikia, A., Queisser-Wahrendorf, A., Gold, R., Hellwig, K., 2016. Interferon-beta exposure during first trimester is safe in women with multiple sclerosis-a prospective cohort study from the German Multiple Sclerosis and Pregnancy Registry. Mult. Scler. 22 (6), 801–809.
Vaughn, C., Bushra, A., Kolb, C., Weinstock-Guttman, B., 2018. An update on the use of disease-modifying therapy in pregnant patients with multiple sclerosis. CNS Drugs 32 (2), 161–178.
Vukusic, S., Confavreux, C., 2013. One can prevent post-partum MS relapses by exclusive breast feeding: no. Mult. Scler. 19 (12), 1565–1566.
Vukusic, S., Coyle, P., Jurgensen, S., Truffinet, P., Benamor, M., Chambers, C., 2017. Pregnancy outcomes in patients with MS treated with teriflunomide: clinical study and post-marketing data. Mult. Scler. 23 (S3), 63.
Vukusic, S., Marignier, R., 2015. Multiple sclerosis and pregnancy in the 'treatment era'. Nat. Rev. Neurol. 11 (5), 280–289.
Wesselink, A.K., Rothman, K.J., Hatch, E.E., Mikkelsen, E.M., Sorensen, H.T., Wise, L.A., 2017. Age and fecundability in a North American preconception cohort study. Am J. Obstet. Gynecol. 217 (6), 667 e661-667 e668.
World Health Organization, 2015. Medical Eligibility Criteria for Contraceptive Use. http://www.who.int/reproductivehealth/publications/family_planning/MEC-5/en/. Accessed 21 August 2018.
Wundes, A., Pebdani, R.N., Amtmann, D., 2014. What do healthcare providers advise women with multiple sclerosis regarding pregnancy? Mult. Scler.Mult. Scler. Int. 2014, 819216.
Xia, Z., White, C.C., Owen, E.K., Von Korff, A., Clarkson, S.R., McCabe, C.A., Cimpean, M., Winn, P.A., Hoesing, A., Steele, S.U., Cortese, I.C., Chitnis, T., Weiner, H.L., Reich, D.S., Chibnik, L.B., De Jager, P.L., 2016. Genes and environment in multiple sclerosis project: a platform to investigate multiple sclerosis risk. Ann. Neurol. 79 (2), 178–189.
Yalcin, S.E., Yalcin, Y., Yavuz, A., Akkurt, M.O., Sezik, M., 2017. Maternal and perinatal outcomes in pregnancies with multiple sclerosis: a case-control study. J. Perinat. Med. 45 (4), 455–460.
Zhu, B., Nestorov, I., Zhao, G., Meka, V., Leahy, M., Kam, J., Sheikh, S.I., 2017. Evaluation of potential drug-drug interaction between delayed-release dimethyl fumarate and a commonly used oral contraceptive (norgestimate/ethinyl estradiol) in healthy women. Clin. Pharmacol. Drug Dev. 6 (6), 604–613.