R E V I E W

Updated Perspectives on the Challenges of Managing Multiple Sclerosis During Pregnancy

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Abstract: Multiple sclerosis (MS) is a chronic immune-mediated, inflammatory, and degenerative disease that is up to three times more frequent in young women. MS does not alter fertility and has no impact on fetal development, the course of pregnancy, or childbirth. The Pregnancy in Multiple Sclerosis Study in 1998 showed that pregnancy, mostly in untreated women, did not adversely affect MS, as disease activity decreased during pregnancy (although it significantly increased in the first trimester postpartum). These findings, together with the limited information available on the potential risks of fetal exposure to disease modifying treatments (DMTs), meant that women were advised to delay the onset of DMTs, stop them prior to conception, or, in case of unplanned pregnancy, discontinue them when pregnancy was confirmed. Now, many women with MS receive DMTs before pregnancy and, despite being considered a period of MS stability, up to 30% of patients could relapse in the first trimester postpartum. Factors associated with an increased risk of relapse and disability during pregnancy and postpartum include relapses before and during pregnancy, a greater disability at the time of conception, the occurrence of relapses after DMT cessation before conception, and the use of high-efficacy DMTs before conception, especially natalizumab or fingolimod. Strategies to prevent postpartum activity are needed in some patients, but consensus is lacking regarding the therapeutic strategies for women with MS of a fertile age. This, along with the increasing number of DMTs, means that the decision-making processes in aspects related to family planning and therapeutic strategies before, during, and after pregnancy are increasingly more complex. The purpose of this review is to provide an update on pregnancy-related issues in women with MS, including recommendations for counseling, general management, use of DMTs in pre-pregnancy, pregnancy, and postpartum periods, and breastfeeding-related aspects of DMTs.

Keywords: multiple sclerosis, pregnancy, disease modifying treatments, breastfeeding

Plain Language Summary

Studies in the late 90s showed that the clinical activity of MS clearly decreases during pregnancy and significantly increases after childbirth, mainly in the first trimester. According to these findings, after the irruption of different treatments with unknown fetal safety, women were advised to delay the onset or discontinue their treatments before conception, as the effects of pregnancy-associated hormones over the immune system could potentially control disease activity. It is now known that in certain circumstances, pregnancy by itself is not able to control the disease. Factors associated with an increased risk of disease activity during pregnancy and after delivery have been identified and several strategies to prevent postpartum reactivation (including, among others, exclusive breastfeeding) have been also proposed. These results, as well as the increasing experience with different MS treatments during early pregnancy and breastfeeding, warrant the application of an individualized approach in women of a fertile age

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with MS; furthermore, different treatment strategies can be applied in women with MS prior to conception, during pregnancy, and postpartum.

Introduction

Multiple sclerosis (MS) is a chronic immune-mediated, inflammatory, and degenerative disease of the central nervous system that is up to three times more frequent in women than in men,[1–3] with a female-to-male ratio incidence that has increased over time.[4,5] The higher prevalence of MS in young women, which can reach 200 cases per 100,000 inhabitants,[6,7] a delay in childbearing, and the introduction and implementation of new diagnostic criteria[8] contribute to the increasing proportion of women who become pregnant after an MS diagnosis. Up to 50% of couples who have not had children before an MS diagnosis have reported wanting to start a family in the future, and up to 25% of women have been reported to plan a pregnancy in the 2 years following their diagnosis.[9] It has been estimated that 20–30% of women with MS will deliver a child after disease onset.[9–11]

In the past, many couples have decided to avoid pregnancy for reasons related to MS;[12] furthermore, some authors have recently reported lower birth rates than expected in women with MS,[13] and the proportion of childlessness in women with MS has been reported to be higher than that in age-matched controls.[14] However, other recent studies have indicated that many women with MS plan to conceive after diagnosis,[9] which may explain the increase in the prevalence of pregnancy rates in women with MS and a decrease in women without MS.[15] This seems to reflect a better understanding and greater confidence of patients and neurologists about managing aspects of pregnancy that are related to MS. The annual incidence of pregnancies in a contemporary cohort of women with MS aged between 15 and 45 years was 4.2%, and this incidence reportedly decreases as disability increases.[16]

Sex Differences in MS

Like other autoimmune diseases, MS is more common in women. In the past six decades, the female-to-male ratio has markedly increased;[4,5,17] while this phenomenon appears to have stabilized,[18] this female-to-male ratio has been attributed to changes in lifestyle, environmental exposure, such as sun exposure, vitamin D deficiency, tobacco exposure, and epigenetic factors.[19] Female patients with MS have higher inflammatory activity and therefore have a higher relapse rate[20] and more inflammatory lesions, as revealed by magnetic resonance imaging (MRI).[21] Male patients with MS have more pronounced neurodegeneration, and therefore have a greater risk of disability[22–24] and cognitive dysfunction,[25] and reach secondary progressive MS sooner than women.[26] These sex differences have been explained by genetic differences in immune responses[27] and direct effects of sex hormones.[28] These sex-related differences are thought to disappear with menopause; when MS is diagnosed after the age of 50 years, there seem to be no sex-related differences in its evolution.[29]

Pregnancy and the Risk of MS

The risk of MS onset appears to decrease during pregnancy.[10,30] However, some authors have reported that the risk increases after delivery,[30–32] and others have found no differences in MS onset between the postpartum period and pre-pregnancy period.

Several epidemiological studies have found no association between number of pregnancies and subsequent risk of MS.[11,30,33–36] On the contrary, other authors have reported that MS risk was higher in nulliparous women, and that it increased with age.[10] Data from the Danish MS Registry have provided evidence that having children reduces the risk of MS by about 46% in women (but not in men) in the following 5 years.[37] Similar findings were reported by Ponsonby et al, who reported a 49% reduction in the risk of a first clinical attack of MS for each child born.[38] Recent work found that women with previous pregnancies and childbirths had a median delay of more than 3 years until the first clinical attack of MS compared with those who had never been pregnant.[39] It remains unclear if this proposed protector effect of pregnancy on MS risk is the result of a temporary immunotolerant state during pregnancy or a bias derived from prodromic symptoms of MS that result in choosing not to have children.[40,41] That said, in female patients with radiologically isolated syndrome, pregnancy has been associated with a shorter time of conversion to the first neurological event;[42] however, it is likely that the immunological process has already started in radiologically isolated syndrome, and postpartum reactivation could explain these results.

Effects of MS on Fertility, Pregnancy, and Childbirth

Although endocrinological changes[43,44] that are more pronounced with greater disease activity[45] have been reported

in women with MS, there is now a wide consensus that MS does not significantly alter fertility and has no impact on fetal development, the course of pregnancy, or childbirth.[1,14,46–49] However, an increase of caesarean sections, assisted delivery, preterm births, and lower birth weights have been reported in women with MS.[47,50–54] Some authors have also reported a higher risk of adverse delivery outcomes in patients with higher levels of disability.[55–57] It has been suggested that this is because physicians are more inclined to deliver patients with a presumed higher risk conservatively, rather than reflecting an effect of MS itself.[54] Conversely, women with MS may have an increased risk of infection during pregnancy, particularly genitourinary and upper respiratory infections.[53,58]

The Impact of Pregnancy on MS Course

The Impact of Pregnancy on the Short-Term Course of MS

Most of the current knowledge about the evolution of MS during pregnancy and after delivery has been obtained from the multicenter Pregnancy in Multiple Sclerosis Study,[59–61] which was the first prospective study to explore the relationship between pregnancy and MS. This study included untreated women with MS, most of whom were in their first pregnancy. It showed a reduction of more than 70% in the annualized relapse rate (ARR) during pregnancy, which is more than any therapeutic effect reported to date, and a significant ARR increase in the first 3 months postpartum. Thus, the ARR of the 9 months of pregnancy and the first 3 months after delivery combined was the same as the pre-gestational ARR. Numerous subsequent studies[62–65] and three meta-analyses[66–68] have confirmed that the risk of relapse is reduced during pregnancy and significantly increases after childbirth, mainly in the first trimester, according to pregnancy and pre-pregnancy rates. This pattern has also been demonstrated by MRI studies showing a postpartum increase in T2 and gadolinium-enhanced lesions.[69–71]

Different immunological changes during pregnancy could explain the positive effects of pregnancy on the disease. One leading explanation is the effect of estrogen and progesterone on the T helper 1 cell 1 and T helper 2 cell (Th2) balance, which diverts the immune response to a predominant Th2 response with an increase in anti-inflammatory cytokines.[28,40,72,73] Other mechanisms, such as direct effects on immune cells,[74–76] changes in the levels of regulatory T cells and natural killer cells,[28,71,77–80] down-regulation of adhesion molecules and metalloproteases, decreased antigenic presentation, and immunotolerance induced by exposure to fetal antigens,[73] have also been reported. Moreover, neuroprotective and remyelinating properties have been attributed to progesterone.[81,82] After delivery, there is a reversal of the hormonal changes associated with pregnancy and a sudden return to the immune state prior to pregnancy, causing what has been described as an immune reconstitution inflammatory syndrome-like phenomenon.[28]

Despite being considered a period of disease stability, approximately 15–30% of patients with MS suffer relapse during pregnancy.[56,83–89] Factors associated with a greater risk of relapse during pregnancy include the occurrence of relapses the year prior to pregnancy, a greater disability at the time of pregnancy, the appearance of relapses following disease modifying treatment (DMT) cessation before becoming pregnant, an age less than 35 years, and the preconceptional use of high-efficacy DMTs, especially the cell-trafficking blockers natalizumab or fingolimod with longer washout periods.[83,88,90–92]

Up to 30% of patients relapse in the first 3 months after delivery[83,84,87] and about 50% in the first 6 months after delivery,[69,84,86,93] although more recent population-based studies have suggested that the postpartum relapse risk is lower than this.[66,90,94] A milder MS resulting from the incorporation of new diagnostic criteria that enable an anticipated diagnosis and better pre-pregnancy disease control might contribute to these findings. Postpartum relapses seem to be more severe than relapses prior to pregnancy,[95,96] and lead to an increased risk of disability.[97,98] Proposed risk factors for postpartum relapses include the presence of relapses during pregnancy, a greater disability at the time of conception, a greater number of relapses the year prior to pregnancy, the occurrence of relapses after DMT cessation before conception, and the use of high-efficacy DMTs before conception.[65,87,88,90,92,94,97–99] It also seems that younger patients have a greater risk of relapse 6 months after delivery than do older patients.[90,94,100]

The Impact of Pregnancy on the Long-Term Course of MS

There is no evidence that pregnancy has a negative impact on the long-term course or progression of MS disability.[11,95,101,102] In contrast, there is some evidence that pregnancy after MS onset could have a favorable

long-term effect on the course of MS, as women who deliver one or more children after MS onset appear to have a slower disability progression than nulliparous women with MS.[103,104] In a recent population-based cohort study, nulliparous women had an earlier age at progressive MS onset, and a pregnancy-dose effect on delaying progressive MS and severe disability was observed.[105] Whether pregnancy has a true protective effect on the MS course due to transient immunosuppression, or whether it represents a bias derived from female patients with milder MS being more inclined towards childbearing and causing those with more aggressive MS to avoid pregnancy, warrants further investigation.[103,104]

Management of MS During the Pre-Pregnancy Period (Box 1)

Insufficient maternal vitamin D during pregnancy may increase the risk of MS in offspring,[106] and higher maternal milk and vitamin D intake during pregnancy has been associated with a lower risk of offspring developing MS;[107] thus, preconception vitamin D supplementation is recommended. Folic acid must be taken before trying to conceive following general guidelines in women who wish to become pregnant.[108] Women should also avoid alcohol and smoking, and maintain good sleep hygiene and diet.[1]

For most symptomatic treatments used in MS, such as those for urinary disturbances, spasticity, fatigue, or pain, there is limited evidence of their safety and they should not be used during pregnancy; before a planned pregnancy, these treatments should therefore be stopped or used only at minimum doses for the shortest time.[109] Oral drugs used for the treatment of spasticity-related symptoms (baclofen or tizanidine) and fatigue (modafinil or amantadine) are generally contraindicated during pregnancy and should be discontinued before pregnancy,[110–112] but intrathecal baclofen seems to be safe.[112] Fampridine, which is used for improving gait speed in MS, is also contraindicated as experience of use during pregnancy is scarce, albeit without bad outcomes.[113]

Assisted reproduction technology (ART) is frequently used in patients with MS, with a reported use in up to 14%[114] and in 29%[115] of pregnancies in patients with MS. An increased relapse risk after ART has been described, mostly after unsuccessful cycles in the 3-month period after ART compared to 1 year before ART, and predominantly with gonadotropin-releasing hormone agonists rather than antagonists.[48,116–119] A recent meta-analysis confirmed an increased ARR 3 months after ART with both gonadotropin-releasing hormone agonists and antagonists, independent of whether cycles were successful or not.[120] It has been postulated that continuation of DMTs could prevent the increased risk of relapse after ART.[120,121]

Treatment-Naïve Patients

Women with MS of a childbearing age should be asked about their family plans at or soon after the diagnosis, and physicians must initiate a discussion on pregnancy-related issues, such as the effects of pregnancy on the course of the disease, fetal safety of exposure to DMTs, and DMT exposure while breastfeeding. A recent survey reported that a considerable proportion of patients felt that they did not receive adequate information about the potential teratogenic effects of DMTs.[9] Family planning should be an essential element when choosing an initial therapy for MS, women must be advised about the safety of DMT use during pregnancy, and a planned pregnancy should be recommended.

Some authors have proposed that some patients with immediate pregnancy plans after an MS diagnosis could defer DMT onset.[122] However, there are several arguments in favor of starting DMT. Namely, it is widely accepted that early MS treatment prevents long-term disability[123,124] and the same should apply to women with MS who are planning a pregnancy, which can take up to 7 months.[49,92,99] Moreover, the presence of relapses in the year prior to pregnancy increases the risk of relapse during pregnancy and after delivery, and stabilization of disease could therefore prevent disease activity during pregnancy and after delivery. Thus, DMT exposure in the pre-conception period might be protective against postpartum relapses,[64,99,125] and preconception use of low-efficacy DMTs seems to prevent postpartum relapses compared to no DMT use prior to pregnancy.[90] In conclusion, women who are planning a pregnancy should not delay DMT onset, and it seems reasonable to start a DMT before conception, even in women with milder MS. Clinical and MRI monitoring is recommended before conception,[40] and reaching disease stability is desirable, with a 1-year relapse-free period prior to conception in normal evolving MS, or even 2 years in highly active MS.[109,126,127] Patients should be advised about available contraceptive methods during this period.[128]

The choice of treatment should be individualized, taking into consideration prognostic factors, comorbidities, lifestyle, treatment-related risks, patient preferences, and

Box 1 General Recommendations Before, During and After Pregnancy

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Before pregnancy
- Ask about family plans at or soon after the diagnosis. Discussion about pregnancy-related issues.
- Consider family planning when choosing an initial therapy.
- Do not delay DMT onset.
- A non-teratogenic DMT is preferable in fertile women. Patients should be advised about available contraceptive methods especially during treatment with sphingosine-1-phosphate–receptor modulators and teriflunomide, and at least 4 months after alemtuzumab, 6 months after cladribine and 1 month after anti-CD20 therapies.
- A planned pregnancy and a relapse-free period prior to pregnancy are recommended (1 year in normal evolving MS and even 2 years in highly active MS).
- Pre-conceptional vitamin D and folic acid supplementation. Avoid alcohol and smoking.
- IFN-β, GA, DMF and NTZ could be maintained until conception.
- Teriflunomide, fingolimod, siponimod, ozanimod and ponesimod must be stopped before conception (see Table 1) and switching to other DMT could be recommended.

During pregnancy
- If a pregnancy is confirmed in a woman taking potentially teratogenic treatment, immediately discontinue DMT and recommend an ultrasound study.
- DMF must be discontinued immediately when pregnancy is confirmed. IFN-β and GA could be administered even throughout the pregnancy. NTZ could be maintained until the 30th–34th gestational week at 6- to 8-week intervals.
- Clinical and laboratory monitoring should continue, including John Cunningham virus serology in women treated with natalizumab and monthly blood and urine tests in those treated with alemtuzumab in the previous years.
- Advise that urinary tract infections are more frequent during pregnancy and recommend pelvic floor exercises.
- Apply standard protocols of blood pressure and glycemic control.
- Continue vitamin D and folic acid supplementation.
- If necessary, an MRI without gadolinium could be obtained.
- In case of a disabling relapse the standard high dose of intravenous methylprednisolone can be used, especially in 2nd and 3rd trimesters.
- In all cases of DMT or corticosteroids fetal exposure, consider an organ screening ultrasound at 20–22 weeks of gestation.
- In the 3rd trimester a visit should be programmed to update the neurological status and plan the postpartum period.
- Exclusive breastfeeding should be encouraged whenever possible.
- Advise that the choice of the type of anesthesia and delivery should be based on obstetric criteria.
- Follow the same vaccination indications as the general pregnant population: Inactivated influenza, inactivated diphtheria, tetanus, and acellular pertussis (Tdap) and mRNA Covid-19 vaccines.

After delivery
- Patients should be closely monitored during the first trimester postpartum.
- There is no clear evidence to support the use of intravenous corticosteroids or intravenous immunoglobulins to prevent postpartum relapses.
- Resuming DMT soon after delivery, especially high-efficacy therapies in high-risk patients, is associated with a reduced risk of postpartum relapse.
- Breastfeeding does not have a harmful effect for women with MS and must not be contraindicated.
- Exclusive breastfeeding could prevent relapses after childbirth, and it must be recommended unless a DMT contraindicated during lactation is going to be resumed.
- IFN-β and GA are considered safe during lactation.
- Intravenous methylprednisolone to treat postpartum relapses is not contraindicated. Consider delaying breastfeeding for 2–4 hours after administration to minimize infant exposure.

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risk aversion. Given that a high proportion of pregnancies are unplanned[9,129] and an almost 10% rate of contraceptive failure has been reported,[130] even in women without pregnancy intention, an initial non-teratogenic DMT recommendation is preferable in women of a fertile age, and a pregnancy test should be carried out before starting the drug. Teriflunomide, fingolimod, siponimod, ozanimod,

and cladribine all have teratogenic effects in animal models[109,126,127] and should not be initiated in the short term in women trying to conceive.

Based on data available for thousands of instances of first-trimester exposure, first-line immunomodulatory drugs beta interferon (IFN-β) and glatiramer acetate (GA) are now considered safe, and the European Medicines Agency

(EMA) has withdrawn the contraindication of their use during pregnancy in clinically isolated syndrome and relapsing-remitting MS. These can be maintained until pregnancy is achieved, or even during the entire pregnancy, based on mothers' risk-benefit decision. Reports from large pregnancy registries[131,132] and manufacturer's post-marketing surveillance studies of subcutaneous IFN-β1a,[133] intramuscular IFN-β1a,[134] and IFN-β1b[135] did not find a higher risk of congenital anomalies in newborns exposed to IFN-β. While some studies have reported that there is an adverse effect of intrauterine exposure to IFN-β on birth weight and[125,136–139] preterm delivery,[139,140] others have found no such association.[63,64,89,141] There is sufficient evidence to indicate that exposure to GA is not associated with abortion, premature birth, congenital anomalies, low birthweight, or neonatal size.[63,85,125,138,142,143] Only a few cases exposed throughout pregnancy to GA[65,144–146] or IFN-β[64,147,148] have been reported. There is not enough data to support the use dimethyl fumarate (DMF) during pregnancy. Although harmful fetal effects at high doses have been reported in animals,[149] in the small number of pregnancies exposed during clinical trials and the post-marketing surveillance program, no increased risk of adverse pregnancy outcomes has been detected.[149,150] The short half-life of DMF allows its rapid elimination after being discontinued, which would result in only a brief fetal exposure if it is interrupted once pregnancy has been confirmed. However, according to the prescription information, DMF should only be used during pregnancy after weighing up the risks and benefits (Table 1).[151,152]

Women with an aggressive MS onset generally require a high-efficacy therapy and must be advised to delay pregnancy until 1 or 2 years of disease stabilization has been achieved.[109] If pregnancy is planned in the short term, however, fingolimod and siponimod should not be prescribed because of their teratogenic risk.[153,154] Natalizumab, which is an IgG4 humanized monoclonal antibody, does not cross the placenta unit until the third month of gestation,[155] and its use seems to be safe during the first trimester of pregnancy.[151,156–161] As immune reconstitution therapies, cladribine and alemtuzumab could be attractive alternatives because they can provide long-term disease control once the drug is eliminated, although conception should not be attempted until 4 months after the last dose of alemtuzumab and 6 months after cladribine.[162–165] Ocrelizumab, which is a humanized anti-CD20 B-cell-depleting IgG1 monoclonal antibody prescribed for relapsing MS and primary progressive MS,

actively crosses the placenta after the first trimester[166] once organogenesis has ended. According to regulatory agencies recommendations, pregnancy should not be attempted until 6 months (US Food and Drug Administration; FDA) or 12 months (EMA) after the last infusion.[167,168] However, based on its short half-life of 26 days[169] and its similarities with rituximab, which is a chimeric anti-CD20 monoclonal antibody used off-label in MS, pregnancies could be attempted from 1 month after the last infusion to prevent fetal exposure while retaining the long-lasting preventive effects (Table 1).[170]

Patients Receiving DMTs

Currently, nearly 80% of patients with early MS receive DMTs.[9,65,171–173] This could be explained by the implementation of new diagnostic criteria, the acceptance of early therapeutic interventions in MS and clinically isolated syndrome,[122,123,162,174–176] and of indefinite treatment in patients even with stable MS,[177] among others. Furthermore, the delay in childbearing and the fact that nearly 50% of pregnancies are unplanned[62,129,178,179] mean that it is increasingly more common for women with MS to start treatment before pregnancy. Consensus is lacking regarding the therapeutic strategies in women with MS undergoing DMT who wish to become pregnant.

Women planning pregnancy have typically been advised to stop their treatments and, in the case of unplanned pregnancy, discontinue treatment when pregnancy was confirmed, except in high-activity disease.[52,54,122,170,180–182] These recommendations are probably in place because disease activity during pregnancy decreases to a greater degree than it does with classical immunomodulatory drugs,[183] and the fact that there is limited information about the potential risks of fetal exposure to DMT. The appropriateness of this approach has been supported by reports that the use of DMT 1 year before pregnancy was not associated with a lower risk of postpartum relapses,[94] and that disease activity in women exposed to DMT at conception versus untreated women was similar during pregnancy[64,66] and postpartum.[94,100] Thus, according to recent population-based studies, the proportion of patients on DMT immediately prior to pregnancy is low, even in highly active MS.[58,184] However, one possible bias of population-based studies could be that patients with more benign MS decide to stop DMTs before pregnancy, and those with more aggressive MS maintain them. Conversely, other authors have shown that pre-pregnancy use of DMTs could prevent postpartum relapses,[64,90,99,125] and exposure to IFN-β or

Table 1 Pregnancy-Related Aspects of Multiple Sclerosis Disease-modifying Therapies

DMT	Pre-Pregnancy Washout	Pregnancy	Breastfeeding	Newborn Precautions
Beta interferon	Not required	EMA: May be considered during pregnancy FDA: Use only if the benefit justifies the potential risk to the fetus.	Can be used during breastfeeding	
Glatiramer acetate	Not required	Use only if the benefit justifies the potential risk to the fetus	Limited data. Considered safe	
Teriflunomide	Accelerated elimination procedure until plasma concentrations are less than 0.02 mg/L	Contraindicated during pregnancy	Contraindicated during breastfeeding	Risk of birth defects
Dimethyl fumarate	Not required	Use only if the benefit justifies the potential risk to the fetus	Limited data. Risks not excluded. Use with caution	
Fingolimod	2 months (risk of rebound effect)	Contraindicated during pregnancy	Contraindicated during breastfeeding	Risk of fetal loss and birth defects in animal models
Siponimod	10 days	Contraindicated during pregnancy	Contraindicated during breastfeeding	Risk of fetal loss and birth defects in animal models
Ozanimod	3 months	Contraindicated during pregnancy	Contraindicated during breastfeeding	Risk of fetal loss and birth defects in animal models
Natalizumab	Not required (risk of rebound effect)	Use only if the benefit justifies the potential risk to the fetus at least until first trimester or 30–34 weeks	EMA: Contraindicated during breastfeeding FDA: Use only if the benefit justifies the potential risk to the infant	Risk of hematological abnormalities in infants exposed in the third trimester
Alemtuzumab	4 months after last dose	Use only if the benefit justifies the potential risk to the fetus	EMA: Discontinue during each course and for 4 months following the last infusion. Benefits may outweigh the risks for the infant FDA: Discontinue either alemtuzumab or breastfeeding	Untreated maternal hypothyroidism increases the risk for miscarriage and may have effects on the fetus. Risk of neonatal Graves` disease in mothers with Graves` disease
Ocrelizumab	EMA: 12 months FDA: 6 months	Use only if the benefit justifies the potential risk to the fetus	EMA: Contraindicated during breastfeeding FDA: Use only if benefit justifies the potential risk to the infant	Risk of B-cell depletion after intrauterine or breast milk exposure

(*Continued*)

Table 1 (Continued).

DMT	Pre-Pregnancy Washout	Pregnancy	Breastfeeding	Newborn Precautions
Cladribine	6 months after last dose	Contraindicated during pregnancy	Breastfeeding contraindicated during treatment and for 1 week after the last dose	Risk of congenital anomalies
Ofatumumab[271]	6 months after last dose	Use only if the benefit justifies the potential risk to the fetus	Use only if benefit justifies the potential risk to the infant.	Risk of B-cell depletion after intrauterine or breast milk exposure
Ponesimod[272]	1 week after last dose	Contraindicated during pregnancy	Contraindicated during breastfeeding	Risk of fetal loss and birth defects in animal models

Abbreviations: DMT, disease-modifying therapy; EMA, European Medicines Agency; FDA, United States Food and Drug Administration.

GA during the first weeks of pregnancy could prevent relapses during pregnancy and after delivery.[85,89] Furthermore, it has been consistently reported that discontinuation of cell-trafficking blockers fingolimod or natalizumab, especially with long washout periods, is associated with a high risk of relapse and disability progression prior to conception, during pregnancy, and postpartum,[88,91,157,171,185] as well as with radiological activity.[186] Even the discontinuation of low-efficacy DMTs in the case of planned pregnancy has been reported to result in an increase in relapse activity before conception.[92]

In the past 5 to 10 years, an increasing trend in the proportion of pregnancies conceived on therapy has been observed,[16,90] which is likely to reflect a greater confidence in the safety of DMT use during the first weeks of pregnancy and an awareness of the risks of treatment discontinuation in highly active MS.

First-line therapies (Table 1): Patients taking IFN-β or GA can continue treatment until conception (see above). Patients on teriflunomide must perform an accelerated elimination procedure with cholestyramine or activated charcoal for 11 days prior to attempting conception, and contraception should be recommended until plasma concentrations of teriflunomide are less than 0.02 mg/L.[187] Switching to IFN-β or GA could be indicated after teriflunomide elimination and, in that case, a period of observation must be performed to assess disease stabilization. The short half-life of DMF allows its rapid elimination after being discontinued, such that it can be maintained until conception, resulting in only a brief fetal exposure. However, DMF should only be used during pregnancy

after weighing up the risks and benefits, and if risks are not accepted, a switch to IFN-β or GA should be considered.

High-efficacy or second-line DMTs (Table 1): Fingolimod is contraindicated during pregnancy and must be stopped at least 2 months before conception. A marked increase in clinical and radiological activity before and during pregnancy has been reported after discontinuing fingolimod to become pregnant.[91,171] In some cases, this reactivation is greater than that of the pre-fingolimod period, which can be considered as a rebound phenomenon.[188–192] A longer washout period and lymphopenia (less than 300/μL) in the first 3 months after fingolimod onset have been associated with a greater risk of MS reactivation.[88,91,171,188] Therefore, switching to immunomodulatory drugs, natalizumab (especially in John Cunningham virus seronegative patients), anti-CD20 monoclonal antibody, cladribine, or alemtuzumab could be optimal, depending on the patient's characteristics and risk acceptance. A period of at least 6 or 12 months to check disease stability is recommended.

Siponimod has a shorter half-life than fingolimod, which allows women to stop the drug 10 days before conception. Disease reactivation has been described after withdrawal from siponimod[193] and switching to another drug before trying to conceive should probably be recommended. Ozanimod takes about 3 months to be eliminated, so women planning a pregnancy in the short term should stop it at least 3 months before conception,[194,195] and switching to other DMTs, as with fingolimod, would be reasonable.

The EMA and FDA have stated that natalizumab should only be used during pregnancy if the potential benefit to the patient justifies the potential risk to the fetus.[196,197] It has been extensively reported that discontinuing natalizumab before conception can result in a high risk of relapse during pregnancy and postpartum, radiological activity, and disability progression.[90,91,157,171,185,198–200] Stopping natalizumab prior to pregnancy is associated with rebound relapses and up to 37% of women who stopped it prior to pregnancy reportedly suffered relapses during pregnancy.[157] A longer washout period seems to be associated with a greater risk of relapse during pregnancy[91,171,201] and disability progression.[201] Given that natalizumab does not cross the placental barrier during the first trimester of pregnancy, no clear adverse pregnancy outcomes have been reported after fetal exposure during the first trimester, and receiving natalizumab after the last menstrual period has been associated with a three-fold reduction of relapse risk during pregnancy;[158,160,161] thus, this DMT should not be stopped before pregnancy. In women who do not accept any risks and have no immediate pregnancy plans, switching to anti-CD20 depleting antibodies, cladribine, or alemtuzumab could be considered.

Women treated with cladribine or alemtuzumab should attempt pregnancy from 6 months and 4 months, respectively, after the last dose, whereby the long-lasting effects of these treatments can provide long-term disease control once the drug is eliminated without fetal exposure.[164,165]

Although labelling recommendations state that pregnancy should not be attempted until 6 months (FDA) or 12 months (EMA) after the last infusion, ocrelizumab only crosses the placenta after the first trimester. Based on its half-life, women treated 1 month or longer before conception theoretically do not expose their fetus to the drug, yet the long-lasting preventive effects persist. Moreover, its biological effects wear off slowly and cessation is not associated with rebound disease activity. The same considerations could be applied to rituximab, which is frequently used as an off-label treatment in MS. In an observational retrospective cohort study, discontinuing rituximab before pregnancy was found to result in a significantly better control of disease activity during pregnancy and postpartum versus stopping natalizumab.[199]

Management of MS During Pregnancy (Box 1)

During pregnancy, women should ideally be clinically monitored every trimester. Laboratory monitoring should continue during pregnancy, including regular John Cunningham virus serology in women treated with natalizumab and monthly blood and urine tests in women treated with alemtuzumab in the previous years. Alemtuzumab-associated autoimmune disorders, especially thyroid disorders, can severely affect the fetus. If a thyroid disorder is confirmed, woman should be immediately referred to an endocrinologist for the initiation of appropriate thyroid treatment, and monitored during pregnancy in a specialist setting.[165,202,203] Pregnant women with MS must be advised that urinary tract infections are more frequent during pregnancy,[204] should be trained to recognize initial urinary tract infection symptoms, and advised to perform pelvic floor exercises.[205] Standard protocols of blood pressure and glycemic control should also be applied.

Women must continue with folic acid supplements to prevent newborn neural tube defects, as well as with vitamin D supplementation, which, in addition to its immunomodulatory effects, seems to diminish the risk of bad pregnancy outcomes.[206] If necessary, in case of disease reactivation or safety concerns (such as women at risk of developing progressive multifocal leukoencephalopathy), an MRI without gadolinium can be obtained.[205,207] According to the results of a large, single-center cohort study, gadolinium is contraindicated during pregnancy unless it is essential to the health of the woman or fetus, as it crosses the placenta and could cause a fibrotic condition in the fetus called nephrogenic systemic fibrosis, stillbirth, or neonatal death.[208–210]

Considering that nearly half of pregnancies are unplanned,[62,129,178,179] it is not unusual for women on potentially teratogenic DMTs to become pregnant. If pregnancy is confirmed in a woman taking fingolimod, siponimod, ozanimod, teriflunomide, or cladribine, she should be advised to immediately discontinue treatment, and an ultrasound study should be recommended. In the case of teriflunomide, washout with cholestyramine or activated charcoal must be prescribed. Women taking GA or IFN-β can stop treatment after positive pregnancy test or maintain it throughout the pregnancy, and this choice generally depends on pre-pregnancy activity and a woman's risk aversion. Women taking DMF should immediately stop it at the time of conception. It has been reported that maintaining natalizumab during the first trimester can reduce the risk of relapse and disability progression during pregnancy compared to discontinuing it at the time of pregnancy,[156] and a 24.5% reduction in relapse risk during

pregnancy per month continued has been demonstrated.[90] Considering that transient hematological abnormalities have been showed in newborns exposed to natalizumab during the third trimester,[211–213] some authors recommend maintaining natalizumab during pregnancy up until the 30th–34th gestational week at 6- to 8-week extended intervals.[126,127,170,205,212,214] A reduced dose has also been proposed[212] to reduce circulating natalizumab levels and therefore reduce fetal exposure. Extended interval dosing of natalizumab has not been associated with a decreased efficacy in MS.[215–218]

There are conflicting data concerning the safety of corticosteroids during pregnancy. In addition to the risk of precipitating gestational diabetes, some studies have reported an increased risk of lower birth weight[89,219] and malformations, especially cleft palate,[220,221] that have been questioned in recent publications,[222,223] and adverse long-term neurodevelopment outcomes have also been reported.[224] Women who decide to stop DMTs to become pregnant because of the fear of potential risks of fetus exposure should be advised that they could suffer more relapses during pregnancy, and could require more frequent corticosteroid treatment, which are not totally exempt from risks.[85,89] Methylprednisolone and prednisone are metabolized and inactivated by the placenta, and only a minimal part of the dose reaches the fetus; on the contrary, betamethasone and dexamethasone are minimally metabolized and they should be avoided during pregnancy.[225] The standard treatment of MS relapses with high doses of methylprednisolone, which are generally 1000 milligrams intravenously daily for 3–5 days, could therefore be used, especially in the second and third trimesters in cases of disabling relapses while avoiding oral tapering.[109,205,226] Severe steroid-refractory relapses could be treated with therapeutic apheresis.[109,205,214] The most common complications of plasma exchange or immunoadsorption are hypotension, thromboembolism, coagulopathy, thrombocytopenia and catheter-associated infections, thrombosis, and dislocations.[227] In the case of rebound relapses after natalizumab or fingolimod cessation, resuming natalizumab or starting anti-CD20 depleting monoclonal antibodies have been proposed.[170] In all cases of DMT or corticosteroids fetal exposure, an organ screening ultrasound should be considered at 20–22 weeks of gestation.

In the third trimester, a visit should be programmed to make an updated report of the neurological status and plan the postpartum period. Exclusive breastfeeding should be encouraged whenever possible. Women must be advised that MS does not contraindicate any type of obstetric anesthesia, and that epidural analgesia can be safely performed. There is no negative effect of obstetric anesthesia on postpartum relapses or disability progression,[54] and the choice of the type of anesthesia and delivery should be based on obstetric criteria.

Pregnant women with MS have the same vaccination indications as the general pregnant population (only live vaccines are contraindicated due to the theoretical risk to the fetus), and so should be vaccinated according to local recommendations. Inactivated influenza and the inactivated diphtheria, tetanus, and acellular pertussis (Tdap) are routinely offered to pregnant women with MS.[228,229] Preliminary findings have shown no obvious safety issues among pregnant women who received an mRNA Covid-19 vaccine,[230] and since pregnancy itself is associated with an increased risk of severe infection, mRNA Covid-19 vaccines should be recommended and may be administered at the same time as other vaccines routinely administered in pregnancy (eg, influenza, Tdap). A separation period between vaccinations is unnecessary,[231] although some authors recommend a 7- to 14-day gap between receiving a COVID-19 vaccine and the flu vaccine.[232,233] Other vaccines may be considered in cases of high risk or specific exposure to certain infectious agents.[228,234]

Management of MS After Delivery (Box 1)

After delivery, especially the first trimester postpartum, is a critical period for an increased risk of clinical and radiological activity, during which patients should be closely monitored. In recent years, the risk of postpartum relapses seem to be attenuated[66,90,94] *up to 30%*,[66] partly due to a statistical effect derived from the diagnosis of milder forms of the disease using the new diagnostic criteria, but perhaps also due to a better management of pregnancy-related issues; indeed, shorter DMT washout periods[91] and an increased use of DMT before pregnancy and at the time of conception have been reported in recent work.[16,90] Although some reports have not found there to be a relationship between the use of DMT before or at the time of conception with the occurrence of relapses during pregnancy or after delivery,[66] others have found that exposure to DMT before pregnancy or during the first weeks of gestation could decrease the risk of MS activity during pregnancy or postpartum.[64,85,89,90,99,125]

Several predictive factors associated with postpartum relapses have been described, including a higher relapse

rate and a higher disability score before pregnancy, occurrence of relapses during pregnancy,[65,87,90,97–99,235] the use of high-efficacy DMT prior to pregnancy,[88,90] and a younger age at the time of conception.[94,100] As mentioned before, one of the key aspects in the management of pregnancy in patients with MS is the prevention of relapses and disability postpartum, and some strategies must be applied before and during pregnancy. Proposed strategies include achieving disease stabilization before conception, using DMT prior to pregnancy, exposure to immunomodulatory drugs before or even during first weeks of gestation, and, in patients treated with cell-trafficking blockers (natalizumab or fingolimod), preventing longer washout periods and maintaining natalizumab until the first 1–2 trimesters of pregnancy.[64,85,89,91,99,109,125,126,156,157,201]

Various measures have been proposed to prevent postpartum relapses and disability progression after delivery. Some studies have shown that intravenous immunoglobulins, at different doses and with different administration schedules, both during pregnancy and immediately after delivery, can reduce the risk of postpartum relapse.[236–240] However, other reports[241,242] and a recent meta-analysis[243] have failed to confirm these benefits, and so there is no clear evidence to support the routine use of intravenous immunoglobulins.[214] Methylprednisolone, 1000 milligrams monthly for 6 months, has been found to be effective in preventing postpartum relapses in a small case-control study.[244] Another study with few patients and different treatment schedules also reported there to be a positive effect of corticosteroids,[245] but there are no prospective data that support the use of corticosteroids to prevent postpartum relapses. Attempts to control the increase in postpartum activity with hormonal therapy (progesterone and estradiol) have not been shown to be effective.[246]

When resuming DMT soon after delivery,[88] even DMTs with a slow mechanism of action, such as GA and IFN-β, are associated with a decrease in postpartum relapse risk,[86,235,239] although other authors have found no such association.[94,247] It seems clear that resuming high-efficacy therapies, mostly natalizumab, in high-risk patients previously treated with these DMTs is associated with a reduced risk of postpartum relapse.[88,90,157,200]

Breastfeeding does not have a harmful effect for women with MS and must not be contraindicated.[248,249] The protective role of breastfeeding on postpartum activity in MS has long been a matter of controversy. According to some authors, exclusive breastfeeding prevents relapses after childbirth;[94,100,250] however, others have found that breastfeeding has no effect on postpartum relapses, and could be a confounding factor considering that women with higher levels of disability and disease activity before and during pregnancy are less likely to choose natural breastfeeding.[87,93,98] A recent meta-analysis showed that breastfeeding, mostly exclusive than not exclusive, appears to be protective against postpartum relapses, with a 43% lower relapse rate, although it is not possible to exclude the possibility of residual confounding.[249] Breastfeeding, especially exclusive breastfeeding, determines short- and long-term maternal and newborn health benefits,[251–253] and women with MS must be encouraged to breastfeed whenever possible. However, until recently, the safety of DMTs during lactation has remained unknown, and breastfeeding was not officially recommended if a patient was on any DMT. Factors related to MS activity and the previous use of DMTs determine the choice of breastfeeding, and so mothers with relapses during pregnancy and more aggressive MS choose to breastfeed less frequently.[87,93,97,98,250] Resuming DMT seems to be the determinant factor to refuse breastfeeding,[62,94,250] as the proportion of women with MS who choose to breastfeed is lower among those who have previously received DMT,[98,100,247] and breastfeeding is the main reason for delaying the resumption of DMT.[94] Human data on lactation and DMT are scarce, but drugs could theoretically be classified according to their biological plausibility to be transferred into human milk based on their molecular size, protein binding, volume of distribution, lipid solubility, known active transport mechanisms for the drug and possibility of transport from the infant's gut into the bloodstream, known toxic effects in adults, and potential effects on newborn systems.[170,254]

Large molecules such as IFN-β and GA are unlikely to be transferred to breast milk and are now considered safe. Only a minimal fraction of the IFN-β maternal dose is detected in breast milk,[255] and the EMA has approved its use during breastfeeding.[256] Oral DMTs are all small molecules that can be transferred to human milk, and are not therefore recommended during breastfeeding. Cladribine is transferred to breast milk, but its short half-life means that breastfeeding is contraindicated only during treatment and for 1 week after the last dose.[164,257] Monoclonal antibodies (mAbs) are large molecules that can be detected only at low levels in human milk, and are likely to be partially destroyed in the infant's

gastrointestinal tract such that absorption by the infant is minimal.[258] Several reports of nursing mothers on natalizumab have found that there is a correlation between the time since the last natalizumab infusion[259] and the increase in breast milk concentrations over time with repeat infusions.[260,261] However, there is thought to be a limited absorption in an infant's gastrointestinal tract, and no longer-term effects on infant immunity and childhood development were observed in a series of 23 infants from mothers treated with natalizumab or anti-CD20 mAbs during lactation,[262] or in a series of 368 infants followed for ≥6 months after exposure to breast milk of mothers treated with mAbs.[260] Only a few cases of newborns exposed to ocrelizumab through breast milk have been reported, and transient peripheral B-cell depletion has been observed in one infant (Table 1).[263]

Corticosteroids are only minimally transferred to human milk, levels in milk peak 1 hour after intravenous methylprednisolone administration, and newborn exposure is low.[264] Thus, the use of intravenous methylprednisolone to treat postpartum relapses is not contraindicated,[62,205] although some authors recommend delaying breastfeeding for 2–4 hours after administration to minimize infant exposure.[265] According to these findings, DMT use and breastfeeding are not mutually exclusive and, although not validated, there may be an additive therapeutic effect from DMT to the benefits of breastfeeding[248] based on an individualized approach. Women without DMT before pregnancy who are stable during pregnancy could be advised to partake in exclusive breastfeeding for at least 6 months and delay the start of DMTs; however, patients who do not wish to breastfeed, and were receiving DMTs prior to pregnancy and stopped them before pregnancy or at conception, should immediately resume their DMTs after delivery.

Women who maintain IFN-β or GA throughout pregnancy should be advised to maintain them during breastfeeding. Mothers who have stopped taking IFN-β or GA before pregnancy or at conception, especially those at high risk for postpartum relapses, could be advised to both breastfeed and resume DMTs as early as possible, since both are considered safe during lactation.[205,255] After a benefit–risk discussion, women with a higher risk of postpartum activity (highly active MS pre-pregnancy, a pre-pregnancy Expanded Disability Status Scale score ≥2, previously treated with second-line DMTs, who suffered relapses during pregnancy, or received natalizumab or anti-CD 20 depleting antibodies during pregnancy)

could be advised to breastfeed and start or resume natalizumab or anti-CD20 mAbs, in the first 3 days after delivery.[61] If a woman does not accept the risks, breastfeeding should probably be discouraged and high-efficacy DMTs resumed in the first 3 days after delivery. A case of reversible cerebral vasoconstriction syndrome associated with fingolimod therapy 3 months after childbirth has been reported, which highlights the need to monitor patients who resume DMT soon after delivery if associated symptoms appear.[266]

Patients should be closely monitored during the first year postpartum; MRI is not contraindicated during breastfeeding and, although only a low dose of gadolinium passes to the breast milk and a minimum quantity seems to be absorbed from the infant's gastrointestinal tract,[208] a breastfeeding pause of 24 hours has been recommended after maternal gadolinium administration,[72,170,267] but it is probably not necessary.[54,127,268] After delivery, bowel and urinary disturbances could appear or worsen. An adequate assessment of urinary function, lifestyle recommendations, pelvic floor exercises, and symptomatic medication, if necessary, are recommended.

Newborns exposed to natalizumab during pregnancy, especially in the third trimester, should be monitored after delivery for hematological abnormalities.[211–213] Predelivery umbilical cord sampling and intravenous immunoglobulin administration could reduce the hematological effects on newborns.[212,269] The B cell count should be monitored in infants exposed to anti-CD20 mAbs during pregnancy or through breast milk, because B-cell depletion can result in perinatal and neonatal immunosuppression and subsequent infection.[127,263,269,270] In cases of B-cell depletion, vaccines should not be administered until B-cell reconstitution.[109] Children of mothers previously treated with alemtuzumab should be monitored for thyroid disorders (Table 1).[170]

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