

MANAGEMENT OF MULTIPLE SCLEROSIS DURING PREGNANCY

What are the recommendations for preconception counseling?

Plans for pregnancy must be considered when choosing between various disease modifying therapy (DMT) types.¹ MS symptoms should ideally be adequately controlled² and disease activity stable for at least 6-12 months prior to conception.³ Women with MS who are planning to become pregnant are advised to take prenatal vitamins, including folic acid and vitamin D.⁴

MS and fertility and assisted reproductive technology

We advise that in general there are no significant differences in conception or fertility rates between patients with MS and the general population. Recent studies indicate that women with MS can conceive at similar rates to the general population. Approximately 10% of women with MS have difficulty becoming or staying pregnant², not significantly different from the 10-15% of women in the US general population that have impaired fecundity.⁵ Although the use of assisted reproductive technology (ART) has not been widely studied in patients with MS, an association with increased relapse risk has been reported, with the most significant risk in the first three months following unsuccessful cycles.^{6,7}

What are the recommendations for contraception?

Women with MS of childbearing potential on DMT are encouraged to use some form of contraception. In general, all contraceptive methods are safe and effective for women with MS, though progestin-only and combined hormonal contraceptives are not recommended in patients that have mobility limitations due to the risk of venous thromboembolism.⁸ There are no known major interactions between DMTs and oral contraceptives. Potential interactions of symptomatic therapies with contraception should be considered.

What is the impact of MS on pregnancy outcomes?

MS itself does not confer any increased risk of congenital malformation or miscarriage and does not necessitate categorization as a high-risk pregnancy.⁹ There is a possibility that MS may be associated with lower birth weights, although the magnitude is small and clinically insignificant.⁶

What is the risk of relapse in pregnant patients with MS?

During pregnancy the immune system adjusts to prevent immunologic rejection of the fetus (i.e., a state of immune tolerance) and the overall risk of severe relapse during pregnancy is thought to be low (estimated to be around 10%).^{10,11} Women with higher relapse rates prior to conception appear to be at higher risk of ongoing inflammatory disease during pregnancy.¹²

What disease modifying treatments are safe for use during pregnancy?

The use of DMT is not generally recommended during pregnancy unless the need outweighs the risks to the fetus, and no DMT is considered entirely safe.¹³ Treatment plans must consider the benefits and risks posed to the mother (based on level of disease activity and risk for relapse and/or disability worsening off DMT) and the associated risks of exposure to the fetus (Table 1).

What disease modifying treatments require a washout (discontinuation period) in patients considering pregnancy?

Washout periods are considered for all DMTs (Table 1), taking the characteristics of the patient's MS and level of disease activity into consideration. Recommended washout periods are based on the pharmacology of the individual treatments. Whenever feasible, treatment and conception timing are coordinated, with the aim of keeping DMT washout periods as short as possible to mitigate the risk of relapse.²

What is the risk for rebound disease activity following washout?

Women who were treated with S1P modulators or natalizumab prior to conception may have increased risk for severe rebound disease following medication withdrawal.³⁴ Due to the risk of rebound disease activity in patients treated with these medications, changing to an alternate therapy (e.g., an anti-CD20 agent) may be considered prior to discontinuing contraception (especially in patients with highly active disease).¹⁵⁻¹⁷

Anti-CD20 agents infused intravenously (ocrelizumab, rituximab-pvvr, and rituximab) confer prolonged protective effects against MS relapses for several months (6-9 m) following administration. They are not recommended to be routinely administered during pregnancy but can be administered prior to conception in patients with highly active disease. The FDA-approved prescribing information recommends that women continue contraception for 6 months following last treatment of ocrelizumab and 12 months following last treatment of rituximab.¹⁸⁻²⁰ Ofatumumab is administered by subcutaneous injection, and the FDA-approved prescribing information recommends contraception for 3 months following last treatment.²¹

However, in some cases (particularly women with highly inflammatory disease prior to initiation of anti-CD20 therapy) treatment with a high efficacy therapy may be necessary for minimization of time off DMT. These patients may receive an infusion and then discontinue contraception / attempt to become pregnant after 1-3 months.²²⁻²⁵ The rationale for this is that these therapies are eliminated by 3.5-4.5 months after an infusion (based on half-lives).^{18-19, 21} In the first trimester, there is minimal placental transfer of IgG.²⁶ Therefore, if a patient conceives 1-3 m after the last dose of anti-CD20 therapy, the risk of fetal exposure in the second trimester is low.²³ The main risk to an exposed fetus is transient B cell lymphopenia. A pregnancy test should be checked prior to subsequent dosing. Contraceptive methods should be implemented if therapy is resumed. Decision making regarding anti-CD20 therapy and pregnancy planning needs to consider the patient's degree of disease activity and their individual preferences.

What if a patient becomes pregnant while on DMT?

It is recommended that DMT be discontinued at the time pregnancy is suspected. Patients who become pregnant on interferon beta or glatiramer acetate do not require additional monitoring during pregnancy. Those becoming pregnant on oral therapies (including dimethyl fumarate, diroximel fumarate, and S1P modulators) are referred for an early ultrasound to screen for major malformations. If a patient on teriflunomide becomes pregnant, a rapid elimination procedure is initiated as soon as possible (see below), and women are referred for an early ultrasound to screen for major malformations. Women that become pregnant on cladribine, teriflunomide, or natalizumab may consider being followed by a high-risk obstetrician. All pregnancy exposures should be registered through the appropriate pregnancy registries. (Table 2).

What disease modifying treatments require an elimination procedure in pregnant patients?

If a patient becomes pregnant on teriflunomide, treatment is immediately discontinued, and a rapid elimination procedure is undertaken. Cholestyramine is administered orally, 8g every 8 hours for 11 days (if tolerated). If the patient is unable to tolerate this regimen a 4g dose may be used. Alternatively, activated charcoal powder may be administered orally, 50g every 12 hours for 11 days. Both procedures have been shown to be effective in decreasing plasma concentrations by > 98%. Once the accelerated drug elimination procedure is complete, verification that the teriflunomide plasma concentration is < 0.02 mg/L is required.²⁷ If plasma concentrations remain elevated, the elimination procedure must be continued until the concentration reaches an appropriate level.

How should MS relapses be managed during pregnancy?

Management of MS relapses during pregnancy is discussed and coordinated with the patient's obstetrician. Mild relapses (with non-disabling symptoms or spontaneous improvement) may not require intervention. When indicated (for moderately to severely disabling relapses), the recommended first-line pharmacological treatment for relapses during pregnancy is high-dose corticosteroids. This therapy is used for clinically significant relapses, as it does carry slightly increased risk for adverse fetal outcomes (specifically cleft palate and low birthweight).²² Corticosteroid use are avoided during the first trimester when possible. Plasma exchange may be considered for patients with disabling steroid-refractory relapses.²⁸

Is MRI safe for pregnant or breastfeeding patients with MS?

Routine MRI during pregnancy is not recommended, but it probably can be done if necessary. There are no studies to date which have demonstrated adverse outcomes or harms attributable to MRI during any trimester of pregnancy.²⁹ However, gadolinium-based contrast use is contraindicated, as prior studies have demonstrated increased risk of stillbirth, neonatal death, and various inflammatory conditions.³⁰ The use of contrast is also not recommended while breastfeeding, as small amounts are detectable in breastmilk. However, if use of gadolinium is necessary to determine if active inflammation is present, patients may refrain from breast feeding or discard breastmilk for 24 hours following administration.⁶³⁻⁶⁴

Are there special considerations for delivery?

For most women, we have no special recommendations for delivery. Additional considerations depend on the individual patient's needs, such as planning for use of assisted delivery methods and/or Caesarean section in women with significant disease-related disability. The use of any anesthetic type is acceptable when clinically indicated.³¹ Assisted vaginal delivery or Caesarean section may need to be considered in patients with severe disability.²

How should patients with MS be managed in the postpartum period?

Women with MS are recommended to receive routine obstetric postpartum care. Duration of birth hospitalizations have been found to be within normal range in prior studies.³² Given the rapid shift in gestation-related hormones, patients are at increased risk for both clinical and MRI disease activity for the first three months following delivery,³³⁻³⁵ with approximately 13% of patients having relapses.¹² Higher relapse rates prior to pregnancy are associated with higher rates of relapse in the postpartum period.^{34,36-37} We recommend that an MRI be obtained 2-3 months following delivery to evaluate for radiographic disease activity.

When should disease modifying therapy be resumed after delivery?

In general, we recommend that plans for breastfeeding and timing of DMT resumption be discussed prior to delivery. The decision about when to recommence DMT is an individual decision for each patient and needs to account for both previous disease activity and personal breastfeeding plans. Re-initiation of DMT early in the postpartum period is considered for patients who had very active disease prior to conception, had relapse(s) during pregnancy, or have a poor prognostic profile.² Conversely, in patients with a low burden of inflammatory disease, DMT resumption may be deferred for up to 6 months while patients are exclusively breastfeeding (see below).

Is breastfeeding safe for patients on disease modifying therapies?

In general, the decision to breastfeed and the duration of breastfeeding is deferred to the patient's decision after conferring with their obstetrician/pediatrician. Exclusive breastfeeding is recommended in most cases for about 6 months due to known benefits to the infant.³⁸ However, the decision to breastfeed is associated with a delay in resumption of DMT (which may increase the risk of relapse), and therefore the individual patient's disease characteristics must be considered. The effect of breastfeeding on relapse rates has previously been controversial.³⁴ It is believed that exclusive breast feeding (defined as no formula feedings) for at least 2 months may decrease the risk of relapse.^{12,23,39-41} The recommendation to shorten breastfeeding duration may be made in patients considered to be at higher risk of relapse to resume DMT.

No DMT is considered completely safe for use during breastfeeding. The interferon beta and glatiramer acetate molecules measure over 20 kDa and 5-9 kDa respectively, and the amount of transfer to breast milk is very low.⁴² Anti-CD20 agents are much larger molecules (on the scale 100,000 kDa), though transfer to breast milk does occur and may have clinically significant implications for the infant (B-cell depletion and impaired vaccine responses). The low oral bioavailability is likely to limit the absorption by the newborn (with relative infant dose of less than 10%).⁴³ Dimethyl fumarate and natalizumab are smaller molecules that are detectable in

breast milk, and therefore should also be used with caution. Fingolimod, alemtuzumab, cladribine, and teriflunomide should not be used during breastfeeding given their risk profile. Our general recommendation in patients who have stable MS, without recent disease activity, is that DMT be held during breastfeeding and restarted once breastfeeding has concluded.

If a patient develops a relapse while breastfeeding, use of corticosteroids may be considered. Transfer of methylprednisolone through breastmilk is thought to be minimal and may be further minimized by delaying breastfeeding for 2-4 hours after infusion (as levels peak in approximately 2 hours and rapidly decline thereafter).⁴⁴ For patients receiving oral steroids, the dose ingested by the infant through breastmilk is thought to be negligible. Because there is a small risk of growth retardation in the infant, however, breastmilk may be discarded for 24-48 hours following treatment out of an abundance of caution.⁶⁰

Are there any considerations for men with MS with regards to childbearing?

Male patients treated with teriflunomide need to practice effective contraception until after the medication is cleared by metabolism or by rapid clearance protocol. Female partners of male patients on teriflunomide are also counselled on the potential risks of fetal exposure as well as use of effective contraceptive therapy.²²

Cladribine may lead to an increase in non-motile sperm, leading to reversible infertility.⁴⁵ Animal studies demonstrated an increase in embryo lethality, and men are advised to not father children for at least six months following treatment.⁴⁶ Alemtuzumab may also cause reversible infertility due to inactivation of mature sperm.⁴⁷ All men treated with these therapies are counseled on the importance of (and adherence to) contraceptive use for at least six months following last dose, even when pregnancy is not planned, given the significant potential risks.

Are there special considerations for patients considering autologous hematopoietic stem cell transplant (AHSCT) for management of MS?

Infertility is common in both males and females following AHSCT. Gonadal toxicity often results from the associated cytotoxic conditioning therapies.⁶¹ Pre-treatment counselling about the risks of infertility is critical. Patients may wish to consider fertility preservation methods, including cryopreservation of sperm, mature oocytes, or fertilized embryos, and referral to an oncofertility specialist may be considered.⁶² Though data are limited, it does not appear that there is an increased risk of congenital abnormalities in infants born to women who have undergone AHSCT.

Table 1: Disease Modifying Therapies in Pregnancy

Medication	Recommended Washout	Special Considerations	Use in Pregnancy
Interferon Beta	2 weeks		Use if benefit outweighs risks
Glatiramer Acetate	None		Use if benefit outweighs risks
Fumarates			
Dimethyl Fumarate	1 week		DO NOT USE
Diroximel Fumarate	1 week		DO NOT USE
S1P Modulators - Fingolimod - Siponimod - Ozanimod - Ponesimod	Fingolimod: 2-3 months Siponimod: 2 weeks Ozanimod: 3 months Ponesimod: 2 weeks	Risk for rebound disease activity; consider transition to CD20 agent prior to contraception discontinuation	DO NOT USE
Cladribine	6 months		DO NOT USE
Teriflunomide	Rapid elimination procedure required (goal serum concentration below 0.02 mg/L)	Stop treatment and eliminate drug before discontinuing contraception	DO NOT USE
Natalizumab	2-3 months	High risk for rebound disease activity; consider transition to CD20 agent prior to contraception discontinuation	DO NOT USE
Anti-CD20 Agents			
Ocrelizumab	1-3 months*		DO NOT USE
Ofatumumab	1-3 months*		DO NOT USE
Rituximab	1-3 months*		DO NOT USE
Alemtuzumab	4 months		DO NOT USE

This table reflects our clinical practice and our review of combined recommendations of the prescribing information, and key articles.^{2, 21, 48-59}

Pregnancy testing is recommended before commencement or re-infusion for all DMTs in women of childbearing potential.

* See corresponding paragraph for in depth discussion regarding anti-CD20 therapies and pregnancy timing.

Table 2. Summary of Risks and Management Recommendations for Fetal Exposure to Disease Modifying Therapies during Pregnancy

Medication	First Trimester Exposure	Exposure Risks	Registry Information
Interferon Beta	No additional fetal or neonatal monitoring	Possible slight risk of decreased birthweight and increased embryofetal death based on animal data	Plegridy: https://www.plegridypregnancyregistry.com/
Glatiramer Acetate	No additional fetal or neonatal monitoring	None	NA
Fumarates			
Dimethyl Fumarate	Early ultrasound for major malformations recommended	Uncertain risk to fetus; animal studies have shown low birthweight, delayed development, delayed ossification, spontaneous abortions, decreased fetal viability, and impaired learning and memory	Tecfidera: https://www.tecfiderapregnancyregistry.com/
Diroximel Fumarate	Early ultrasound for major malformations recommended	Based on animal data, may cause fetal harm including skeletal abnormalities, increased mortality, decreased body weight, and neurobehavioral impairment	NA
S1P Modulators - Fingolimod - Siponimod - Ozanimod - Ponesimod	Early ultrasound for major malformations recommended	Teratogenic effect likely; risk of neural tube defects, fetal loss and fetal abnormalities including external, urogenital, skeletal, and vascular malformations (tetralogy of Fallot); risk for preterm labor	Gilenya: https://clinicaltrials.gov/ct2/show/NCT01285479
Cladribine	Patient may be followed by high-risk obstetrician	Risk of congenital malformations and embryolethality based on animal studies	Mavenclad: https://www.mslinefelines.com/ms-support
Teriflunomide	Early screening for major and minor malformations recommended; patient may be followed by high-risk obstetrician	Highly teratogenic; risk of serious birth defects in fetus; risk of preterm labor; risk of low birthweight	Aubagio: https://mothertobaby.org/ongoing-study/aubagio/
Natalizumab	Screen neonate for liver dysfunction, pancytopenia	Risk of mild to moderate hematologic alterations (pancytopenia with late pregnancy exposure)	NA
Anti-CD20 Agents			
Ocrelizumab	Screen neonate for B-cell depletion and/or pancytopenia	Risk of B-cell depletion in fetus/infant with 2 nd and 3 rd trimester exposure	Ocrevus: https://www.ocrevuspregnancyregistry.com/
Ofatumumab	Screen neonate for B-cell depletion and/or pancytopenia	Risk of B-cell depletion in fetus/infant with 2 nd and 3 rd trimester exposure	NA
Rituximab	Screen neonate for B-cell depletion and/or pancytopenia	Risk of B-cell depletion in fetus/infant with 2 nd and 3 rd trimester exposure; risk of congenital malformations in fetus and neonatal infections	NA
Alemtuzumab	Thyroid studies should be monitored	Risk of thyroid disease in mother (autoimmune thyroiditis in up to 40%); risk of low birthweight, preterm birth, preeclampsia; risk of neonatal Grave’s Disease and cognitive impairment	Lemtrada: (email) pregnancyregistries@syneoshealth.com

This table reflects our clinical practice and our review of combined recommendations of the prescribing information, and key articles. ^{2, 21, 48-59}

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